**Investigational Medicinal Product (IMP) Dossier**

The OPTIMISE2 trial intervention is to stop one or more antihypertensive medications in line with GP preference and existing guidelines, where appropriate. During the trial, one of any number of antihypertensive drug/doses may be stopped, making it difficult to provide a Summary of Product Characteristics (SmPC) for every drug potentially removed. With this in mind, the following SmPCs have been provided to give an example of the most commonly prescribed drug and dose for each drug class which might potentially be removed during the trial:

|  |  |  |
| --- | --- | --- |
| **No.** | **Drug class** | **SmPC example given** |
|  | Direct renin inhibitors | Aliskiren (Rasilez) 150 mg |
|  | Calcium channel blockers | Amlodipine 10 mg |
|  | Thiazide diuretic | Bendroflumethiazide 2.5 mg |
|  | Beta-blockers | Bisoprolol 1.25 mg |
|  | Alpha blockers | Doxazosin 2 mg |
|  | Angiotensin II receptor blocker | Losartan 12.5 mg |
|  | Centrally acting antihypertensives  Angiotensin-converting  enzyme inhibitors | Moxonidine 0.2mg  Ramipril 1.25 mg |
|  | Angiotensin-converting  enzyme inhibitors | Ramipril 1.25 mg |
|  | Aldosterone antagonists | Spironolactone 25 mg |

As there are no sections of the SmPC which detail expected adverse events as a result of medication withdrawal (the study IMP), for SAEs that require reporting, expectedness of SARs will be determined based on evidence from our previous OPTiMISE study. On this basis, SAEs for Ischemic stroke, Cardiac arrest, Hemiparesis, and Acute coronary syndrome will be considered as expected.

OPTIMISE 2

IMP Dossier v2.0 27-Jun-2025

REC Ref: 23/EM/0054 IRAS ID: 1006598

Page **1** of **1**

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

1

1. **NAME OF THE MEDICINAL PRODUCT**

Rasilez 150 mg film-coated tablets   
Rasilez 300 mg film-coated tablets

1. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Rasilez 150 mg film-coated tablets

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate).

Rasilez 300 mg film-coated tablets

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate).

For the full list of excipients, see section 6.1.

1. **PHARMACEUTICAL FORM**Film-coated tablet.

Rasilez 150 mg film-coated tablets

Light-pink, biconvex, round tablet, imprinted “IL” on one side and “NVR” on the other side.

Rasilez 300 mg film-coated tablets

Light-red, biconvex, ovaloid tablet, imprinted “IU” on one side and “NVR” on the other side.

1. **CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Treatment of essential hypertension in adults.

**4.2 Posology and method of administration**Posology

The recommended dose of Rasilez is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300 mg once daily.

The antihypertensive effect is substantially present within two weeks (85-90%) after initiating therapy with 150 mg once daily.

Rasilez may be used alone or in combination with other antihypertensive agents with the exception of use in combination with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m2) (see sections 4.3, 4.4 and 5.1).

*Special populations*

*Renal impairment*

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2). Aliskiren is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m2).

2

*Hepatic impairment*

No adjustment of the initial dose is required for patients with mild to severe hepatic impairment (see

section 5.2).

*Elderly patients aged 65 years and over*

The recommended starting dose of aliskiren in elderly patients is 150 mg. No clinically meaningful additional blood pressure reduction is observed by increasing the dose to 300 mg in the majority of elderly patients.

*Paediatric population*

Rasilez is contraindicated in children from birth to less than 2 years. Rasilez should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3). The safety and efficacy of Rasilez in children aged 6 to 17 years have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2. Use of Rasilez is not recommended in this population.

Method of administration

Oral use. The tablets should be swallowed whole with some water. Rasilez should be taken once a day, always with or always without food, preferably at the same time each day. Patients should establish a convenient daily schedule of medicinal product intake and maintain a steady temporal relationship with food intake. Concomitant intake with fruit juice and/or drinks containing plant extracts (including herbal teas) should be avoided (see section 4.5).

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- History of angioedema with aliskiren.

- Hereditary or idiopathic angioedema.

- Second and third trimesters of pregnancy (see section 4.6).

- The concomitant use of aliskiren with ciclosporin and itraconazole, two highly potent P-glycoprotein (P-gp) inhibitors, and other potent P-gp inhibitors (e.g. quinidine), is contraindicated (see section 4.5).

- The concomitant use of Rasilez with an angiotensin converting enzyme inhibitor(ACEI) or an angiotensin II receptor blocker (ARB) is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.5 and 5.1).

- Children from birth to less than 2 years (see sections 4.2 and 5.3).

**4.4 Special warnings and precautions for use**

General

In the event of severe and persistent diarrhoea, Rasilez therapy should be stopped (see section 4.8).

Aliskiren should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV) (see section 5.1).

Aliskiren should be used with caution in patients with heart failure treated with furosemide or torasemide (see section 4.5).

3

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Hypotension, syncope, stroke, hyperkalaemia, and decreased renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system (see section 5.1). Dual blockade of the RAAS by combining aliskiren with an ACEI or an ARB is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Risk of symptomatic hypotension

Symptomatic hypotension could occur after initiation of treatment with aliskiren in the following cases:

- Patients with marked volume depletion or patients with salt depletion (e.g. those receiving high doses of diuretics) or

- Combined use of aliskiren with other agents acting on the RAAS.

The volume or salt depletion should be corrected prior to administration of Rasilez, or the treatment

should start under close medical supervision.

Renal impairment

In clinical studies aliskiren has not been investigated in hypertensive patients with severe renal impairment (serum creatinine ? 150 μmol/l or 1.70 mg/dl in women and ? 177 μmol/l or 2.00 mg/dl in men and/or estimated GFR < 30 ml/min/1.73 m2), history of dialysis, nephrotic syndrome or renovascular hypertension. It is not recommended in patients with severe renal impairment (GFR < 30 ml/min/1.73 m2).

As for other medicinal products acting on the renin-angiotensin system, caution should be exercised when aliskiren is given in the presence of conditions pre-disposing to kidney dysfunction such as hypovolaemia (e.g. due to blood loss, severe prolonged diarrhoea, prolonged vomiting, etc.), heart disease, liver disease, diabetes mellitus or kidney disease. Acute renal failure, reversible upon discontinuation of treatment, has been reported in at-risk patients receiving aliskiren in post-marketing experience. In the event that any signs of renal failure occur, aliskiren should be promptly discontinued.

Increases in serum potassium have been observed with aliskiren in post-marketing experience and these may be exacerbated by concomitant use of other agents acting on the RAAS or by non-steroidal anti-inflammatory drugs (NSAIDs). Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary.

Renal artery stenosis

No controlled clinical data are available on the use of aliskiren in patients with unilateral or bilateral renal artery stenosis, or stenosis to a solitary kidney. However, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren. Therefore, caution should be exercised in these patients. If renal failure occurs, treatment should be discontinued.

Anaphylactic reactions and angioedema

Anaphylactic reactions have been observed during treatment with aliskiren from post-marketing experience (see section 4.8). Angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have been reported in patients treated with aliskiren.

A number of these patients had a history of angioedema or symptoms suggestive of angioedema, which in some cases followed use of other medicinal product that can cause angioedema, including RAAS blockers (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) (see

4

section 4.8).

In post-marketing experience, angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs (see section 4.8).

In a post-authorisation observational study, the co-administration of aliskiren with ACEIs or ARBs has been associated with an increased risk of angioedema. The mechanism of this effect has not been established. In general, dual blockade of the RAAS by combining aliskiren with an ACEI or an ARB is not recommended (see section “Dual blockade of the renin-angiotensin-aldosterone system

(RAAS)” above and also sections 4.5 and 4.8).

Special caution is necessary in patients with a hypersensitivity predisposition.

Patients with a history of angioedema may be at increased risk of experiencing angioedema during treatment with aliskiren (see sections 4.3 and 4.8). Caution should therefore be exercised when prescribing aliskiren to patients with a history of angioedema, and such patients should be closely monitored during treatment (see section 4.8) especially at the beginning of the treatment.

If anaphylactic reactions or angioedema occur, treatment should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Patients should be informed to report to the physician any signs suggestive of allergic reactions, in particular difficulties in breathing or swallowing, swelling of face, extremities, eyes, lips or tongue. Where there is involvement of the tongue, glottis or larynx adrenaline should be administered. In addition, measures necessary to maintain patent airways should be provided.

Paediatric population

Aliskiren is a P-glycoprotein (P-gp) substrate, and there is a potential for aliskiren overexposure in children with an immature P-gp drug transporter system. The age at which the transporter system is mature cannot be determined (see sections 5.2 and 5.3). Therefore, Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years (see sections 4.2 and 4.3). The safety and efficacy of aliskiren in children aged 6 to 17 years have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2.

**4.5 Interaction with other medicinal products and other forms of interaction** Contraindicated (see section 4.3)

*P-gp potent inhibitors*

A single dose interaction study in healthy subjects has shown that ciclosporin (200 and 600 mg) increases Cmax of aliskiren 75 mg approximately 2.5-fold and AUC approximately 5-fold. The increase may be higher with higher aliskiren doses. In healthy subjects, itraconazole (100 mg) increases AUC and Cmax of aliskiren (150 mg) by 6.5-fold and 5.8-fold, respectively. Therefore, concomitant use of aliskiren and P-gp potent inhibitors is contraindicated (see section 4.3).

Not recommended

*Fruit juice and drinks containing plant extracts*

Administration of fruit juice with aliskiren resulted in a decrease in AUC and Cmax of aliskiren. Co-administration of grapefruit juice with aliskiren 150 mg resulted in a 61% decrease in aliskiren AUC and co-administration with aliskiren 300 mg resulted in a 38% decrease in aliskiren AUC. Co-administration of orange or apple juice with aliskiren 150 mg resulted in a 62% decrease in aliskiren AUC or in a 63% decrease in aliskiren AUC, respectively. This decrease is likely due to an inhibition of organic anion transporting polypeptide-mediated uptake of aliskiren by components of fruit juice in the gastrointestinal tract. Therefore, because of the risk of therapeutic failure, fruit juice should not be taken together with aliskiren. The effect of drinks containing plant extracts (including herbal teas) on the absorption of aliskiren has not been investigated. However, compounds potentially

5

inhibiting organic anion transporting polypeptide-mediated uptake of aliskiren are widely present in fruits, vegetables, and many other plant products. Therefore, drinks containing plant extracts, including herbal teas, should not be taken together with aliskiren (see section 4.2)

*Dual blockade of the RAAS with aliskiren, ARBs or ACEIs*

Clinical trial data has shown that dual blockade of the RAAS through the combined use of ACEIs, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, stroke, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Caution required with concomitant use

*P-gp interactions*

MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in preclinical studies (see section 5.2). Rifampicin, which is an inducer of P-gp, reduced aliskiren bioavailability by approximately 50% in a clinical study. Other inducers of P-gp (St. John’s wort) might decrease the bioavailability of aliskiren. Although this has not been investigated for aliskiren, it is known that P-gp also controls tissue uptake of a variety of substrates and P-gp inhibitors can increase the tissue-to-plasma concentration ratios. Therefore, P-gp inhibitors may increase tissue levels more than plasma levels. The potential for drug interactions at the P-gp site will likely depend on the degree of inhibition of this transporter.

*Moderate P-gp inhibitors*

Co-administration of ketoconazole (200 mg) or verapamil (240 mg) with aliskiren (300 mg) resulted in a 76% or 97% increase in aliskiren AUC, respectively. The change in plasma levels of aliskiren in the presence of ketoconazole or verapamil is expected to be within the range that would be achieved if the dose of aliskiren were doubled; aliskiren doses of up to 600 mg, or twice the highest

recommended therapeutic dose, have been found to be well tolerated in controlled clinical studies. Preclinical studies indicate that aliskiren and ketoconazole co-administration enhances aliskiren gastrointestinal absorption and decreases biliary excretion. Therefore, caution should be exercised when aliskiren is administered with ketoconazole, verapamil or other moderate P-gp inhibitors (clarithromycin, telithromycin, erythromycin, amiodarone).

*Medicinal products affecting serum potassium levels*

Concomitant use of other agents affecting the RAAS, of NSAIDs or of agents that increase serum potassium levels (e.g. potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, heparin) may lead to increases in serum potassium. If co-administration with an agent affecting the level of serum potassium is considered necessary, routine monitoring of potassium levels would be advisable.

*Non-steroidal anti-inflammatory drugs (NSAIDs)*

NSAIDs may reduce the anti-hypertensive effect of aliskiren. In some patients with compromised renal function (dehydrated patients or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination of aliskiren with an NSAID requires caution, especially in elderly patients.

*Furosemide and torasemide*

Oral co-administration of aliskiren and furosemide had no effect on the pharmacokinetics of aliskiren but reduced exposure to furosemide by 20-30% (the effect of aliskiren on furosemide administered intramuscularly or intravenously has not been investigated). After multiple doses of furosemide (60 mg/day) co-administered with aliskiren (300 mg/day) to patients with heart failure the urinary sodium excretion and the urine volume were reduced during the first 4 hours by 31% and 24%, respectively, as compared to furosemide alone. The mean weight of patients concomitantly treated with furosemide and 300 mg aliskiren (84.6 kg) was higher than the weight of patients treated with furosemide alone (83.4 kg). Smaller changes in furosemide pharmacokinetics and efficacy were observed with aliskiren 150 mg/day.

6

The available clinical data did not indicate that higher doses of torasemide were used after co-administration with aliskiren. Torasemide renal excretion is known to be mediated by organic anion transporters (OATs). Aliskiren is minimally excreted via the renal route, and only 0.6% of the aliskiren dose is recovered in urine following oral administration (see section 5.2). However, since aliskiren has been shown to be a substrate for the organic anion-transporting polypeptide 1A2 (OATP1A2) (see section “Organic anion transporting polypeptide (OATP” below) inhibitors), there is a potential for aliskiren to reduce plasma torasemide exposure by an interference with the absorption process.

In patients treated with both aliskiren and oral furosemide or torasemide, it is therefore recommended that the effects of furosemide or torasemide be monitored when initiating and adjusting furosemide, torasemide or aliskiren therapy to avoid changes in extracellular fluid volume and possible situations of volume overload (see section 4.4).

*Warfarin*

The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.

*Food interactions*

Although meals (low or high fat content) have been shown to reduce the absorption of aliskiren substantially, the efficacy of aliskiren was shown to be similar when taken either with a light meal or without a meal (see section 4.2). The available clinical data do not suggest an additive effect of different types of foods and/or drinks, however the potential for decreased aliskiren bioavailability due to this additive effect has not been studied and therefore cannot be excluded.

*Pharmacokinetic interaction with other medicinal products*

Compounds that have been investigated in clinical pharmacokinetic studies include acenocoumarol, atenolol, celecoxib, pioglitazone, allopurinol, isosorbide-5-mononitrate and hydrochlorothiazide. No interactions have been identified.

Co-administration of aliskiren with either metformin (↓28%), amlodipine (129%) or cimetidine (119%) resulted in between 20% and 30% change in Cmax or AUC of Rasilez. When administered with atorvastatin, steady-state Rasilez AUC and Cmax increased by 50%. Co-administration of Rasilez had no significant impact on atorvastatin, metformin or amlodipine pharmacokinetics. As a result no dose adjustment for Rasilez or these co-administered medicinal products is necessary.

Digoxin and verapamil bioavailability may be slightly decreased by Rasilez.

*CYP450 interactions*

Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A). Aliskiren does not induce CYP3A4. Therefore, aliskiren is not expected to affect the systemic exposure of substances that inhibit, induce or are metabolised by these enzymes. Aliskiren is metabolised minimally by the cytochrome P450 enzymes. Hence, interactions due to inhibition or induction of CYP450 isoenzymes are not expected. However, CYP3A4 inhibitors often also affect P-gp. Increased aliskiren exposure during co-administration of CYP3A4 inhibitors that also inhibit P-gp can therefore be expected (see other P-gp references in section 4.5).

*P-gp substrates or weak inhibitors*

No relevant interactions with atenolol, digoxin, amlodipine or cimetidine have been observed. When administered with atorvastatin (80 mg), steady-state aliskiren (300 mg) AUC and Cmax increased by 50%. In experimental animals, it has been shown that P-gp is a major determinant of Rasilez bioavailability. Inducers of P-gp (St. John’s wort, rifampicin) might therefore decrease the bioavailability of Rasilez.

*Organic anion transporting polypeptide (OATP) inhibitors*

Preclinical studies indicate that aliskiren might be a substrate of organic anion transporting

polypeptides. Therefore, the potential exists for interactions between OATP inhibitors and aliskiren

7

when administered concomitantly (see section “Fruit juice and drinks containing plant extracts” above).

**4.6 Fertility, pregnancy and lactation**Pregnancy

There are no data on the use of aliskiren in pregnant women. Aliskiren was not teratogenic in rats or rabbits (see section 5.3). Other substances that act directly on the RAAS have been associated with serious foetal malformations and neonatal death. As for any medicine that acts directly on the RAAS, alsikiren should not be used during the first trimester of pregnancy or in women planning to become pregnant and is contraindicated during the second and third trimesters (see section 4.3). Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, treatment should be discontinued accordingly.

Breast-feeding

It is unknown whether aliskiren/metabolites are excreted in human milk. Aliskiren was secreted in the milk of lactating rats. A risk to the newborns/infants cannot be excluded. Aliskiren should not be used during breast-feeding.

Fertility

There are no clinical data on fertility.

**4.7 Effects on ability to drive and use machines**

Rasilez has minor influence on the ability to drive and use machines. When driving vehicles or using machines it must be borne in mind that dizziness or drowsiness may occasionally occur when taking Rasilez.

**4.8 Undesirable effects**Summary of the safety profile

Serious adverse reactions include anaphylactic reaction and angioedema which have been reported in post-marketing experience and may occur rarely (less than 1 case per 1,000 patients). The most common adverse reaction is diarrhoea.

Tabulated list of adverse reactions

Aliskiren has been evaluated for safety in more than 7,800 patients, including over 2,300 treated for over 6 months, and more than 1,200 for over 1 year. The adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (?1/10); common (?1/100 to <1/10); uncommon (?1/1,000 to <1/100); rare (?1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

8

*Table 1*

**Immune system disorders**

Rare: Anaphylactic reactions, hypersensitivity reactions **Nervous system disorders**

Common: Dizziness   
**Ear and labyrinth disorders**

Not known: Vertigo   
**Cardiac disorders**

Uncommon: Palpitations, oedema peripheral   
**Vascular disorders**

Uncommon: Hypotension

**Respiratory, thoracic and mediastinal disorders**

Uncommon: Cough

Not known: Dyspnoea   
**Gastrointestinal disorders**

Common: Diarrhoea

Not known: Nausea, vomiting   
**Hepatobiliary disorders**

Not known: Liver disorder\*, jaundice, hepatitis, liver   
failure\*\* **Skin and subcutaneous tissue disorders**

Uncommon: Severe cutaneous adverse reactions (SCARs) including Stevens Johnson syndrome, toxic epidermal necrolysis (TEN) and oral mucosal reactions, rash, pruritus, urticaria

Rare: Angioedema, erythema   
**Musculoskeletal and connective tissue disorders**

Common: Arthralgia   
**Renal and urinary disorders**

Uncommon: Acute renal failure, renal impairment   
**Investigations**

Common: Hyperkalaemia

Uncommon: Liver enzyme increased

Rare: Haemoglobin decreased, haematocrit decreased, blood creatinine increased

N o t k n o w n : H y p o n a t r a e m i a

\*Isolated cases of liver disorder with clinical symptoms and laboratory evidence of more

marked hepatic dysfunction.

\*\*Including one case of ‘liver failure fulminant’ reported in the post-marketing experience, for which

a causal relationship with aliskiren cannot be excluded.

Description of selected adverse reactions

*Hypersensitivity reactions including anaphylactic reactions and angioedema*

In controlled clinical studies, angioedema and hypersensitivity reactions occurred rarely during

treatment with aliskiren with rates comparable to treatment with placebo or comparators.

Cases of angioedema or symptoms suggestive of angioedema (swelling of the face, lips, throat and/or tongue) have also been reported in post-marketing experience. A number of these patients had a history of angioedema or symptoms suggestive of angioedema which in some cases was associated with the administration of other medicines known to cause angioedema, including RAAS blockers (ACEIs or ARBs).

In post-marketing experience, cases of angioedema or angioedema-like reactions have been reported when aliskiren was co-administered with ACEIs and/or ARBs.

Hypersensitivity reactions including anaphylactic reactions have also been reported in post-marketing experience (see section 4.4).

9

In the event of any signs suggesting a hypersensitivity reaction/angioedema (in particular difficulties in breathing or swallowing, rash, itching, hives or swelling of the face, extremities, eyes, lips and/or tongue, dizziness) patients should discontinue treatment and contact the physician (see section 4.4).

Arthralgia has been reported in post-marketing experience. In some cases this occurred as part of a hypersensitivity reaction.

*Renal dysfunction*

In post-marketing experience, renal dysfunction and cases of acute renal failure have been reported in

patients at risk (see section 4.4).

Laboratory findings

In controlled clinical trials, clinically relevant changes in standard laboratory parameters were uncommonly associated with the administration of aliskiren. In clinical studies in hypertensive patients, Rasilez had no clinically important effects on total cholesterol, high density lipoprotein cholesterol (HDL-C), fasting triglycerides, fasting glucose or uric acid.

*Haemoglobin and haematocrit*

Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.05 mmol/l and 0.16 volume percent, respectively) were observed. No patients discontinued therapy due to anaemia. This effect is also seen with other agents acting on the renin-angiotensin system, such as ACEIs and ARBs.

*Serum potassium*

Increases in serum potassium have been observed with aliskiren and these may be exacerbated by concomitant use of other agents acting on the RAAS or by NSAIDs. Consistent with standard medical practice, periodic determination of renal function including serum electrolytes is advised if co-administration is considered necessary.

Paediatric population

Aliskiren has been evaluated for safety in a randomised, double-blind, 8-week study in

267 hypertensive patients aged 6 to 17 years, mostly overweight/obese, followed by an extension study including 208 patients treated for 52 weeks. An additional 52 to 104 week non-interventional observational extension study in 106 patients (no study treatment administered) was conducted with the objective to evaluate the long-term safety in terms of growth and development of children 6-17 years of age with hypertension (primary or secondary) at baseline in the core study, previously treated with aliskiren.

The frequency, type and severity of adverse reactions in children were generally similar to those seen in hypertensive adults. No overall clinically relevant adverse impact on paediatric patients aged 6 to 17 years was observed after treatment with aliskiren for up to one year based on physical development, assessed in patients with primary or secondary hypertension, and neurocognitive development assessed only in patients with secondary hypertension (19 patients: 9 previously treated with aliskiren and 10 previously treated with enalapril) (see section 4.2, 4.8, 5.1 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V.](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2013/03/WC500139752.doc)

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**4.9 Overdose**Symptoms

Limited data are available related to overdose in humans. The most likely manifestations of overdosage would be hypotension, related to the antihypertensive effect of aliskiren.

Treatment

If symptomatic hypotension should occur, supportive treatment should be initiated.

In a study conducted in patients with end stage renal disease (ESRD) receiving haemodialysis, dialysis clearance of aliskiren was low (< 2% of oral clearance). Therefore, dialysis is not adequate to treat aliskiren over-exposure.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; renin inhibitor, ATC code: C09XA02

Mechanism of action

Aliskiren is an orally active, non-peptide, potent and selective direct inhibitor of human renin.

Pharmacodynamic effects

By inhibiting the enzyme renin, aliskiren inhibits the RAAS at the point of activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Whereas other agents that inhibit the RAAS (ACEI and angiotensin II receptor blockers (ARB)) cause a compensatory rise in plasma renin activity (PRA), treatment with aliskiren decreases PRA in hypertensive patients by approximately 50 to 80%. Similar reductions were found when aliskiren was combined with other antihypertensive agents. The clinical implications of the differences in effect on PRA are not known at the present time.

Clinical efficacy and safety

In hypertensive patients, once-daily administration of aliskiren at doses of 150 mg and 300 mg provided dose-dependent reductions in both systolic and diastolic blood pressure that were maintained over the entire 24-hour dose interval (maintaining benefit in the early morning) with a mean peak to trough ratio for diastolic response of up to 98% for the 300 mg dose. 85 to 90% of the maximal blood-pressure-lowering effect was observed after 2 weeks. The blood-pressure-lowering effect was sustained during long-term treatment, and was independent of age, gender, body mass index and ethnicity. Aliskiren has been studied in 1,864 patients aged 65 years or older, and in 426 patients aged 75 years or older.

Aliskiren monotherapy studies have shown blood pressure lowering effects comparable to other classes of antihypertensive agents including ACEI and ARB. Compared to a diuretic (hydrochlorothiazide - HCTZ), Rasilez 300 mg lowered systolic/diastolic blood pressure by 17.0/12.3 mmHg, compared to 14.4/10.5 mmHg for HCTZ 25 mg after 12 weeks of treatment.

Combination therapy studies are available for aliskiren added to the diuretic hydrochlorothiazide, the calcium channel blocker amlodipine and the beta blocker atenolol. These combinations were well tolerated. It induced an additive blood-pressure-lowering effect when added to hydrochlorothiazide. In

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patients who did not adequately respond to 5 mg of the calcium channel blocker amlodipine, the addition of aliskiren 150 mg had a blood-pressure-lowering effect similar to that obtained by increasing amlodipine dose to 10 mg, but had a lower incidence of oedema (aliskiren

150 mg/amlodipine 5 mg 2.1% vs. amlodipine 10 mg 11.2%).

The efficacy and safety of aliskiren-based therapy were compared to ramipril-based therapy in a 9-month non-inferiority study in 901 elderly patients (2 65 years) with essential systolic hypertension. Aliskiren 150 mg or 300 mg per day or ramipril 5 mg or 10 mg per day were administered for 36 weeks with optional add-on therapy of hydrochlorothiazide (12.5 mg or 25 mg) at week 12, and amlodipine (5 mg or 10 mg) at week 22. Over the 12 week period, aliskiren monotherapy lowered systolic/diastolic blood pressure by 14.0/5.1 mmHg, compared to 11.6/3.6 mmHg for ramipril, consistent with aliskiren being non-inferior to ramipril at the doses chosen and the differences in systolic and diastolic blood pressure were statistically significant. Tolerability was comparable in both treatment arms, however cough was more often reported with the ramipril regimen than the aliskiren regimen (14.2% vs. 4.4%), whilst diarrhoea was more common with the aliskiren regimen than for the ramipril regimen (6.6% vs. 5.0%).

In a 8-week study in 754 hypertensive elderly (2 65 years) and very elderly patients (30% 2 75 years) aliskiren at doses of 75 mg, 150 mg and 300 mg provided statistically significant superior reduction in blood pressure (both systolic and diastolic) when compared to placebo. No additional blood pressure lowering effect was detected with 300 mg aliskiren compared to 150 mg aliskiren. All three doses were well tolerated in both elderly and very elderly patients. In a pooled analysis of efficacy and safety data from clinical studies up to 12 months duration, there was no statistically significant difference in blood pressure reduction between aliskiren 300 mg and aliskiren 150 mg in elderly patients

(2 65 years).

In obese hypertensive patients who did not adequately respond to HCTZ 25 mg, add-on treatment with aliskiren 300 mg provided additional blood pressure reduction that was comparable to add-on treatment with irbesartan 300 mg or amlodipine 10 mg.

There has been no evidence of first-dose hypotension and no effect on pulse rate in patients treated in controlled clinical studies. Excessive hypotension was uncommonly (0.1%) seen in patients with uncomplicated hypertension treated with aliskiren alone. Hypotension was also uncommon (<1%) during combination therapy with other antihypertensive agents. With cessation of treatment, blood pressure gradually returned towards baseline levels over a period of several weeks, with no evidence of a rebound effect for blood pressure or PRA.

In a 36-week study involving 820 patients with ischaemic left ventricular dysfunction, no changes in ventricular re-modelling as assessed by left ventricular end systolic volume were detected with aliskiren compared to placebo on top of background therapy.

The combined rates of cardiovascular death, hospitalisation for heart failure, recurrent heart attack, stroke and resuscitated sudden death were similar in the aliskiren group and the placebo group. However, in patients receiving aliskiren there was a significantly higher rate of hyperkalaemia, hypotension and kidney dysfunction when compared to the placebo group.

Aliskiren was evaluated for cardiovascular and/or renal benefit in a double-blind placebo controlled randomised trial in 8,606 patients with type 2 diabetes and chronic kidney disease (evidenced by proteinuria and/or GFR < 60 ml/min/1.73 m2) with or without cardiovascular disease. In most patients arterial blood pressure was well controlled at baseline. The primary endpoint was a composite of cardiovascular and renal complications.

In this study, aliskiren 300 mg was compared to placebo when added to standard of care which included either an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The study was discontinued prematurely because the participants were unlikely to benefit from aliskiren. The final study results indicated a hazard ratio for the primary endpoint of 1.097 in favour of placebo

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(95.4% Confidence Interval: 0.987, 1.218, 2-sided p=0.0787). In addition, an increased incidence of adverse events was observed with aliskiren compared to placebo (38.2% versus 30.3%). In particular there was an increased incidence of renal dysfunction (14.5% versus 12.4%), hyperkalaemia (39.1% versus 29.0%), hypotension-related events (19.9% versus 16.3%) and adjudicated stroke endpoints (3.4% versus 2.7%). The increased incidence of stroke was greater in patients with renal insufficiency.

Aliskiren 150 mg (increased to 300 mg if tolerated) added to conventional therapy was evaluated in a double-blind placebo-controlled randomised trial in 1,639 patients with reduced ejection fraction hospitalised for an episode of acute heart failure (NYHA Class III–IV) who were haemodynamically stable at baseline. The primary endpoint was cardiovascular death or heart failure rehospitalisation within 6 months; secondary endpoints were assessed within 12 months.

The study showed no benefit of aliskiren when administered on top of standard therapy for acute heart failure and an increased risk of cardiovascular events in patients with diabetes mellitus. Study results indicated a non-significant effect of aliskiren with a hazard ratio of 0.92 (95% Confidence Interval: 0.76-1.12; p=0.41, aliskiren vs. placebo). Different treatment effects of aliskiren were reported for overall mortality within 12 months dependent on diabetes mellitus status. In the subgroup of patients with diabetes mellitus the hazard ratio was 1.64 in favour of placebo (95% Confidence Interval: 1.15­2.33), whereas the hazard ratio in the subgroup of patients without diabetes was 0.69 in favour of aliskiren (95% Confidence Interval: 0.50-0.94); p-value for interaction = 0.0003. An increased incidence of hyperkalaemia (20.9% versus 17.5%), renal impairment/renal failure (16.6% versus 12.1%) and hypotension (17.1% versus 12.6%) was observed in the aliskiren group compared with placebo and was greater in patients with diabetes.

Aliskiren was evaluated for cardiovascular mortality and morbidity benefit in a double-blind active controlled randomised study in 7,064 patients with chronic heart failure and reduced left ventricular ejection fraction, of which 62% had a history of hypertension. The primary endpoint was a composite of cardiovascular death and first hospitalisation for heart failure.

In this study, aliskiren at a target dose of 300 mg was compared to enalapril at a target dose of 20 mg when added to standard of care which included a beta blocker (and a mineralocorticoid receptor antagonist in 37% of patients) and a diuretic as needed. The study also evaluated the combination of aliskiren and enalapril. Mean duration of follow-up was 3.5 years. The final results of the study did not demonstrate statistically that aliskiren was non-inferior to enalapril on the primary endpoint, however there was essentially no difference in the observed incidence rates between aliskiren and enalapril (hazard ratio of 0.99 with 95% Confidence Interval: 0.90-1.10). There was no significant benefit of adding aliskiren to enalapril (primary endpoint: hazard ratio of 0.93 with 95% Confidence Interval: 0.85-1.03; p=0.1724, combination versus enalapril). Treatment effects were similar in patients with diabetes and with renal insufficiency. The incidence of adjudicated stroke was not significantly different between the aliskiren and enalapril groups (4.4% versus 4.0%; HR 1.12, 95% CI 0.848, 1.485) or between the combination and enalapril groups (3.7% versus 4.0%; HR 0.93, 95% CI 0.697, 1.251). The incidence of adverse events tended to be higher in patients with diabetes, or with GFR <60 ml/min/1.73 m2, or with age ≥ 65 years; however, there was no difference between patients treated with aliskiren and those treated with enalapril.

The incidence of certain adverse events was similar between aliskiren and enalapril groups while there was an increased incidence of adverse events with the combination of aliskiren and enalapril: hyperkalaemia (21.4%, 13.2%, and 15.9% for combination, aliskiren and enalapril respectively); renal impairment/renal failure (23.2%, 17.4% and 18.7%) and hypotension related events (27.0%, 22.3% and 22.4%).

There was a statistically significant increased incidence of syncope with the combination of aliskiren and enalapril compared to enalapril in the overall population (4.2% versus 2.8%; RR 1.51, 95% CI 1.11-2.05) and in the subgroups NYHA I/II overall (4.8% versus 3.0%; RR 1.62, 95% CI 1.14-2.29).

The incidence of atrial fibrillation was 11.1%, 13.3%, and 11.0% in the combination, aliskiren, and enalapril groups, respectively.

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Statistically significantly higher incidences in the occurrence of cardiac failure and ischaemic stroke were also found for aliskiren compared to enalapril in patients with NYHA I/II with hypertension, and in the occurrence of chronic cardiac failure and ventricular extrasystole in patients with NYHA III/IV with hypertension. For the combination of aliskiren and enalapril there were statistically significant differences in the rate of angina unstable compared to enalapril.

No clinically relevant differences in efficacy or safety results were observed in the subpopulation of elderly patients with a history of hypertension and chronic heart failure Class I-II compared to the overall study population.

Cardiac electrophysiology

No effect on QT interval was reported in a randomised, double-blind, placebo, and active-controlled study using standard and Holter electrocardiography.

Paediatric population

In a multicentre, randomised, double-blind, 8-week study with aliskiren monotherapy (3 dose groups by weight category [220 kg to <50 kg; 250 kg to <80 kg; 280 kg to ≤150 kg]: low 6.25/12.5/25 mg [0.13-0.31 mg/kg]; mid 37.5/75/150 mg [0.75-1.88 mg/kg]; and high dose 150/300/600 mg [3.0-7.5 mg/kg], with a wide dose ratio between the low, mid and high dose groups [1:6:24]) in 267 paediatric hypertensive patients aged 6 to 17 years, mostly overweight/obese, aliskiren lowered office and ambulatory blood pressure in a dose-dependent manner during the initial 4 week dose-finding phase of the study (Phase 1). However, in the subsequent 4 week randomised withdrawal phase of the study (Phase 2), the effect of aliskiren overlapped with the effects observed in patients switched to placebo in all dose groups (low, p=0.8894; mid, p=0.9511; high, p=0.0563). The average differences between aliskiren and placebo for the low and mid dose groups were <0.2 mmHg. The treatment with aliskiren was well tolerated in this study.

This study was extended with a 52-week double-blind, randomised study to evaluate the safety, tolerability and efficacy of aliskiren compared to enalapril in 208 paediatric hypertensive patients aged 6 to 17 years (at baseline in the previous study). The starting dose in each group was assigned depending on weight with three groups: 220 to <50 kg, 250 to <80 kg, and 280 to ≤150 kg. The starting doses for aliskiren were 37.5/75/150 mg in the low, mid and high weight groups, respectively. The starting doses for enalapril were 2.5/5/10 mg in the low, mid and high weight groups, respectively. Optional titration of the respective study drug doses to the next highest weight-based dose level was available by doubling the dose with each of the two allowed dose titrations, up to 600 mg (highest studied dose in adults) for aliskiren and 40 mg for enalapril in the 280 to ≤150 kg weight group, if medically necessary to control the mean sitting systolic blood pressure (i.e. msSBP should be less than the 90th percentile for age, gender and height). Overall, the mean age of the patients was 11.8 years with 48.6% of patients being in the 6-11 years age group and 51.4% in the 12-17 years age group. Mean weight was 68.0 kg with 57.7% of patients having BMI greater than or equal to the 95th percentile for age and gender. At the end of this extension study, changes in msSBP from baseline were similar with aliskiren compared to enalapril (-7.63 mmHg vs. -7.94 mmHg) in the full analysis set. However, the significance of the non-inferiority testing was not maintained when the analysis was performed on the per-protocol set in which the least square mean change in msSBP from baseline was -7.84 mmHg with aliskiren and -9.04 mmHg with enalapril. In addition, due to the possibility of up-titration if medically necessary to control the msSBP, no conclusion can be drawn on the appropriate posology of aliskiren in patients aged 6 to 17 years.

After the first 52 week extension study, eligible male and female paediatric patients aged 6 to 17 years with primary or secondary hypertension, were enrolled in a 52 to 104 week off-therapy non-interventional observational extension study designed to evaluate the LT growth and development, through height and weight measurement, with added neurocognitive and renal function evaluations as

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follow-up measures performed only in patients with secondary hypertension (19 patients: 9 previously treated with aliskiren and 10 previously treated with enalapril).

There were no statistically significant differences in the mean changes in weight, height, or BMI between the treatment groups from Baseline to LT Visit 18 (Week 104) (primary analysis).

In patients after 104 weeks (at LT Visit 19 [Week 156]), there were LS mean decreases from Baseline in weight and BMI in both treatment groups, with a slightly larger decrease in the aliskiren compared to the enalapril treatment group.

There was a greater LS mean increase from Baseline in height after 104 weeks (at LT Visit 19 [Week 156], secondary hypertension patients) compared to the increase observed after 52 weeks (at LT Visit 18 [Week 104], primary hypertension patients), which is expected in these growing paediatric patients.

Results of the neurocognitive assessments showed some improvements in most of the test scores, with no meaningful difference between the treatment groups.

The European Medicines Agency has deferred the obligation to submit the results of studies with aliskiren in one or more subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**Absorption

Following oral absorption, peak plasma concentrations of aliskiren are reached after 1-3 hours. The absolute bioavailability of aliskiren is approximately 2-3%. Meals with a high fat content reduce Cmax by 85% and AUC by 70%. At steady state meals with low fat content reduce Cmax by 76% and AUC0-tau by 67% in hypertensive patients. However, the efficacy of aliskiren was similar when taken with a light meal or under fasted state. Steady-state-plasma concentrations are reached within 5-7 days following once-daily administration and steady-state levels are approximately 2-fold greater than with the initial dose.

Transporters

MDR1/Mdr1a/1b (P-gp) was found to be the major efflux system involved in intestinal absorption and biliary excretion of aliskiren in pre-clinical studies.

Distribution

Following intravenous administration, the mean volume of distribution at steady state is approximately 135 litres, indicating that aliskiren distributes extensively into the extravascular space. Aliskiren plasma protein binding is moderate (47-51%) and independent of the concentration.

Biotransformation

Approximately 1.4% of the total oral dose is metabolised. The enzyme responsible for this metabolism is CYP3A4.

Elimination

The mean half-life is about 40 hours (range 34-41 hours). Aliskiren is mainly eliminated as unchanged compound in the faeces (78%). Approximately 0.6% of the dose is recovered in urine following oral administration. Following intravenous administration, the mean plasma clearance is approximately 9 l/h.

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Linearity/non-linearity

Exposure to aliskiren increased more than in proportion to the increase in dose. After single dose administration in the dose range of 75 to 600 mg, a 2-fold increase in dose results in a ~2.3 and 2.6-fold increase in AUC and Cmax, respectively. At steady state the non-linearity may be more pronounced. Mechanisms responsible for deviation from linearity have not been identified. A possible mechanism is saturation of transporters at the absorption site or at the hepatobiliary clearance route.

Characteristics in patients

Aliskiren is an effective once-a-day antihypertensive treatment in adult patients, regardless of gender, age, body mass index and ethnicity.

*Renal impairment*

The pharmacokinetics of aliskiren were evaluated in patients with varying degrees of renal insufficiency. Relative AUC and Cmax of aliskiren in subjects with renal impairment ranged between 0.8 to 2 times the levels in healthy subjects following single dose administration and at steady state. These observed changes, however, did not correlate with the severity of renal impairment. No adjustment of the initial dosage of treatment is required in patients with mild to moderate renal impairment (see sections 4.2 and 4.4). It is not recommended in patients with severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m2).

The pharmacokinetics of aliskiren were evaluated in patients with end stage renal disease receiving haemodialysis. Administration of a single oral dose of 300 mg aliskiren was associated with very minor changes in the pharmacokinetics of aliskiren (change in Cmax of less than 1.2 fold; increase in AUC of up to 1.6 fold) compared to matched healthy subjects. Timing of haemodialysis did not significantly alter the pharmacokinetics of aliskiren in ESRD patients. Therefore, if administration of aliskiren in ESRD patients receiving haemodialysis is considered necessary, no dose adjustment is warranted in these patients. However, the use of aliskiren is not recommended in patients with severe renal impairment (see section 4.4).

*Hepatic impairment*

The pharmacokinetics of aliskiren were not significantly affected in patients with mild to severe liver disease. Consequently, no adjustment of the initial dose of aliskiren is required in patients with mild to severe hepatic impairment.

*Elderly patients aged 65 years and over*

The AUC is 50% higher in elderly (> 65 years) than in young subjects. Gender, weight and ethnicity

have no clinically relevant influence on aliskiren pharmacokinetics.

*Paediatric population*

In a pharmacokinetic study of aliskiren treatment in 39 paediatric hypertensive patients aged 6 to 17 years given daily doses of 2 mg/kg or 6 mg/kg aliskiren administered as granules (3.125 mg/tablet), pharmacokinetic parameters were similar to those in adults. The results of this study did not suggest that age, body weight or gender have any significant effect on aliskiren systemic exposure (see section 4.2).

In an 8-week randomised, double-blind study with aliskiren monotherapy in 267 paediatric hypertensive patients aged 6 to 17 years, mostly overweight/obese, fasting trough aliskiren concentrations at day 28 were comparable to those observed in other studies in both adults and children using similar aliskiren doses (see section 5.1).

Results from an in vitro MDR1 human tissue study suggested an age and tissue dependent pattern of MDR1 (P-gp) transporter maturation. A high inter-individual variability of mRNA expression levels was observed (up to 600-fold). Hepatic MDR1 mRNA expression was statistically significantly lower in samples from foetuses, neonates and infants up to 23 months.

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The age at which the transporter system is mature cannot be determined. There is a potential for aliskiren overexposure in children with an immature MDR1 (P-gp) system (see section “Transporters” above and sections 4.2, 4.4 and 5.3).

**5.3 Preclinical safety data**

Safety pharmacology studies did not reveal any adverse effects on central nervous, respiratory or cardiovascular function. Findings during repeat-dose toxicity studies in animals were consistent with the known local (gastrointestinal tract) irritation potential or the expected pharmacological effects of aliskiren.

No carcinogenic potential for aliskiren was detected in a 2-year rat study and a 6-month

transgenic mouse study. One colonic adenoma and one caecal adenocarcinoma recorded in rats at the dose of 1500 mg/kg/day were not statistically significant.

Although aliskiren has known local (gastrointestinal tract) irritation potential, safety margins obtained in humans at the dose of 300 mg during a study in healthy volunteers were considered to be appropriate at 9-11-fold based on faecal concentrations or 6-fold based on mucosa concentrations in comparison with 250 mg/kg/day in the rat carcinogenicity study.

Aliskiren was devoid of any mutagenic potential in the *in vitro* and *in vivo* mutagenicity studies.

Reproductive toxicity studies with aliskiren did not reveal any evidence of embryofoetal toxicity or teratogenicity at doses up to 600 mg/kg/day in rats or 100 mg/kg/day in rabbits. Fertility, pre-natal development and post-natal development were unaffected in rats at doses up to 250 mg/kg/day. The doses in rats and rabbits provided systemic exposures of 1 to 4 and 5 times higher, respectively, than the maximum recommended human dose (300 mg).

Juvenile animal studies

In a juvenile toxicity study in 8-day-old rats, aliskiren administration at 100 mg/kg/day and 300 mg/kg/day (2.3- and 6.8-fold the maximum recommended human dose) was associated with high mortality and severe morbidity. In another juvenile toxicity study in 14-day-old rats, aliskiren administration at 300 mg/kg/day (8.5-fold the maximum recommended human dose) was associated with delayed mortality. The systemic exposure to aliskiren in 8-day old rats was >400-fold higher than in adult rats. Results from a mechanistic study showed that the MDR1 (P-gp) gene expression in juvenile rats was significantly lower when compared to adult rats. The increased aliskiren exposure in juvenile rats appears to be attributed mainly to lack of maturation of P-gp in the gastrointestinal tract. There is therefore a potential for aliskiren overexposure in paediatric patients with immature MDR1 efflux system (see sections 4.2, 4.3 and 5.2).

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1. **PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Crospovidone, type A

Magnesium stearate

Microcrystalline cellulose

Povidone, K-30

Colloidal anhydrous silica

Hypromellose substitution type 2910 (3 mPa·s)

Macrogol 4000

Talc

Black iron oxide (E 172)

Red iron oxide (E 172)

Titanium dioxide (E 171)

**6.2 Incompatibilities**Not applicable.

**6.3 Shelf life**3 years

**6.4 Special precautions for storage**

Do not store above 25**C. Store in the original package in order to protect from moisture.

**6.5 Nature and contents of container**Rasilez 150 mg film-coated tablets

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:

Unit packs containing 14, 28, 30, 50, 56, 90 or 98 tablets.

Unit packs containing 56x1 tablets in perforated unit dose blisters.

Multipacks containing 280 (20x14) tablets.

Multipacks containing 98 (2x49x1) tablets in perforated unit dose blisters.

Rasilez 300 mg film-coated tablets

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters:

Unit packs containing 14, 28, 30, 50, 56, 90 or 98 tablets.

Unit packs containing 56x1 tablets in perforated unit dose blisters.

Multipacks containing 280 (20x14) tablets.

Multipacks containing 98 (2x49x1) tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

1. **MARKETING AUTHORISATION HOLDER**Noden Pharma DAC

1 8

D'Olier Chambers   
16A D'Olier Street   
Dublin 2

Ireland

1. **MARKETING AUTHORISATION NUMBER(S)**

Rasilez 150 mg film-coated tablets   
EU/1/07/405/021-030

Rasilez 300 mg film-coated tablets   
EU/1/07/405/031-040

1. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 22 August 2007   
Date of latest renewal: 22 May 2017

1. **DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency [http://www.ema.europa.eu](http://www.ema.europa.eu/)

1 9

**ANNEX II**

1. **MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
2. **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
3. **OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
4. **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

20

1. **MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Noden Pharma DAC

D'Olier Chambers

16A D'Olier Street

Dublin 2

Ireland

1. **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE** Medicinal product subject to medical prescription.
2. **OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

* **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

* **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

* At the request of the European Medicines Agency;
* Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

21

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

22

**A. LABELLING**

23

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING   
CARTON FOR UNIT PACK CONTAINING PCTFE/PVC BLISTERS**

|  |
| --- |
| 1. **NAME OF THE MEDICINAL PRODUCT** |

Rasilez 150 mg film-coated tablets   
aliskiren

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| 1. **STATEMENT OF ACTIVE SUBSTANCE(S)** |

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate).

|  |
| --- |
| 1. **LIST OF EXCIPIENTS** |

|  |
| --- |
| 1. **PHARMACEUTICAL FORM AND CONTENTS** |

14 film-coated tablets   
28 film-coated tablets   
30 film-coated tablets   
50 film-coated tablets   
56 film-coated tablets   
56 x 1 film-coated tablets   
90 film-coated tablets   
98 film-coated tablets

|  |
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| 1. **METHOD AND ROUTE(S) OF ADMINISTRATION** |

Read the package leaflet before use.   
Oral use

|  |
| --- |
| 1. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN** |

Keep out of the sight and reach of children.

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| 1. **OTHER SPECIAL WARNING(S), IF NECESSARY** |

|  |
| --- |
| 1. **EXPIRY DATE** |

EXP

24

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| 1. **SPECIAL STORAGE CONDITIONS** |

Do not store above 25°C.

Store in the original package in order to protect from moisture.

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| 1. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE** |

|  |
| --- |
| 1. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER** |

Noden Pharma DAC   
D'Olier Chambers   
16A D'Olier Street   
Dublin 2

Ireland

|  |
| --- |
| 1. **MARKETING AUTHORISATION NUMBER(S)** |

EU/1/07/405/021 14 film-coated tablets



28 film-coated tablets 30 film-coated tablets

90 film-coated tablets 98 film-coated tablets

50 film-coated tablets

56 film-coated tablets

56 x 1 film-coated tablet

|  |
| --- |
| EU/1/07/405/022 EU/1/07/405/023 EU/1/07/405/024 EU/1/07/405/025 EU/1/07/405/026 EU/1/07/405/027 EU/1/07/405/028 |

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| --- |
| 1. **BATCH NUMBER** |

Lot

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| 1. **GENERAL CLASSIFICATION FOR SUPPLY** |

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| 1. **INSTRUCTIONS ON USE** |

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| --- |
| 1. **INFORMATION IN BRAILLE** |

Rasilez 150 mg

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| --- |
| 1. **UNIQUE IDENTIFIER** – **2D BARCODE** |

2D barcode carrying the unique identifier included.

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**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

P C :   
S N :   
N N :

26

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS   
BLISTER**

**BLISTER (CALENDAR)**

1. **NAME OF THE MEDICINAL PRODUCT**

Rasilez 150 mg film-coated tablets   
aliskiren

1. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Noden Pharma DAC

1. **EXPIRY DATE**

EXP

1. **BATCH NUMBER**

Lot

1. **OTHER**

Monday   
Tuesday   
Wednesday   
Thursday   
Friday   
Saturday   
Sunday



27

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PCTFE/PVC BLISTERS**

|  |
| --- |
| 1. **NAME OF THE MEDICINAL PRODUCT** |

Rasilez 150 mg film-coated tablets   
aliskiren

|  |
| --- |
| 1. **STATEMENT OF ACTIVE SUBSTANCE(S)** |

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate).

|  |
| --- |
| 1. **LIST OF EXCIPIENTS** |

|  |
| --- |
| 1. **PHARMACEUTICAL FORM AND CONTENTS** |

14 film-coated tablets. Component of a multipack. Not to be sold separately.

49 x 1 film-coated tablets. Component of a multipack. Not to be sold separately.

|  |
| --- |
| 1. **METHOD AND ROUTE(S) OF ADMINISTRATION** |

Read the package leaflet before use.   
Oral use

|  |
| --- |
| 1. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN** |

Keep out of the sight and reach of children.

|  |
| --- |
| 1. **OTHER SPECIAL WARNING(S), IF NECESSARY** |

|  |
| --- |
| 1. **EXPIRY DATE** |

EXP

|  |
| --- |
| 1. **SPECIAL STORAGE CONDITIONS** |

Do not store above 25°C.

Store in the original package in order to protect from moisture.

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| --- |
| 1. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE** |

|  |
| --- |
| 1. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER** |

Noden Pharma DAC   
D'Olier Chambers   
16A D'Olier Street   
Dublin 2

Ireland

|  |
| --- |
| 1. **MARKETING AUTHORISATION NUMBER(S)** |

|  |  |  |
| --- | --- | --- |
| EU/1/07/405/029 |  | 98 film-coated tablets (2x49x1) |
| EU/1/07/405/030 |  |
|  | 280 film-coated tablets (20x14) |

|  |
| --- |
| 1. **BATCH NUMBER** |

Lot

|  |
| --- |
| 1. **GENERAL CLASSIFICATION FOR SUPPLY** |

|  |
| --- |
| 1. **INSTRUCTIONS ON USE** |

|  |
| --- |
| 1. **INFORMATION IN BRAILLE** |

Rasilez 150 mg

29

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PCTFE/PVC BLISTERS**

|  |
| --- |
| 1. **NAME OF THE MEDICINAL PRODUCT** |

Rasilez 150 mg film-coated tablets   
aliskiren

|  |
| --- |
| 1. **STATEMENT OF ACTIVE SUBSTANCE(S)** |

Each film-coated tablet contains 150 mg aliskiren (as hemifumarate).

|  |
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| 1. **LIST OF EXCIPIENTS** |

|  |
| --- |
| 1. **PHARMACEUTICAL FORM AND CONTENTS** |

Multipack: 280 (20 packs of 14) film-coated tablets   
Multipack: 98 (2 packs of 49 x 1) film-coated tablets

|  |
| --- |
| 1. **METHOD AND ROUTE(S) OF ADMINISTRATION** |

Read the package leaflet before use.   
Oral use

|  |
| --- |
| 1. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN** |

Keep out of the sight and reach of children.

|  |
| --- |
| 1. **OTHER SPECIAL WARNING(S), IF NECESSARY** |

|  |
| --- |
| 1. **EXPIRY DATE** |

EXP

|  |
| --- |
| 1. **SPECIAL STORAGE CONDITIONS** |

Do not store above 25°C.

Store in the original package in order to protect from moisture.

1. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS**

3 0

**OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

1. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Noden Pharma DAC   
D'Olier Chambers   
16A D'Olier Street   
Dublin 2

Ireland

1. **MARKETING AUTHORISATION NUMBER(S)**

|  |  |  |
| --- | --- | --- |
| EU/1/07/405/029 |  | 98 film-coated tablets (2x49x1) |
| EU/1/07/405/030 |  | 280 film-coated tablets (20x14) |

1. **BATCH NUMBER**

Lot

1. **GENERAL CLASSIFICATION FOR SUPPLY**
2. **INSTRUCTIONS ON USE**
3. **INFORMATION IN BRAILLE**

Rasilez 150 mg

1. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

1. **UNIQUE IDENTIFIER - HUMAN READABLE DATA**

P C :   
S N :   
N N :

31

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON BOX FOR UNIT PACK CONTAINING PCTFE/PVC BLISTERS**

|  |
| --- |
| 1. **NAME OF THE MEDICINAL PRODUCT** |

Rasilez 300 mg film-coated tablets   
aliskiren

|  |
| --- |
| 1. **STATEMENT OF ACTIVE SUBSTANCE(S)** |

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate).

|  |
| --- |
| 1. **LIST OF EXCIPIENTS** |

|  |
| --- |
| 1. **PHARMACEUTICAL FORM AND CONTENTS** |

14 film-coated tablets   
28 film-coated tablets   
30 film-coated tablets   
50 film-coated tablets   
56 film-coated tablets   
56 x 1 film-coated tablets   
90 film-coated tablets   
98 film-coated tablets

|  |
| --- |
| 1. **METHOD AND ROUTE(S) OF ADMINISTRATION** |

Read the package leaflet before use.   
Oral use

|  |
| --- |
| 1. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN** |

Keep out of the sight and reach of children.

|  |
| --- |
| 1. **OTHER SPECIAL WARNING(S), IF NECESSARY** |

|  |
| --- |
| 1. **EXPIRY DATE** |

EXP

32

|  |
| --- |
| 1. **SPECIAL STORAGE CONDITIONS** |

Do not store above 25°C.

Store in the original package in order to protect from moisture.

|  |
| --- |
| 1. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE** |

|  |
| --- |
| 1. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER** |

Noden Pharma DAC   
D'Olier Chambers   
16A D'Olier Street   
Dublin 2

Ireland

|  |
| --- |
| 1. **MARKETING AUTHORISATION NUMBER(S)** |

EU/1/07/405/031 14 film-coated tablets



28 film-coated tablets 30 film-coated tablets

90 film-coated tablets 98 film-coated tablets

50 film-coated tablets

56 film-coated tablets

56 x1 film-coated tablets

|  |
| --- |
| EU/1/07/405/032 EU/1/07/405/033 EU/1/07/405/034 EU/1/07/405/035 EU/1/07/405/036 EU/1/07/405/037 EU/1/07/405/038 |

|  |
| --- |
| 1. **BATCH NUMBER** |

Lot

|  |
| --- |
| 1. **GENERAL CLASSIFICATION FOR SUPPLY** |

|  |
| --- |
| 1. **INSTRUCTIONS ON USE** |

|  |
| --- |
| 1. **INFORMATION IN BRAILLE** |

Rasilez 300 mg

|  |
| --- |
| 1. **UNIQUE IDENTIFIER** – **2D BARCODE** |

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

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34

P C : S N :

NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS   
BLISTER**

**BLISTER (CALENDAR)**

1. **NAME OF THE MEDICINAL PRODUCT**

Rasilez 300 mg film-coated tablets   
aliskiren

1. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Noden Pharma DAC

1. **EXPIRY DATE**

EXP

1. **BATCH NUMBER**

Lot

1. **OTHER**

Monday   
Tuesday   
Wednesday   
Thursday   
Friday   
Saturday   
Sunday



35

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**INTERMEDIATE CARTON OF MULTIPACKS (WITHOUT BLUE BOX) CONTAINING PCTFE/PVC BLISTERS**

|  |
| --- |
| 1. **NAME OF THE MEDICINAL PRODUCT** |

Rasilez 300 mg film-coated tablets   
aliskiren

|  |
| --- |
| 1. **STATEMENT OF ACTIVE SUBSTANCE(S)** |

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate).

|  |
| --- |
| 1. **LIST OF EXCIPIENTS** |

|  |
| --- |
| 1. **PHARMACEUTICAL FORM AND CONTENTS** |

14 film-coated tablets. Component of a multipack. Not to be sold separately.

49 x 1 film-coated tablets. Component of a multipack. Not to be sold separately.

|  |
| --- |
| 1. **METHOD AND ROUTE(S) OF ADMINISTRATION** |

Read the package leaflet before use.   
Oral use

|  |
| --- |
| 1. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN** |

Keep out of the sight and reach of children.

|  |
| --- |
| 1. **OTHER SPECIAL WARNING(S), IF NECESSARY** |

|  |
| --- |
| 1. **EXPIRY DATE** |

EXP

36

|  |
| --- |
| 1. **SPECIAL STORAGE CONDITIONS** |

Do not store above 25°C.

Store in the original package in order to protect from moisture.

|  |
| --- |
| 1. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE** |

|  |
| --- |
| 1. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER** |

Noden Pharma DAC   
D'Olier Chambers   
16A D'Olier Street   
Dublin 2

Ireland

|  |
| --- |
| 1. **MARKETING AUTHORISATION NUMBER(S)** |

|  |  |  |
| --- | --- | --- |
| EU/1/07/405/039 |  | 98 film-coated tablets (2x49x1) |
| EU/1/07/405/040 |  | 280 film-coated tablets (20x14) |

|  |
| --- |
| 1. **BATCH NUMBER** |

Lot

|  |
| --- |
| 1. **GENERAL CLASSIFICATION FOR SUPPLY** |

|  |
| --- |
| 1. **INSTRUCTIONS ON USE** |

|  |
| --- |
| 1. **INFORMATION IN BRAILLE** |

Rasilez 300 mg

37

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF MULTIPACKS (INCLUDING BLUE BOX) CONTAINING PCTFE/PVC BLISTERS**

|  |
| --- |
| 1. **NAME OF THE MEDICINAL PRODUCT** |

Rasilez 300 mg film-coated tablets   
aliskiren

|  |
| --- |
| 1. **STATEMENT OF ACTIVE SUBSTANCE(S)** |

Each film-coated tablet contains 300 mg aliskiren (as hemifumarate).

|  |
| --- |
| 1. **LIST OF EXCIPIENTS** |

|  |
| --- |
| 1. **PHARMACEUTICAL FORM AND CONTENTS** |

Multipack: 280 (20 packs of 14) film-coated tablets   
Multipack: 98 (2 packs of 49 x 1) film-coated tablets

|  |
| --- |
| 1. **METHOD AND ROUTE(S) OF ADMINISTRATION** |

Read the package leaflet before use.   
Oral use

|  |
| --- |
| 1. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN** |

Keep out of the sight and reach of children.

|  |
| --- |
| 1. **OTHER SPECIAL WARNING(S), IF NECESSARY** |

|  |
| --- |
| 1. **EXPIRY DATE** |

EXP

|  |
| --- |
| 1. **SPECIAL STORAGE CONDITIONS** |

Do not store above 25°C.

Store in the original package in order to protect from moisture.

1. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS**

3 8

**OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

1. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Noden Pharma DAC   
D'Olier Chambers   
16A D'Olier Street   
Dublin 2

Ireland

1. **MARKETING AUTHORISATION NUMBER(S)**

|  |  |  |
| --- | --- | --- |
| EU/1/07/405/039 |  | 98 film-coated tablets (2x49x1) |
| EU/1/07/405/040 |  |
|  | 280 film-coated tablets (20x14) |

1. **BATCH NUMBER**

Lot

1. **GENERAL CLASSIFICATION FOR SUPPLY**
2. **INSTRUCTIONS ON USE**
3. **INFORMATION IN BRAILLE**

Rasilez 300 mg

1. **UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

1. **UNIQUE IDENTIFIER - HUMAN READABLE DATA**

P C :   
S N :   
N N :

39

**B. PACKAGE LEAFLET**

4 0

**Package leaflet: Information for the user**

**Rasilez 150 mg film-coated tablets   
Rasilez 300 mg film-coated tablets**Aliskiren

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your doctor or pharmacist.

- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Rasilez is and what it is used for
2. What you need to know before you take Rasilez
3. How to take Rasilez
4. Possible side effects
5. How to store Rasilez
6. Contents of the pack and other information
7. **What Rasilez is and what it is used for**

This medicine contains an active substance called aliskiren. Aliskiren belongs to a class of medicines called renin inhibitors. Renin inhibitors reduce the amount of angiotensin II the body can produce. Angiotensin II causes blood vessels to tighten, which increases the blood pressure. Reducing the amount of angiotensin II allows the blood vessels to relax, which lowers blood pressure.

This helps to lower high blood pressure in adult patients. High blood pressure increases the workload of the heart and arteries. If this continues for a long time, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure, heart attack or kidney failure. Lowering the blood pressure to a normal level reduces the risk of developing these disorders.

1. **What you need to know before you take Rasilez**

**Do not take Rasilez**

- if you are allergic to aliskiren or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

- if you have experienced the following forms of angioedema (difficulties in breathing or swallowing, or swelling of the face, hands and feet, eyes, lips and/or tongue):

- angioedema when taking aliskiren.

- hereditary angioedema.

- angioedema without any known cause.

- during the last 6 months of pregnancy or if you are breast-feeding, see section “Pregnancy and breastfeeding”.

- if you are taking ciclosporin (a medicine used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis), itraconazole (a medicine used to treat fungal infections) or quinidine (a medicine used to correct heart rhythm).

41

- if you have diabetes or impaired kidney function and you are treated with either of the following classes of medicines used to treat high blood pressure:

- an angiotensin converting enzyme inhibitor such as enalapril, lisinopril, ramipril or

- an angiotensin II receptor blocker such as valsartan, telmisartan, irbesartan.

- if the patient is less than 2 years of age.

**Warnings and precautions**

Talk to your doctor before taking Rasilez:

- if you are taking a diuretic (a type of medicine also known as “water” tablets which increases the amount of urine you produce).

- if you are taking either of the following classes of medicines used to treat high blood pressure:

- an angiotensin converting enzyme inhibitor such as enalapril, lisinopril, ramipril or

- an angiotensin II receptor blocker such as valsartan, telmisartan, irbesartan.

- if you have impaired kidney function, your doctor will carefully consider whether this medicine is suitable for you and may wish to monitor you carefully.

- if you have already experienced angioedema (difficulties in breathing or swallowing, or

swelling of the face, hands and feet, eyes, lips and/or tongue). If this happens, stop taking this medicine and contact your doctor.

- if you have renal artery stenosis (narrowing of the blood vessels to one or both kidneys).

- if you have serious congestive heart failure (a type of heart disease where the heart cannot pump enough blood around the body).

If you have severe and persistent diarrhoea you should stop taking Rasilez.

Your doctor may check your kidney function, blood pressure and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also section “Do not take Rasilez”.

**Children and adolescents**

This medicine must not be used in babies from birth to less than 2 years of age. It should not be used in children from 2 to less than 6 years of age, and is not recommended for use in children and adolescents from 6 to less than 18 years of age. This is because the safety and benefits of this medicine are not known in this population.

**Elderly**

The usual recommended starting dose of aliskiren in elderly patients aged 65 years or older is 150 mg. In the majority of patients aged 65 years or older, the 300 mg dose of Rasilez shows no additional benefit in reducing blood pressure compared to the 150 mg dose.

**Other medicines and Rasilez**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other

medicines.

Your doctor may need to change your dose and/or to take other precautions if you are taking one of the following medicines:

- medicines that increase the amount of potassium in your blood. These   
include potassium-sparing diuretics, potassium supplements.

- furosemide or torasemide, medicines belonging to the type known as diuretics, or “water” tablets, which are used to increase the amount of urine you produce.

- an angiotensin II receptor blocker or an angiotensin converting enzyme inhibitor (see sections “Do not take Rasilez” and “Warnings and precautions”).

- ketoconazole, a medicine used to treat fungal infections.

- verapamil, a medicine used to lower high blood pressure, to correct heart rhythm or to treat

4 2

angina pectoris.

- certain types of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs).

**Rasilez with food and drink**

You should take this medicine either with a light meal or without a meal once a day, preferably at the same time each day. You should avoid taking this medicine together with fruit juice and/or drinks containing plant extracts (including herbal teas), as it could cause a decrease in the effectiveness of this medicine.

**Pregnancy and breast-feeding**

Pregnancy

Do not take this medicine if you are pregnant (see section “Do not take Rasilez”). If you become pregnant while taking this medicine, stop taking it immediately and talk to your doctor. If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Your doctor will normally advise you to stop taking this medicine before you become pregnant and will advise you to take another medicine instead of this medicine. It is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. This medicine is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed.

**Driving and using machines**

This medicine may make you feel dizzy and this can affect your ability to concentrate. Before you drive a vehicle, use machinery, or carry out other activities that require concentration, you should make sure you know how you react to the effects of this medicine.

**3. How to take Rasilez**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

People who have high blood pressure often do not notice any signs of the problem. Many may feel quite normal. It is very important that you take this medicine exactly as your doctor tells you to get the best results and reduce the risk of side effects. Keep your appointments with the doctor even if you are feeling well.

The usual starting dose is one 150 mg tablet once daily. The blood pressure lowering effect is present within two weeks after beginning treatment.

**Elderly people**

The usual recommended starting dose of aliskiren in elderly patients is 150 mg. In the majority of patients aged 65 years or older, the 300 mg dose of aliskiren shows no additional benefit in reducing blood pressure compared to the 150 mg dose.

Depending on how you respond to the treatment your doctor may prescribe a higher dose of one

300 mg tablet once daily. Your doctor may prescribe this medicine together with other medicines used

to treat high blood pressure.

**Method of administration**

Swallow the tablet whole with some water. You should take this medicine once a day, always with or always without food, preferably at the same time each day. You should establish a convenient daily schedule to take the medicine the same way each day, in a regular pattern with respect to the timing of

4 3

your meals. You should avoid taking this medicine together with fruit juice and/or drinks containing plant extracts (including herbal teas). During your treatment, your doctor may adjust your dose depending on your blood pressure response.

**If you take more Rasilez than you should**

If you have accidentally taken too many tablets of this medicine, consult a doctor immediately. You

may require medical attention.

**If you forget to take Rasilez**

If you forget to take a dose of this medicine, take it as soon as you remember and then take the next dose at its usual time. However, if it is almost time for your next dose you should simply take the next tablet at the usual time. Do not take a double dose to make up for a forgotten dose.

1. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects can be serious (frequency not known):**

A few patients have experienced these serious side effects. **If any of the following occur, tell your**

**doctor straight away:**

**** Severe allergic reaction with symptoms such as rash, itching, swelling of face or lips or tongue, difficulty breathing, dizziness.

**Possible side effects:**

Common *(may affect up to 1 in 10 people)*: Diarrhoea, joint pain (arthralgia), high level of potassium in the blood, dizziness.

Uncommon *(may affect up to 1 in 100 people)*: Skin rash (this may also be a sign of allergic reactions or angioedema – see “Rare” side effects below), kidney problems including acute renal failure (severely decreased urine output), swelling of hands, ankles or feet (peripheral oedema), severe skin reactions (toxic epidermal necrolysis and/or oral mucosal reactions - red skin, blistering of the lips, eyes or mouth, skin peeling, fever), low blood pressure, palpitations, cough, itching, itchy rash (urticaria), increased liver enzymes.

Rare *(may affect up to 1 in 1,000 people)*: increased level of creatinine in the blood, decreased level of haemoglobin in the blood (anaemia), decreased level of red blood cells, red skin (erythema). Not known *(frequency cannot be estimated from the available data)*: spinning sensation, low level of sodium in the blood, shortness of breath, nausea, vomiting, signs of liver disorder (nausea, loss of appetite, dark coloured urine or yellowing of skin and eyes).

**If any of these affect you severely, tell your doctor. You may need to stop Rasilez.**

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V.](http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2013/03/WC500139752.doc) By reporting side effects, you can help provide more information on the safety of this medicine.

1. **How to store Rasilez**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister. The expiry date

refers to the last day of that month.

Do not store above 25°C.

Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to

4 4

throw away medicines you no longer use. These measures will help protect the environment.

**6. Contents of the pack and other information**

**What Rasilez contains**

- The active substance is aliskiren (as hemifumarate).

Rasilez 150 mg film-coated tablets

- Each tablet contains 150 mg aliskiren (as hemifumarate). The other ingredients are crospovidone type A, hypromellose substitution type 2910 (3 mPa s), magnesium stearate, macrogol 4000, microcrystalline cellulose, povidone K-30, colloidal anhydrous silica, talc, titanium dioxide (E 171), black iron oxide (E 172), red iron oxide (E 172).

Rasilez 300 mg film-coated tablets

- Each tablet contains 300 mg aliskiren (as hemifumarate). The other ingredients are crospovidone type A, hypromellose substitution type 2910 (3 mPa s), magnesium stearate, macrogol 4000, microcrystalline cellulose, povidone K-30, colloidal anhydrous silica, talc, titanium dioxide (E 171), black iron oxide (E 172), red iron oxide (E 172).

**What Rasilez looks like and contents of the pack**

Rasilez 150 mg film-coated tablets are light-pink, biconvex round tablets, imprinted “IL” on one side

and “NVR” on the other side.

Rasilez 300 mg film-coated tablets are light-red, biconvex, ovaloid tablets, imprinted “IU” on one side and “NVR” on the other side.

Rasilez 150 mg film-coated tablets are available in the following packs:

- Unit packs containing 14, 28, 30, 50, 56, 90 or 98 tablets

- Unit packs containing 56x1 tablets in perforated unit-dose blisters

- Multipacks containing 280 (20x14) tablets

- Multipacks containing 98 (2x49x1) tablets in perforated unit-dose blisters

Rasilez 300 mg film-coated tablets are available in the following packs:

- Unit packs containing 14, 28, 30, 50, 56, 90 or 98 tablets

- Unit packs containing 56x1 tablets in perforated unit-dose blisters

- Multipacks containing 280 (20x14) tablets

- Multipacks containing 98 (2x49x1) tablets in perforated unit-dose blisters

Not all pack sizes may be available in your country.

**Marketing Authorisation Holder**

Noden Pharma DAC

D'Olier Chambers

16A D'Olier Street

Dublin 2

Ireland

**Manufacturer**

Noden Pharma DAC   
D'Olier Chambers   
16A D'Olier Street   
Dublin 2

Ireland

45

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency website:

[http://www.ema.europa.eu](http://www.ema.europa.eu/)

46

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1 NAME OF THE MEDICINAL PRODUCT**

Amlodipine 10 mg Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains amlodipine maleate equivalent to 10mg amlodipine. For the full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Tablet.

White, oval, biconvex, smooth surfaced tablets, embossed R on one side and 178 on the other side.

**4. CLINICAL PARTICULARS**

**4.1. Therapeutic indications**

Hypertension

Chronic stable angina pectoris

Vasospastic (Prinzmetal’s) angina

**4.2 Posology and method of administration**

Posology

*Adults*

For both hypertension and angina the usual initial dose is 5 mg Amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient’s response. In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Amlodipine may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

No dose adjustment of Amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations

*Elderly patients*

Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care (see sections 4.4 and 5.2).

*Patients with hepatic impairment*

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine has not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

*Patients with renal impairment*

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

*Paediatric population*

Children and adolescents with hypertension from 6 years to 17 years of age The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients (see sections 5.1 and 5.2).

Doses of amlodipine 2.5 mg are not possible with this medicinal product.

*Children under 6 years old*No data are available.

Method of administration   
Tablet for oral administration.

**4.3 Contraindications**

Amlodipine is contraindicated in patients with:

* Hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients listed in section 6.1.
* Severe hypotension.
* Shock (including cardiogenic) shock.
* Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis).
* Haemodynamically unstable heart failure after acute myocardial infarction.

**4.4 Special warnings and precautions for use**

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Patients with hepatic impairment

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly patients

In the elderly increase of the dosage should take place with care (see sections 4.2 and

5.2).

Patients with renal impairment

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

**4.5 Interaction with other medicinal products and other forms of interaction**

Effects of other medicinal products on amlodipine

*CYP3A4 inhibitors*

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

*CYP3A4 inducers*

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

*Dantrolene (infusion)*

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration

of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure

lowering effects of other medicinal products with antihypertensive properties.

*Tacrolimus*

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

*Mechanistic Target of Rapamycin (mTOR) Inhibitors*

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

*Cyclosporine*

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed.

Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

*Simvastatin*

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3)

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

**4.7. Effects on ability to drive and use machines**

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

**4.8 Undesirable effects**

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common ( 1/10); common ( 1/100 to <1/10); uncommon ( 1/1,000 to 1/100); rare ( 1/10,000 to 1/1,000); very rare ( 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

|  |  |  |
| --- | --- | --- |
| System Organ Class | Frequency | Adverse reaction |
| Blood and lymphatic  system disorders | Very rare | Leukocytopenia,  thrombocytopenia |
| Immune system disorders | Very rare | Allergic reactions |
| Metabolism and nutrition disorders | Very rare | Hyperglycaemia |
| Psychiatric disorders | Uncommon | Depression, mood changes (including anxiety), insomnia |
| Rare | Confusion |
| Nervous system disorders | Common | Somnolence, dizziness, headache (especially at the beginning of the treatment) |
| Uncommon | Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia |
| Very rare | Hypertonia, peripheral  neuropathy |
| Not known | Extrapyramidal disorder |
| Eye disorders | Common | Visual disturbance (including diplopia) |
| Ear and labyrinth disorders | Uncommon | Tinnitus |

|  |  |  |
| --- | --- | --- |
| Cardiac disorders | Common | Palpitations |
| Uncommon | Arrhythmia  (including bradycardia,  ventricular tachycardia and atrial fibrillation) |
| Very rare | Myocardial infarction |
| Vascular disorders | Common | Flushing |
| Uncommon | Hypotension |
| Very rare | Vasculitis |
| Respiratory, thoracic and mediastinal disorders | Common | Dyspnoea |
| Uncommon | Cough, rhinitis |
| Gastrointestinal disorders | Common | Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation) |
| Uncommon | Vomiting, dry mouth |
| Very rare | Pancreatitis, gastritis, gingival hyperplasia |
| Hepato-biliary disorders | Very rare | Hepatitis, jaundice, hepatic enzymes increased\* |
| Skin and subcutaneous tissue disorders | Uncommon | Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria |
| Very rare | Angioedema, erythema  multiforme, exfoliative  dermatitis,  Stevens-Johnson syndrome, Quincke oedema, photosensitivity |
| Not known | Toxic epidermal necrolysis |
| Musculoskeletal and connective tissue disorders | Common | Ankle swelling, muscle cramps |
| Uncommon | Arthralgia, myalgia, back pain |
| Renal and urinary disorders | Uncommon | Micturition disorder, nocturia, increased urinary frequency |
| Reproductive system and breast disorders | Uncommon | Impotence, gynecomastia |
| General disorders and administration site conditions | Very common | Oedema |
| Common | Fatigue, asthenia |
| Uncommon | Chest pain, pain, malaise |
| Investigations | Uncommon | Weight increased, weight  decreased |

\*mostly consistent with cholestasis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

**4.9 Overdose**

In humans, experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel

blockers with mainly vascular effects.

ATC Code: C08C A01

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal’s or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1-mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with coronary artery disease (CAD)

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-centre, randomized, double- blind, placebo-controlled study of 1997 patients; Comparison of amlodipine vs. enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1. Incidence of significant clinical outcomes for CAMELOT

Cardiovascular event rates, Amlopidine vs. Placebo No. (%)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcomes | Amlodipine | Placebo | Enalapril | Hazard Ratio 95-%-CI | P Value |
| Primary Endpoint | | | | | |
| Adverse | 110 (16.6) | 151 (23.1) | 136 (20.2) | 0.69 | 0.003 |
| cardiovascular events |  |  |  | (0.54 - 0.88) |  |
| Individual Components | | | | | |
| Coronary | 78 (11.8) | 103 (15.7) | 95 (14.1) | 0.73 | 0.03 |
| revascularization |  |  |  | (0.54 - 0.98) |  |
| Hospitalization | 51 (7.7) | 84 (12.8) | 86 (12.8) | 0.58 | 0.002 |
| for angina |  |  |  | (0.41 - 0.82) |  |
| Nonfatal MI | 14 (2.1) | 19 (2.9) | 11 (1.6) | 0.73 | 0.37 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | (0.37 | - 1.46) |  |
| Stroke or TIA | 6 (0.9) | 12 (1.8) | 8 (1.2) | 0.50  (0.19 | - 1.32) | 0.15 |
| Cardiovascular death | 5 (0.8) | 2 (0.3) | 5 (0.7) | 2.46  (0.48 | - 12.7) | 0.27 |
| Hospitalization for CHF | 3 (0.5) | 5 (0.8) | 4 (0.6) | 0.59  (0.14 | - 2.47) | 0.46 |
| Resuscitated cardiac arrest | 0 | 4 (0.6) | 1 (0.1) | N/A |  | 0.04 |
| New-onset peripheral vascular disease | 5 (0.8) | 2 (0.3) | 8 (1.2) | 2.6  (0.50 | - 13.4) | 0.24 |

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.

Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and angiotensin converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure.

In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT)

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.”

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90­1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the

amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

Use in children (aged 6 years and older)

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

**5.2 Pharmacokinetic properties**

Absorption, distribution, plasma protein binding

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

*Hepatic impairment*

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

*Elderly population*

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC elimination and half-life in elderly patients. Increases in AUC and elimination half life in patients with congestive heart failure were as expected for the patient age group studied

*Paediatric population*

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

**5.3 Preclinical safety data**

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times

greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times\* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice\* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

\*Based on patient weight of 50 kg

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**Microcrystalline cellulose   
Sodium starch glycolate   
Colloidal anhydrous silica   
Magnesium stearate.

**6.2 Incompatibilities**Not applicable.

**6.3 Shelf life**

HDPE-bottles: 18 months

Blisters: 24 months.

**6.4 Special precautions for storage**Do not store above 25ºC.

Store in the original package.

**6.5 Nature and contents of container**

10, 20, 28, 30, 50, 98 and 100 tablets in blister.

90, 100 and 500 tablets in HDPE bottles.

**6.6. Special precautions for disposal and handling**

Any unused product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

Dr Reddy’s Laboratories (UK) Ltd

410 Cambridge Science Park,

Milton Road, Cambridge,

CB4 0PE,

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 08553/0235

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25/03/2004   
Date of latest renewal: 17/09/2009

**10 DATE OF REVISION OF THE TEXT**

06/02/2024

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1 NAME OF THE MEDICINAL PRODUCT**Bendroflumethiazide Tablets 2.5mg

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION** Bendroflumethiazide 2.5 mg per tablet.

For excipients, see 6.1.

**3 PHARMACEUTICAL FORM**Tablet.

White flat bevelled edge tablets engraved with the company logo on one side and A268 on the other.

**4.1 Therapeutic indications**

Oedema: Bendroflumethiazide is indicated in the treatment of oedema

associated with conditions such as congestive heart failure, nephrotic   
syndrome, cirrhosis of the liver and pre-menstrual oedema.

In non-oedematous patients, there may be little noticeable diuretic effect.

Essential hypertension: Bendroflumethiazide produces a moderate but fully prolonged fall of blood pressure in hypersensitive patients.

Bendroflumethiazide may be used as the sole antihypertensive agent or   
used concurrently with other drugs whose action it potentiates.

Bendroflumethiazide may also be used to suppress lactation

Cases where the reduction of fluid retention by dieresis is required; oedema of

cardiac, renal or hepatic origin and iatrogenic oedema

**4.2 Posology and method of administration**

Route of administration: Oral

**ADULTS:**

Oedema:

Initially: 5 - 10mg in the morning, once daily or on alternative days.

Maintenance: 5mg-10mg one to three times a week.

Essential hypertension: 2.5 mg in the morning, Higher doses are rarely necessary.

alone or in conjunction with other antihypertensive agents in more severe hypertension. the dosage of such agents should be reduced and then adjusted as necessary

The dosage should be reduced in the elderly with impaired renal function.

Suppression of lactation: 5mg in the morning and 5mg at midday for about five days. Pre-menstrual oedema: 2.5mg each morning for seven days before the period is due.

**CHILDREN** under 12 years of age:

Initial: 0.4 mg per kg of body-weight per day.

Maintenance: 0.05 to 0.1 mg per kg of body-weight per day. A more appropriate

dosage form

may be required.

0.05 to 0.4 mg/kg body-weight per day as a single dose or in two divided daily doses, adjusted according to response

**ELDERLY:**

The dosage of thiazide diuretics may need to be reduced in the elderly, particularly when renal function is impaired, because of the possibility of electrolyte imbalance.

**4.3 Contraindications**

Hypersensitivity to Bendroflumethiazide or any of the excipients and other sulphonamide-derived drugs.

Bendroflumethiazide is contra-indicated in patients with:

* severe renal insufficiency or anuria
* Addison's disease
* refractory hypokalaemia
* hyponatraemia
* hypercalcaemia
* serious hepatic disorders (risk of precipitation of encephalopathy)
* symptomatic hyperuricaemia.

**4.4 Special warnings and special precautions for use**

**Hypokalaemia**

Electrolytes should be monitored during treatment as continued or intensive use of bendroflumethiazide may result in hypokalaemia. This effect may be enhanced with concomitant use of medicines that can also cause hypokalaemia such as other diuretics or beta-2 agonists. Hypokalaemia can increase the risk of cardiac arrhythmia particularly when the patient is also taking an anti arrhythmic, anti-histamine, anti-malarial, anti-psychotic or digoxin (see section 4.5).

Potassium replacement or conservation may be necessary in patients at risk from the cardiac effects of hypokalaemia, such as those with prolonged QT intervals, severe heart disease, those taking digitalis preparations or high doses

of diuretics and in patients with severe liver disease. If hypokalaemia (< 3.4 mmol potassium) is detected, it must be corrected and it should be prevented in at-risk patients.

Potassium supplements should not be given in renal insufficiency complicated by hyperkalaemia.

Potassium supplementation alone may not be sufficient to correct hypokalaemia in patients who are also deficient in magnesium.

**Hyponatraemia**

Some patients may be particularly susceptible to hyponatraemia, including the elderly and those with severe heart failure who are very oedematous, particularly with large doses of thiazides in conjunction with restricted salt in the diet. The onset of hyponatraemia can be sudden and life-threatening. All patients, including the elderly who may be particularly susceptible, should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy.

Regular serum electrolyte determinations should be performed in the elderly and in patients receiving long-term therapy.

**Hypomagnesaemia**

There is an increased risk of hypomagnesaemia in patients with alcoholic cirrhosis taking bendroflumethiazide. Hypomagnesaemia has been implicated as a risk factor for arrhythmias. Electrolyte levels including magnesium should be monitored during treatment of patients with alcoholic cirrhosis.

**Hypercalcaemia**

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

**Choroidal effusion, acute myopia and secondary angle-closure glaucoma:** Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Regular ongoing monitoring and blood tests are to be performed in elderly patients and patients who are on long term treatment with bendroflumethiazide.

**Mild or moderate hepatic or renal impairment**

Use with caution in renal impairment (severe renal insufficiency is a contraindication to use, see 4.3). Renal function should be monitored during bendroflumethiazide therapy. Thiazides can cause electrolyte balance which is more severe in patients with hepatic and renal impairment and in those receiving higher or prolonged doses.

Use with caution in hepatic impairment (severe hepatic impairment is a contraindication to use, see 4.3). In case of hepatic impairment, thiazide diuretics may precipitate hepatic encephalopathy, particularly in case of electrolyte imbalance. Administration of the diuretic must be stopped

immediately if this occurs.

Regular ongoing monitoring and blood tests are to be performed in elderly patients and patients who are on long term treatment with

bendroflumethiazide.

**Concomitant use with lithium**

Bendroflumethiazide inhibits the tubular elimination of lithium resulting in an elevated plasma lithium concentration and risk of toxicity. Both lithium and thiazide and related diuretics can cause hypokalaemia, increasing the risk of torsade de pointes. Avoid concurrent use unless lithium levels and potassium concentrations can be closely monitored and the lithium dose adjusted as necessary. Advise patients to report lithium adverse effects (tremor, dysarthria, ataxia, confusion) (see section 4.5).

**Concomitant use with pimozide, sertindole or thioridazine** Diuretic-induced hypokalaemia increases the risk of ventricular arrhythmias with pimozide, sertindole and thioridazine therefore concomitant use should be avoided (see section 4.5).

**Photosensitivity**

Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

**Systemic lupus erythematosus**

Thiazide diuretics can induce a cutaneous lupus-like adverse reaction. Thiazide diuretics may also exacerbate or activate systemic lupus erythematosus (SLE) in susceptible patients.

**Pancreatitis**

Pancreatitis has been reported during thiazide therapy. Thiazide therapy is associated with hypercalcaemia and hyperlipidaemia both of which are risk factors for pancreatitis.

**Gout**

Thiazide use may aggravate gout. Serum uric acid levels may be raised with or

without gout in some patients.

**Diabetes mellitus**

Bendroflumethiazide may precipitate diabetes mellitus and may impair

glycaemic control in patients with diabetes.

**Hyperlipidaemia**

Caution should be exercised when used in patients with hyperlipidaemia.

**Lactose**

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of Interaction**

**Pharmacodynamic and Pharmacokinetic interactions**

Analgesics: Diuretics such as bendroflumethiazide increase the risk of

nephrotoxicity associated with non-steroidal anti-inflammatory analgesics (NSAIDs). NSAIDs, particularly indometacin and ketorolac may

antagonise the natriuresis and increase in plasma renin activity caused by   
thiazide diuretics. It may also reduce the antihypertensive effect and

increase in urine volume caused by thiazide diuretics, possibly by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention. Concomitant use with opiates leads to an increased risk of postural hypotension. The effects of concurrent use should be monitored and the dose of bendroflumethiazide modified if necessary.

Alcohol

Co-administration of alcohol may potentiate orthostatic hypotension.

Aldesleukin

Enhanced hypotensive effect may occur when aldesleukin and thiazide

diuretics are used concomitantly.

Anaesthetics, general

Enhanced hypotensive effect may occur when general anaesthetics and

thiazide diuretics are used concomitantly.

Antibacterials

Severe hyponatraemia may occur with concomitant administration of

bendroflumethiazide and trimethoprim.

Anti-depressants

Co-administration of tricyclic antidepressants may increase the risk of postural hypotension. Enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs). Possibly increased risk of hypokalaemia if thiazides given with reboxetine.

Anion-exchange resins: colestyramine and colestipol lead to decreased absorption of

thiazides. It has been recommended that administration is at least 2 hours prior to, or after the ingestion of bendroflumethiazide.

Antidiabetics:

Bendroflumethiazide may antagonise the hypoglycaemic effects of antidiabetic drugs including insulin possibly necessitating adjustment of the dose of the antidiabetic agent.

Chlorpropamide increases the risk of hyponatraemia associated with taking

thiazides such as bendroflumethiazide in combination with potassium-sparing diuretics.

Antiepileptics: There is an increased risk of hyponatraemia with carbamazepine.

Antifungals: There is an increased risk of hypokalaemia if thiazides are given with amphotericin.

Antihistamines: Patients with hypokalaemia or other electrolyte imbalance

have an increased risk of ventricular arrhythmias with arrhythmias with

drugs that prolong the QT interval, such as astemizole and terfenadine.

Antihypertensives: Concurrent use of bendroflumethiazide with antihypertensives enhances the hypotensive effect including angiotensin-converting enzyme (ACE) inhibitors

(potential for enhanced first-dose hypotension), angiotensin-II antagonists, calcium channel blockers, beta-blockers, hydralazine and

diazoxide. The dosage of concomitantly administered antihypertensive drugs may need to be reduced when bendroflumethiazide is added to the regimen. There is an increased risk of first-dose hypotensive effect of post- synaptic alpha-blockers such as prazosin. Intravascular immune haemolysis may occur in patients taking bendroflumethiazide and methyldopa.

Antipsychotics: Patients with hypokalaemia have an increased risk of

ventricular arrhythmias with pimozide. Concomitant use should be avoided.

Alprostadil: Concomitant use with alprostadil enhances the hypotensive effect.

Anti-arrhythmics: The cardiac toxicity associated with amiodarone, disopyramide, flecainide, and quinidine is increased if hypokalaemia occurs. The action of lidocaine and mexiletine is antagonised by hypokalaemia. Hypokalaemia increases risk of ventricular

arrhythmias with sotalol, a beta-blocker

Antidepressants: There is a possible increased risk of postural hypotension with tricyclic antidepressants and of hypokalaemia if thiazides are given with reboxetine.

Antimalarials (see section 4.4)

Bendroflumethiazide -induced hypokalaemia may increase the risk of

arrhythmias with drugs that prolong the QT interval, such as halofantrine.

Antipsychotics (see section 4.4)

Diuretic-induced hypokalaemia increases the risk of ventricular arrhythmias with pimozide, sertindole and thioridazine therefore concomitant use should be avoided. Enhanced hypotensive effect may occur when phenothiazines and thiazide diuretics are used concomitantly.

Antigout agents

Potential for increased toxicity and hypersensitivity/allergic reactions with

concomitant use of allopurinol and thiazide diuretics.

Barbiturates

Postural hypotension associated with therapy may be enhanced by

concomitant ingestion of barbiturates

Calcium salts & Vitamins: There is an increased risk of hypercalcaemia with

thiazides such as bendroflumethiazide. There is an increased risk of developing milk-alkali syndrome in patients given large amounts of calcium or vitamin D in combination with thiazides

Calcium-channel blockers and peripheral vasodilators: Concomitant use with

bendroflumethiazide enhances the hypotensive effect and moxisylyte may be enhanced when co-administered with bendroflumethiazide.

Cardiac glycosides: The concurrent use of cardiac glycosides with thiazide diuretics may enhance the possibility of cardiac toxicity associated with hypokalaemia, resulting in cardiac arrhythmias.

Corticosteroids, Xanthines, beta-agonists, ACTH: There is an increased risk of hypokalaemia with thiazides such as bendroflumethiazide and the diuretic

effect is antagonised mainly with the naturally occurring corticosteroids such as cortisone and hydrocortisone..

Cytotoxics: Concurrent use of diuretics such as bendroflumethiazide with

cisplatin increases the risk of nephrotoxicity and ototoxicity.

Ciclosporin

Increased risk of nephrotoxicity and/or hypermagnesaemia with concomitant

use of ciclosporin and thiazide diuretics, such as Bendroflumethiazide

Digoxin (see section 4.4)

Sensitivity to digitalis glycosides may be increased by the hypokalaemic effect of concurrent bendroflumethiazide. Patients should be observed for signs of digitalis intoxication, in particular arrhythmias, and if these appear, treatment with cardiac glycosides may have to be temporarily suspended and a potassium supplement given to restore stability.

Diuretics

Increased risk of hypokalaemia with concurrent administration of other

thiazides and other diuretics including acetazolamide and loop diuretics.

Dopaminergics

Enhanced hypotensive effect may occur when levodopa and thiazide diuretics

are used concomitantly.

Nitrates

Enhanced hypotensive effect may occur when nitrates and thiazide diuretics

are used concomitantly.

Hormone Antagonists: There is an increased risk of hyponatraemia with

aminoglutethimide.

Thiazides such as bendroflumethiazide increase the risk of hypercalcaemia with toremifene.

Moxisylyte: Concomitant use with bendroflumethiazide enhances the hypotensive effect.

Muscle relaxants: An enhanced hypotensive effect is associated with concomitant use with baclofen and tizanidine. Bendroflumethiazide interacts with

nondepolarising neuromuscular blocking drugs leading to prolonged neuromuscular blockade e.g. tubocurarine.

Oestrogens and Progestogens: The diuretic effect is antagonised with oestrogens and combined oral contraceptives.

General

Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome)

Opioids

Postural hypotension associated with therapy may be enhanced by

concomitant ingestion of opioids.

Prostaglandins

Hypotensive effect may be potentiated by alprostadil.

Other diuretics: There is an increased risk of hypokalaemia if thiazides such as

bendroflumethiazide, loop diuretics or acetazolamide are taken together.

Sympathomimetics: There is an increased risk of hypokalaemia if thiazides are

given with high doses of bambuterol, fenoterol, formoterol, reproterol,

ritodrine, salbutamol, salmeterol, terbutaline and tulobuterol. Potentially serious hypokalaemia may result from beta2 agonist therapy.

Theophylline: There is an increased risk of hypokalaemia with thiazides such

as Bendroflumethiazide and Concomitant administration of xanthines   
such as theophylline.

Ulcer-healing Drugs: There is an increased risk of hypokalaemia if thiazides are given with carbenoxolone. Carbenoxolone also antagonises the diuretic effect. Patients should be

monitored and given potassium supplements when required.

Other interactions, vitamin D preparations (leading to increased risk of hypercalcaemia), alcohol and barbiturates (leading to increased risk of postural hypotension) have also been reported.

Lithium (see section 4.4)

Bendroflumethiazide inhibits the tubular elimination of lithium resulting in an elevated plasma lithium concentration and risk of toxicity. Both lithium and thiazide and related diuretics can cause hypokalaemia, increasing the risk of torsade de pointes. Avoid concurrent use unless lithium levels and potassium concentrations can be closely monitored and the lithium dose adjusted as necessary. Advise patients to report lithium adverse effects (tremor, dysarthria, ataxia, confusion).

Muscle relaxants

Diuretic-induced hypokalaemia may enhance the neuromuscular blocking activity of non-depolarising muscle relaxants, such as tubocurarine, gallamine, alcuronium and pancuronium. An enhanced hypotensive effect may occur with tizanidine.

**Interference with tests for parathyroid function**

Because thiazides may affect calcium metabolism, bendroflumethiazide may interfere with tests for parathyroid function. Bendroflumethiazide should be stopped before parathyroid function is tested

**4.6 Fertility, pregnancy and lactation**

Diuretics are best avoided for the management of oedema of pregnancy or

hypertension in pregnancy as their use may be associated with

hypovolaemia, and reduced placental perfusion and increased risk of acute haemorrhagic pancreatitis.

Neonatal jaundice, thrombocytopenia, and severe electrolyte imbalances, including hypokalaemia and hyponatraemia have been reported in newborn infants.

As diuretics pass into breast milk and bendroflumethiazide large dosage can suppress lactation, its use, should be avoided in mothers who wish to breast-feed.

**4.7 Effects on ability to drive and use machines**

Dizziness, drowsiness, postural hypotension, and mental confusion may occur. This may impair ability to drive or operate machinery.

**4.8 Undesirable effects**

Adverse reactions listed below are based on available data for bendroflumethiazide and classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (? 1/10), common (? 1/100 to < 1/10), uncommon (?1/1,000 to < 1/100), rare (? 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

All thiazide diuretics can produce a degree of electrolyte imbalance, e.g. hypokalaemia.

Thiazide diuretics may raise the serum uric acid levels with subsequent

exacerbation

of gout in susceptible subjects.

Thiazide diuretics sometimes lower carbohydrate tolerance and the insulin dosage of the diabetic patient may require adjustment. Care is necessary when bendroflumethiazide is administered to those with a known predisposition to diabetes.

Postural hypotension, mild gastro-intestinal effects and diarrhoea; hypokalaemia,

hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochloraemic alkalosis, hyperuricaemia, gout, hyperglycaemia, and altered plasma lipid concentration.

Nervous system disorders Headache, Dizziness, Paraesthesia, Drowsiness are not known

Eye disorders choroidal effusion is not known

Vascular disorders like Postural hypotension and Vasculitis are not known

Gastrointestinal disorders like Nausea, vomiting, diarrhoea, constipation, dry mouth, thirst

and gastric irritation are not known

Systemic lupus erythematosus and acute interstitial nephritis, oliguria, non

opaque uranari calculi are not known.

Less commonly, rashes, photosensitivity; blood disorders (including neutropenia and

thrombocytopenia – when given in late pregnancy neonatal thrombocytopenia has

been reported); pancreatitis, intrahepatic cholestasis, Cholecystitis and hypersensitivity reactions

(including pneumonitis, pulmonary oedema, severe skin reactions) also reported.

Rarely, blood dyscrasias, including agranulocytosis, including neutropenia aplastic anaemia, thrombocytopenia and leucopenia, and pancreatitis have been reported with long term

therapy. Skin rashes and impotence (reversible on withdrawal of treatment) have

occasionally been reported.

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

**Reporting of suspected adverse reactions:**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). or search for MHRA Yellow Card in the Google Play or Apple App Store.

**4.9 Overdose**

Symptoms of overdosage include anorexia, nausea, vomiting, diarrhoea, diuresis, dehydration, hypotension, dizziness, weakness, muscle cramps, paraesthesia, tetany, convulsions, increased frequency of micturition with polyuria and thirst, hyponatraemia, hypo- or hyperglycaemia, hypomagnesaemia, hypercalcaemia, hypokalaemia can occur and is especially important in patients with preexisting cardiac disease and metabolic alkalosis. Otherwise treatment should be symptomatic and supportive including the correction of fluid and electrolyte imbalance can lead to arrhythmias.

Extreme cases may show depletion of intravascular volume, hypotension and peripheral circulatory failure.

CNS depression (e.g. drowsiness, lethargy and coma) may occur without cardiovascular or respiratory depression

Management of overdose

Treatment should be supportive and directed at fluid and electrolyte replacement which should be monitored together with blood pressure, blood glucose, ECGs and renal function. Cathartics should be avoided.

There is no specific antidote.

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic classification: Low-Ceiling Diuretics Thiazides -

Bendroflumethiazide

ATC code: CO3A A01

Bendroflumethiazide is a thiazide diuretic which reduces the reabsorption of

electrolytes from the renal tubules, thereby increasing the excretion of

sodium and chloride ions, and consequently of water. The excretion of

other electrolytes, notably potassium and magnesium, is also increased. Because potassium excretion is promoted,

metabolic alkalosis may occur secondary to hypokalaemia. There is no important effect upon carbonic anhydrase. Bendroflumethiazide exerts its diuretic effect in about 2 hours and this lasts for 12 to 18 hours or longer. The excretion of other electrolytes, notably potassium and magnesium, is also increased The excretion of calcium is reduced. Thiazides also reduce the carbonic anhydrase activity so that bicarbonate excretion is increased but this effect is generally small and does not appreciably alter the acid base balance or pH of the urine. Thiazides also have a hypotensive effect, due to a reduction in peripheral resistance and enhance the effects of other antihypertensive agents.

**5.2 Pharmacokinetic properties**

*Absorption:* Bendroflumethiazide is completely absorbed from the gastrointestinal tract

and it is fairly extensively metabolised. The duration of the diuretic action of bendroflumethiazide is initiated in about 2 hours and last between 12-18 and 24 hours. The onset of the hypotensive action is generally three or four days.

*Distribution:* Bendroflumethiazide is more than 90% bound to plasma proteins.

*Elimination:* About 30% is excreted unchanged in

the urine with the remainder excreted as uncharacterized metabolites.

*Metabolism:* There is indication that it is fairly extensively metabolised. The onset of diuretic action of the thiazides following oral administration occurs within two hours and the peak effect between three and

eight and half hours after administration.

**5.3 Preclinical safety data**Not applicable

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**Lactose

Maize starch

Pregelatinised starch   
Magnesium stearate

**6.2 Incompatibilities**Not applicable.

**6.3 Shelf life**

As packaged for sale:

3 years for opaque plastic containers.   
3 years for blister packaging.

**6.4 Special precautions for storage**Do not store above 25ºC

**6.5 Nature and contents of container**

Opaque plastic containers composed of polypropylene tubes and polyethylene tamper-evident closures for pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1000 tablets.

Opaque plastic containers composed of either high density polypropylene or high density polyethylene with a tamper-evident or child resistant tamper-evident closure composed of high density polyethylene with a packing inclusion of polyether foam or polyethylene or polypropylene filler in pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1000 tablets.

Blister packs of aluminium/opaque PVC or aluminium/opaque PVC/PVDC subsequently packed in printed cartons in pack sizes of 28, 30, 42, 56, 60, 84, 90 and 112 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special instructions for use/handling.

**7 MARKETING AUTHORISATION HOLDER**

Crescent Pharma Limited,   
Key House,

Sarum Hill, Basingstoke,   
RG21 8SR, UK.

**8 MARKETING AUTHORISATION NUMBER(S)** PL 20416/0027

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

01/11/2003

**10 DATE OF REVISION OF THE TEXT**20/06/2024

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

**Bisoprolol fumarate 1.25 mg film-coated tablets**

Summary of Product Characteristics Updated 01-Aug-2022 I Mylan

1. **Name of the medicinal product**

*1.25 mg tablet only:*

Bisoprolol fumarate 1.25 mg film-coated tablets

*2.5 mg tablet only:*

Bisoprolol fumarate 2.5 mg film-coated tablets

*3.75 mg tablet only:*

Bisoprolol fumarate 3.75 mg film-coated tablets

5 *mg tablet only:*

Bisoprolol fumarate 5 mg film-coated tablets

*7.5 mg tablet only:*

Bisoprolol fumarate 7.5 mg film-coated tablets

*10 mg tablet only:*

Bisoprolol fumarate 10 mg film-coated tablets

1. **Qualitative and quantitative composition**

1.25 *mg tablet only:*

Each tablet contains 1.25 mg of bisoprolol fumarate

2.5 *mg tablet only:*

Each tablet contains 2.5 mg of bisoprolol fumarate

*3.75 mg tablet only:*

Each tablet contains 3.75 mg of bisoprolol fumarate

5 *mg tablet only:*

Each tablet contains 5 mg of bisoprolol fumarate

*7.5 mg tablet only:*

Each tablet contains 7.5 mg of bisoprolol fumarate

*10 mg tablet only:*

Each tablet contains 10 mg of bisoprolol fumarate

Excipient(s) with known effect

5 *mg tablet only:*

Each tablet contains:

0.007 mg sunset yellow (E110).

*7.5 mg tablet only:*

Each tablet contains:

0.010 mg sunset yellow (E110).

*10 mg tablet only:*

Each tablet contains:

0.042 mg sunset yellow (E110).

For the full list of excipients, see section 6.1.

1. **Pharmaceutical form**Film-coated tablet (tablet)   
   1.25 *mg tablet only:*

White, oval, biconvex film coated tablets; approximately 9 mm x 7 mm; 'BL' & '1' engraved on one face of the tablet; 'M' engraved on the other face of the tablet.

<https://www.medicines.org.uk/emc/product/13281/smpc/print> 1/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

*2.5 mg tablet only:*

White to off-white, oval, biconvex film coated tablets with side notches; approximately 9 mm x 7 mm; 'BL' & '2' engraved on either side of the scoreline on one face of the tablet; 'M' engraved on the other face of the tablet.

*3.75 mg tablet only:*

Cream, oval, biconvex film coated tablets with side notches; approximately 9 mm x 7 mm; 'BL' & '3' engraved on either side of the scoreline on one face of the tablet; 'M' engraved on the other face of the tablet.

*5 mg tablet only:*

Pale yellow, oval, biconvex film coated tablets with side notches; approximately 9 mm x 7 mm; 'BL' & '4' engraved on either side of the scoreline on one face of the tablet; 'M' engraved on the other face of the tablet.

*7.5 mg tablet only:*

Yellow, oval, biconvex film coated tablets with side notches; approximately 9 mm x 7 mm; 'BL' *8,* '5' engraved on either side of the scoreline on one face of the tablet; 'M' engraved on the other face of the tablet.

*10 mg tablet only:*

Pale orange to light orange, oval, biconvex film coated tablets with side notches; approximately 9 mm x 7 mm; 'BL' & '6' engraved on either side of the scoreline on one face of the tablet; 'M' engraved on the other face of the tablet.

*2.5mg, 3.75 mg, 5 mg, 7.5 mg, 10 mg tablet only:*The tablet can be divided into equal doses.

**4. Clinical particulars   
4.1 Therapeutic indications**

Treatment of hypertension.

Treatment of chronic stable angina pectoris.

Treatment of stable chronic heart failure with reduced systolic ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides (for additional information see section 5.1).

**4.2 Posology and method of administration**

**Posology**

*Treatment of hypertension and chronic stable angina pectoris*

**Adults**

The dosage should be individually adjusted. It is recommended to start with 5 mg per day. The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day.

**Patients with renal or hepatic impairment**

In patients with severe renal impairment (creatinine clearance < 20 ml/min) and in patients with severe hepatic function disorders the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

**Elderly**

No dosage adjustment is normally required. It is recommended to start with the lowest possible dose.

**Paediatric population**

There is no experience with bisoprolol in children, therefore its use cannot be recommended for children.

**Discontinuation of treatment**

Treatment should not be stopped abruptly (see section 4.4). The dosage should be diminished slowly by a weekly halving of the dose.

*Treatment of stable chronic heart failure***Adults**

Standard treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a beta-blocking agent, diuretics, and when appropriate cardiac glycosides. Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

**Titration phase**

The treatment of stable chronic heart failure with bisoprolol requires a titration phase.

<https://www.medicines.org.uk/emc/product/13281/smpc/print> 2/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

- 1.25 mg once daily for **1** week, if well tolerated increase to

- 2.5 mg once daily for a further week, if well tolerated increase to

- 3.75 mg once daily for a further week, if well tolerated increase to

- 5 mg once daily for the 4 following weeks, if well tolerated increase to

- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to

- 10 mg once daily for the maintenance therapy.

The maximum recommended dose is 10 mg once daily.

Transient worsening of heart failure, hypotension, or bradycardia may occur during the titration period and thereafter.

Close monitoring of vital signs (heart rate, blood pressure) and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may occur within the first day after initiating the therapy.

**Treatment modification**

If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered.

In case of transient worsening of heart failure, hypotension, or bradycardia reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

**Special populations**

**Hepatic or renal impairment:**

There is no information regarding pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired

hepatic or renal function. Titration of the dose in these populations should therefore be made with particular caution.

**Elderly**

No dosage adjustment is normally required.

**Paediatric population**

There is no experience with bisoprolol in children, therefore its use cannot be recommended for children.

**Method of administration**

For oral use.

Bisoprolol fumarate tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

**4.3 Contraindications**

Bisoprolol is contraindicated in patients with:

* hypersensitivity to the active substance or to any of the excipients listed in section 6.1
* acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
* cardiogenic shock
* second or third degree AV block
* sick sinus syndrome
* sinoatrial block
* symptomatic bradycardia
* symptomatic hypotension
* severe bronchial asthma
* severe forms of peripheral arterial occlusive disease or severe forms of Raynaud's syndrome
* untreated phaeochromocytoma (see section 4.4)
* metabolic acidosis

<https://www.medicines.org.uk/emc/product/13281/smpc./print> 3/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

**4.4 Special warnings and precautions for use**

**Special warnings**

**Applies only to chronic heart failure:**

The treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase (see section 4.2)

**Applies to all indications:**

Especially in patients with ischaemic heart disease the cessation of therapy with bisoprolol must not be done abruptly unless clearly indicated, because this may lead to transitional worsening of heart condition (see section 4.2).

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially

'sodium-free'

*5 mg, 7.5 mg and 10 mg tablets only:*

Contains sunset yellow (E110) that may cause allergic reactions.

**Precautions**

**Applies only to hypertension or angina pectoris:**

Bisoprolol must be used with caution in patients with hypertension or angina pectoris and accompanying heart failure.

**Applies only to chronic heart failure:**

The initiation and cessation of treatment with bisoprolol necessitates regular monitoring. For the posology and method of administration please (see section 4.2).

There is no therapeutic experience of bisoprolol treatment in heart failure in patients with the following diseases and conditions:

- insulin dependent diabetes mellitus (type I)

- severely impaired renal function

- severely impaired hepatic function

- restrictive cardiomyopathy

- congenital heart disease

- haemodynamically significant organic valvular disease

- myocardial infarction within 3 months

**Applies to all indications:**

Bisoprolol must be used with caution in:

* bronchospasm (bronchial asthma, obstructive airways diseases)
* diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia (e.g. tachycardia, palpitations, sweating) can be masked
* strict fasting
* ongoing desensitisation therapy. As with other beta-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Epinephrine treatment may not always yield the expected therapeutic effect.
* first degree AV block
* Prinzmetal's angina Cases of coronary vasospasm have been observed. Despite its high beta1-selectivity, angina attacks cannot be completely excluded when bisoprolol is administered to patients with Prinzmetal's angina.
* peripheral arterial occlusive disease. Aggravation of symptoms may occur especially when starting therapy
* general anaesthesia.

Patients with psoriasis or with a history of psoriasis should only be given beta-blockers (e.g. bisoprolol) after a careful balancing of benefits against risks.

The symptoms of thyrotoxicosis may be masked under treatment with bisoprolol.

In patients with phaeochromocytoma bisoprolol must not be administered until after alpha-receptor blockade.

In patients undergoing general anaesthesia beta-blockade reduces the incidence of arrhythmias and myocardial ischemia

during induction and intubation, and the post-operative period. It is currently recommended that maintenance of beta-blockade be continued peri-operatively. The anaesthetist must be aware of beta-blockade because of the potential

<https://www.medicines.org.uk/emc/product/13281/smpc/print> 4/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

for interactions with other drugs, resulting in bradyarrhythmias, attenuation of reflex tachycardia, and decreased reflex ability to compensate for blood loss. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta- blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist, bisoprolol may be used with caution. In patients with obstructive airways diseases, the treatment with bisoprolol should be started at the lowest possible dose and patients should be carefully monitored for new symptoms (e.g. dyspnoea, exercise intolerance, cough). In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, concomitant bronchodilating therapy is recommended. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of beta2-stimulants may have to be increased.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Combinations not recommended:   
Applies only to chronic heart failure:**

* Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine, lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

**Applies to all indications:**

* Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.
* Centrally acting antihypertensive drugs (e.g. clonidine, methyldopa, moxonidine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may further decrease the central sympathetic tonus (and may thus lead to a reduction of heart rate and cardiac output, and to vasodilation). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of "rebound hypertension".

**Combinations to be used with caution:**

**Applies only to hypertension or angina pectoris:**

* Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine, lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

**Applies to all indications:**

* Calcium antagonists of the dihydropyridine type (e.g. nifedipine, amlodipine, felodipine): Concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.
* Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrio-ventricular conduction time may be potentiated.
* Topical beta-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.
* Parasympathomimetic drugs: Concomitant use may increase atrio-ventricular conduction time and the risk of bradycardia.
* Insulin and oral antidiabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoreceptors may mask symptoms of hypoglycaemia.
* Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension (for further information on general anaesthesia see also section 4.4).
* Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.
* Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.
* Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.
* Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. noradrenaline, adrenaline): Combination with bisoprolol may unmask the alpha-adrenoceptor-mediated vasoconstrictor effects of these agents leading to blood pressure increase and exacerbated intermittent claudication. Such interactions are considered to be more likely with nonselective beta-blockers.
* Sympathomimetic agents: Combination with bisoprolol may reduce the effect of both agents. Higher doses of epinephrine may be necessary for treatment of allergic reactions.

<https://www.medicines.org.uk/emc/product/13281/smpc/print> 5/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

* Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

**Combinations to be considered:**

* Mefloquine: increased risk of bradycardia
* Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blockers but also risk for hypertensive crisis.

**Paediatric population**

Interaction studies have only been performed in adults.

**4.6 Fertility, pregnancy and lactation   
Pregnancy**

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/newborn. In general, 3-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the fetus and newborn infant. If treatment with 3-adrenoceptor blockers is necessary, 131-selective adrenoceptor blockers are preferable.

Bisoprolol is not recommended during pregnancy unless clearly necessary. If treatment is considered necessary, monitoring of the uteroplacental blood flow and fetal growth is recommended. In case of harmful effects on pregnancy or the fetus consideration of alternative treatment is recommended. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

**Breast-feeding**

There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. Therefore, breastfeeding is not recommended during administration of bisoprolol.

**4.7 Effects on ability to drive and use machines**

In a study of coronary heart disease patients, bisoprolol did not impair driving performance. However, depending on the individual patient's response to treatment, the ability to drive a vehicle or to use machines may be impaired. This should be considered particularly at the start of treatment and upon change of medication or in conjunction with alcohol.

**4.8 Undesirable effects**

The following definitions apply to the frequency terminology used hereafter:

Very common (a1/10)

Common (ainoo to <1/10)

Uncommon (M/1,000 to <1/100)

Rare (21/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

**Psychiatric disorders:**

Uncommon: sleep disorder, depression.

Rare: nightmare, hallucination.

**Nervous system disorders:**

Common: dizziness\*, headache\*.

Rare: syncope.

**Eye disorders:**

Rare: reduced tear flow (to be considered if the patient uses lenses).

Very rare: conjunctivitis.

**Ear and labyrinth disorders:**

Rare: hearing disorders.

**Cardiac disorders:**

Very common: bradycardia (in patients with chronic heart failure).

<https://www.medicines.org.uk/emc/product/13281/smpc./print> 6/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

Common: worsening of pre-existing heart failure (in patients with chronic heart failure).

Uncommon: AV-conduction disturbances; worsening of pre-existing heart failure (in patients with hypertension or angina pectoris); bradycardia (in patients with hypertension or angina pectoris).

**Vascular disorders:**

Common: feeling of coldness or numbness in the extremities, hypotension especially in patients with heart failure.

Uncommon: orthostatic hypotension.

**Respiratory, thoracic and mediastinal disorders:**

Uncommon: bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.

Rare: allergic rhinitis.

**Gastrointestinal disorders:**

Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation.

**Hepatobiliary disorders:**

Rare: hepatitis.

**Skin and subcutaneous tissue disorders:**

Rare: hypersensitivity reactions such as pruritus, flush, rash and angioedema.

Very rare: alopecia, beta-blockers may provoke or worsen psoriasis or induce psoriasis-like rash.

**Musculoskeletal and connective tissue disorders:**

Uncommon: muscular weakness, muscle cramps.

**Reproductive system and breast disorders:**

Rare: erectile dysfunction.

**General disorders and administration site conditions:**

Common: asthenia (in patients with chronic heart failure), fatigue\*.

Uncommon: asthenia (in patients with hypertension or angina pectoris).

**Investigations:**

Rare: increased triglycerides, increased liver enzymes (ALAT, ASAT).

**Paediatric population:**

No data are available.

applies only to hypertension or angina pectoris:

\*These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1 to 2 weeks.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows

continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard.](http://www.mhra.gov.uk/yellowcard.)

**4.9 Overdose   
Symptoms**

With overdose (e.g. daily dose of 15 mg instead of 7.5 mg) third degree AV-block, bradycardia, and dizziness have been reported. In general, the most common signs expected with overdose of a beta-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol (maximum: 2000 mg) have been reported in patients suffering from hypertension and/or coronary heart disease showing bradycardia and/or hypotension were noted, all patients recovered. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive. Therefore it is mandatory to initiate the treatment of these patients with a gradual uptitration according to the scheme given in section 4.2.

**Management**

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.

<https://www.medicines.org.uk/emc/product/13281/smpc/print> 7/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

Based on the expected pharmacologic actions and recommendations for other beta-blockers, the following general measures may be considered when clinically warranted.

Bradycardia: Administer intravenous atropine. If the response is inadequate, isoprenaline or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

Hypotension: Intravenous fluids and vasopressors should be administered. Intravenous glucagon may be useful.

AV block (second or third degree): Patients should be carefully monitored and treated with isoprenaline infusion or transvenous cardiac pacemaker insertion.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, beta2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialysable.

**5. Pharmacological properties   
5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Beta blocking agents, selective, ATC code: C07 ABO7

**Chronic heart failure:**

**Mechanism of action**

Bisoprolol is a potent, highly beta1-selective adrenoreceptor blocking agent lacking intrinsic sympathomimetic activity and without relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2-mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range.

**Clinical efficacy**

In total 2647 patients were included in the CIBIS II trial. 83% (n = 2202) were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction <35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (relative reduction 34%). A decrease in sudden death (3.6% vs 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admission due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%). The numbers of fatal and disabling strokes during the total study period were 20 in the bisoprolol group and 15 in the placebo group.

The CIBIS III trial investigated 1010 patients aged n5 years with mild to moderate chronic heart failure (CHF; NYHA class II or III) and left ventricular ejection fraction <\_35%, who had not been treated previously with ACE inhibitors, beta-blocking agents, or angiotensin receptor blockers. Patients were treated with a combination of bisoprolol and enalapril for 6 to 24 months after an initial 6 months treatment with either bisoprolol or enalapril.

There was a trend toward higher frequency of chronic heart failure worsening when bisoprolol was used as the initial 6 months treatment. Non inferiority of bisoprolol-first versus enalapril-first treatment was not proven in the per-protocol analysis, although the two strategies for initiation of CHF treatment showed a similar rate of the primary combined endpoint death and hospitalization at study end (32.4% in the bisoprolol-first group vs. 33.1 % in the enalapril-first group, per-protocol population). The study shows that bisoprolol can also be used in elderly chronic heart failure patients with mild to moderate disease.

**Hypertension or angina pectoris:   
Mechanism of action**

Antianginal mechanism: Bisoprolol by inhibiting the cardiac beta receptors inhibits the response given to

sympathetic activation. That results in the decrease of heart rate and contractility this way decreasing the oxygen demand of the cardiac muscle.

In acute administration in patients with coronary heart disease without chronic heart failure bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

**Pharmacodynamic effects**

Bisoprolol is used for the treatment of hypertension and angina pectoris. As with other Beta-1-blocking agents, the method of acting in hypertension is unclear. However, it is known that Bisoprolol reduces plasma renin activity markedly.

<https://www.medicines.org.uk/emc/product/13281/smpc/print> 8/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

**5.2 Pharmacokinetic properties   
Absorption**

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%.

**Distribution**

The plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3.5 I/kg. The total clearance is approximately 15 I/h.

The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage. **Biotransformation**

50 % is metabolised by the liver to inactive metabolites which are then excreted by the

kidneys. **Elimination**

Bisoprolol is excreted from the body by two routes. 50% is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is not required for patients with impaired liver function or renal insufficiency.

**Other special population**

In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half-life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64±21 ng/ml at a daily dose of 10 mg and the half-life is 17±5 hours.

**5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential, toxicity to reproduction and development.

Like other beta-blockers, bisoprolol caused maternal (decreased food intake and decreased body weight) and embryo/fetal toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses but was not teratogenic.

**6. Pharmaceutical particulars   
6.1 List of excipients**

|  |  |  |
| --- | --- | --- |
| **Strength** | **Tablet** | **Film-coat** |
| *1.25 mg tablet only:* | Cellulose microcrystalline  Butylhydroxyanisole  Isopropyl alcohol  Colloidal anhydrous silica  Magnesium stearate  Sodium lauril sulfate  Croscarmellose sodium | Titanium dioxide (E171)  Talc  Hypromellose (E464) |
| *2.5 mg tablet only:* | Cellulose microcrystalline  Butylhydroxyanisole  Isopropyl alcohol  Colloidal anhydrous silica  Magnesium stearate  Sodium lauril sulfate  Iron oxide yellow (E172) Croscarmellose sodium | Titanium dioxide (E171)  Talc  Hypromellose (E464) |
| *3.75 mg tablet only:* | Cellulose microcrystalline Butylhydroxyanisole | Titanium dioxide (E171)  Talc Hypromellose (E464) |

<https://www.medicines.org.uk/emc/product/13281/smpc./print> 9/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

|  |  |  |
| --- | --- | --- |
|  | Isopropyl alcohol  Colloidal anhydrous silica  Magnesium stearate  Sodium lauril sulfate  Iron oxide yellow (E172)  Croscarmellose sodium | Iron oxide yellow (E172) |
| *5 mg tablet only:* | Cellulose microcrystalline  Butylhydroxyanisole  Isopropyl alcohol  Colloidal anhydrous silica  Magnesium stearate  Sodium lauril sulfate  Iron oxide yellow (E172) Croscarmellose sodium | Titanium dioxide (E171)  Talc Hypromellose (E464)  Indigo carmine (E132)  Quinoline yellow (E104)  Sunset yellow (E110) |
| *7.5 mg tablet only:* | Cellulose microcrystalline  Butylhydroxyanisole  Isopropyl alcohol  Colloidal anhydrous silica  Magnesium stearate  Sodium lauril sulfate  Iron oxide yellow (E172) Croscarmellose sodium | Titanium dioxide (E171)  Talc Hypromellose (E464)  Quinoline yellow (E104)  Sunset yellow (E110) |
| *10 mg tablet only:*  **I** | Cellulose microcrystalline  Butylhydroxyanisole  Isopropyl alcohol  Colloidal anhydrous silica  Magnesium stearate  Sodium lauril sulfate  Iron oxide red (E172)  Croscarmellose sodium | Titanium dioxide (E171)  Talc Hypromellose (E464)  Iron oxide yellow (E172)  Sunset yellow (E110) |

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

Blister: 2 years   
Bottle: 2 years

**6.4 Special precautions for storage**

Blister: Store below 30°C.

Bottle: This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

<https://www.medicines.org.uk/emc/product/13281/smpc./print> 10/11

28/10/2022, 13:38 Bisoprolol fumarate 1.25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

PVC/ Al blister packs. Blister pack comprises of clear transparent PVC film with backing of aluminium foil coated with heat seal lacquer containing 10, 20, 28, 30, 50, 56, 84, 90, 98 and 100 film-coated tablets.

White HDPE bottles with white opaque polypropylene cap containing 10, 28, 30, 50, 56, 84, 98, 100, 500 and 1000 film-coated tablets.

Bottle contains a perforated HDPE canister holding silica gel and activated carbon   
desiccant. Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

1. **Marketing authorisation holder**Generics [UK] Ltd t/a Mylan

Station Close,

Potters Bar, Hertfordshire,

EN6 1TL,

United Kingdom

1. **Marketing authorisation number(s)**PL 04569/1254

PL 04569/1255   
PL 04569/1256   
PL 04569/1257   
PL 04569/1258   
PL 04569/1259

1. **Date of first authorisation/renewal of the authorisation**10/10/2015

**1. Date of revision of the text**12/2021

**Company Contact Details**

Mylan

**Address WWW**

Building 4, Trident Place, Mosquito Way, Hatfield, [http://www.mylan.com](http://www.mylan.com/)   
Hertfordshire, AL10 9UL

|  |  |
| --- | --- |
| **Telephone**  +44 (0)1707 853 000  **Medical Information Direct Line**  +44 (0)1707 853 000  **Customer Care direct line**  +44 (0)1707 853 000 select option 2  **Stock Availability**  +44 (0)1707 853 000 select option 2 | **Fax**  +44 (0)1707 261 803  **Medical Information e-mail** [info@mylan.co.uk](mailto:info@mylan.co.uk)  **Medical Information Fax**  +44 (0)1707 261 803 |

<https://www.medicines.org.uk/emc/product/13281/smpc./print> 11/11

28/10/2022, 13:40 Doxazosin 2 mg Tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

**Doxazosin 2 mg Tablets**

Summary of Product Characteristics Updated 13-May-2020 I Dexcel Pharma Ltd

1. **Name of the medicinal product**

Doxazosin 2 mg Tablets   
Doxadura 2 mg Tablets

1. **Qualitative and quantitative composition**

Doxazosin 2 mg (as mesilate).

Excipient(s) with known effect:

Each tablet contains 80.88 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

1. **Pharmaceutical form**

Tablets

Doxazosin 2mg is white to off-white, capsule shaped biconvex tablet, scored on one side.

1. **Clinical particulars**

**4.1 Therapeutic indications**

***Hypertension:*** Doxazosin is indicated for the treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. In patients inadequately controlled on single antihypertensive therapy, Doxazosin may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an angiotensin-converting enzyme inhibitor.

***Benign prostatic hyperplasia:*** Doxazosin is indicated for the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH). Doxazosin may be used in BPH patients who are either

hypertensive or normotensive.

**4.2 Posology and method of administration**

Posology

Doxazosin may be administered in the morning or the evening.

***Hypertension:*** Doxazosin is used in a once daily regimen: the initial dose is 1 mg to minimise the potential for postural hypotension and/or syncope (see section 4.4). Dosage may then be increased to 2 mg after an additional one or two weeks of therapy and thereafter, if necessary to 4 mg. The majority of patients who respond to Doxazosin will do so at a dose of 4 mg or less. Dosage can be further increased if necessary to 8 mg or the maximum recommended dose of 16 mg.

***Benign prostatic hyperplasia:*** The recommended initial dosage of Doxazosin is 1mg given once daily to minimise the potential for postural hypotension and/or syncope (see section 4.4). Depending on the individual patient's urodynamics and **BPH** symptomatology dosage may then be increased to 2 mg and thereafter to 4 mg and up to the maximum recommended dose of 8 mg. The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4 mg daily.

***Paediatric population:*** The safety and efficacy of Doxazosin in children and adolescents have not been established.

***Elderly patients:*** Normal adult dosage.

Hepatic/Renal impairment

***Patients with renal impairment:*** Since there is no change in pharmacokinetics in patients with impaired renal function, the usual adult dose of Doxazosin is recommended.

Doxazosin is not dialysable.

***Patients with hepatic impairment:*** There are only limited data in patients with liver impairment and on the effect of drugs known to influence hepatic metabolism (e.g. cimetidine). As with any drug wholly metabolised by the liver, Doxazosin should be administered with caution to patients with evidence of impaired liver function (see section 4.4 and section 5.2).

**Method of administration**Oral administration.

**4.3 Contraindications**

<https://www.medicines.org.uk/emc/product/2664/smpc/print> 1/7

28/10/2022, 13:40 Doxazosin 2 mg Tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

Doxazosin is contraindicated in:

1. Hypersensitivity to the active substance or other types of quinazolines (e.g. prazosin, terazosin, doxazosin) or to any of the excipients listed in section 6.1.
2. Patients with a history of orthostatic hypotension.
3. Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladders stones.
4. Patients with hypotension (for benign prostatic hyperplasia indication only).

Doxazosin is contraindicated as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

**4.4 Special warnings and precautions for use   
*Postural Hypotension/Syncope:***

***Initiation of Therapy—* In relation with the alpha-blocking properties of doxazosin, patients may experience** postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness (syncope), particularly with the commencement of therapy (see section 4.2). Therefore, it is prudent medical practice to monitor blood pressure on initiation of therapy to minimise the potential for postural effects.

When instituting therapy with any effective alpha-blocker, the patient should be advised how to avoid symptoms resulting from postural hypotension and what measures to take should they develop. The patient should be cautioned to avoid situations where injury could result, should dizziness or weakness occur during the initiation of Doxazosin therapy.

**Use in patients with Acute Cardiac Conditions:**

As with any other vasodilatory anti-hypertensive agent it is prudent medical practice to advise caution when administering doxazosin to patients with the following acute cardiac conditions:

- pulmonary oedema due to aortic or mitral stenosis

- high — output cardiac failure

- right sided heart failure due to pulmonary embolism or pericardial effusion

- left ventricular heart failure with low filling pressure

***Use in Hepatically Impaired patients:***

As with any drug wholly metabolised by the liver, Doxazosin should be administered with particular caution to patients with evidence of impaired hepatic function (see section 4.2). Since there is no clinical experience in patients with severe hepatic impairment use in these patients is not recommended.

***Use with PDE-5 Inhibitors:***

Concomitant administration of doxazosin with phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil and vardenafil) should be done with caution as both drugs have vasodilating effects and may lead to symptomatic hypotension in some patients. To reduce risk of orthostatic hypotension it is recommended to initiate the treatment with phosphodiesterase-5-inhibitors only if the patient is hemodynamically stabilized on alpha-blocker therapy. Furthermore, it is recommended to initiate phosphodiesterase-5-inhibitor treatment with the lowest possible dose and to respect a 6-hour time interval from intake of doxazosin.

***Use in patients undergoing cataract surgery:*** The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with

tamsulosin. Isolated reports have also been received with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

***Priapism***

Prolonged erections and priapism have been reported with alpha-1 blockers including doxazosin in post marketing experience. If priapism is not treated immediately, it could result in penile tissue damage and permanent loss of potency, therefore the patient should seek immediate medical assistance.

***Screening for Prostate Cancer:***

Carcinoma of the prostate causes many of the symptoms associated with **BPH** and the two disorders can co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with doxazosin for treatment of BPH symptoms.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**

<https://www.medicines.org.uk/emc/product/2664/smpc/print> 2/7

28/10/2022, 13:40 Doxazosin 2 mg Tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

Phosphodiesterase-5-inhibitors (eg. sildenafil, tadalafil, vardenafil):

Concomitant administration of doxazosin with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4: Special warnings and precautions for use).

Doxazosin is highly bound to plasma proteins (98%). *In vitro* data in human plasma indicates that doxazosin has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indomethacin).

*In vitro* studies suggest that doxazosin is a substrate of cytochrome P450 3A4 (CYP 3A4). Caution should be exercised when concomitantly administering doxazosin with a strong CYP 3A4 inhibitor, such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole (see section 5.2).

Conventional doxazosin has been administered without any adverse drug interaction in clinical experience with thiazide diuretics, furosemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents or anticoagulants. However, data from formal drug/drug interaction studies are not present.

Doxazosin potentiates the blood pressure lowering activity of other alpha-blockers and other antihypertensives.

In an open-label, randomized, placebo-controlled trial in 22 healthy male volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin, and no statistically significant changes in mean Cmax and mean half-life of doxazosin. The 10% increase in the mean AUC for doxazosin with cimetidine is within intersubject variation (27%) of the mean AUC for doxazosin with placebo.

**4.6 Fertility, pregnancy and lactation**For the hypertension indication:

***Pregnancy.*** As there are no adequate and well-controlled studies in pregnant women, the safety of doxazosin during pregnancy has not yet been established. Accordingly, during pregnancy doxazosin should be used only when, in the opinion of the physician, the potential benefit outweighs potential risk. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses (see section 5.3).

***Breast-feeding:*** The excretion of doxazosin in breast milk was demonstrated to be very low (with the relative infant dose less than 1%) however human data is very limited. A risk to the newborn or infant cannot be excluded and therefore

doxazosin should be used only when in the opinion of the physician, the potential benefit outweighs the potential risk.

For the benign prostatic hyperplasia indication: This section is not applicable.

**4.7 Effects on ability to drive and use machines**

The ability to drive or use machinery may be impaired, especially when initiating therapy.

**4.8 Undesirable effects**

***Hypertension:*** In clinical trials involving patients with hypertension, the most common reactions associated with Doxazosin therapy were of a postural type (rarely associated with fainting) or non-specific.

***Benign prostatic hyperplasia:*** Experience in controlled clinical trials in BPH indicates a similar adverse event profile to that seen in hypertension.

The following undesirable effects have been observed and reported during treatment with Doxazosin with the following frequencies: Very common (>\_1/10); common (M/100 to <1/10); uncommon (>\_1/1,000 to <1/100); rare

(>\_1/10,000 to <1/1,000); very rare (<1/10,000).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **System Organ  Class** | **Very 1**  **Common**  **(?1/10)**  **I** | **Common**  **(M/100 to**  **<1/10)** | **Uncommon**  **(M/1,000 to**  **<1/100)** | **Rare**  **(M/10,000  to**  **<1/1,000)** | **Very Rare**  **(<1/10,000)** | **Unknow**  **n** |
| **Infections and infestations** |  | Respiratory tract infection, urinary tract infection |  |  |  |  |
| **Blood and the lymphatic system disorders** |  |  |  |  | Leukopenia, thrombocytopenia |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Immune system** |  |  | Allergic drug |  |  |  |
| **disorders** |  |  | reaction |  |  |  |

<https://www.medicines.org.uk/emc/product/2664/smpc/print> 3/7

28/10/2022, 13:40 Doxazosin 2 mg Tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Metabolism and nutrition disorders** |  |  | Gout, increased appetite, anorexia |  |  |  |
| **Psychiatric disorders** |  |  | Agitation,  depression,  anxiety,  insomnia, | I |  |  |
| **Nervous system disorders** |  | Somnolence dizziness, headache | Cerebrovascular accident, hypoesthesia, syncope, tremor |  | Postural dizziness, paresthesia  1 |  |
| **Eye disorders** |  |  |  |  | Blurred vision | Intra-operative floppy iris syndrome (see section 4.4) |
| **Ear and labyrinth disorders** |  | Vertigo | Tinnitus |  |  |  |
| **Cardiac disorders** |  | Palpitation, tachycardia | Angina pectoris, myocardial infarction |  | Bradycardia, cardiac arrhythmias |  |
| **Vascular disorders** |  | Hypotension, postural hypotension |  |  | Hot flushes | 1 |
| **Respiratory, thoracic and mediastinal disorders** |  | Bronchitis, cough, dyspnoea, rhinitis | Epistaxis, |  | Bronchospasm |  |
| **Gastrointestinal disorders** |  | Abdominal pain, dyspepsia, dry mouth, nausea | Constipation, flatulence, vomiting, gastroenteritis diarrhoea |  |  |  |
| **Hepato-biliary disorders** |  |  | Abnormal liver function tests |  | Cholestasis, Hepatitis, jaundice, |  |
| **Skin and**  **subcutaneous tissue disorders** |  | Pruritus | Skin rash, |  | Urticaria, alopecia, purpura |  |
| **Musculoskeletal, connective tissue and bone disorders** |  | Back pain, myalgia | Arthralgia | Muscle cramps, muscle weakness |  |  |
| **Renal and urinary disorders** |  | Cystitis,  urinary  incontinence | Dysuria,  micturition  frequency,  hem aturia, | Polyuria | Increased diuresis, micturition disorder, nocturia |  |
| **Reproductive system and breast disorders** |  |  | **Impotence** |  | Gynecomastia, priapism | Retrograde ejaculation |
| **General disorders and administration site conditions** |  | Asthenia, chest pain, influenza- like symptoms, peripheral oedema | Pain, facial oedema |  | Fatigue, malaise |  |

<https://www.medicines.org.uk/emc/product/2664/smpc/print> 4/7

28/10/2022, 13:40 Doxazosin 2 mg Tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

**Investigations** (Weight increase 1





1

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: [www.rnhra.gov.uk/yellowcard](http://www.rnhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store

**4.9 Overdose**

Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position. Other supportive measures may be appropriate in individual cases.

If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressor should then be used. Renal function should be monitored and supported as needed.

Since Doxazosin is highly protein bound, dialysis is not indicated.

**5. Pharmacological properties   
5.1 Pharmacodynamic properties**

*Pharmacotherapeutic group:* Alpha-adrenoreceptor antagonist

*ATC code:* CO2C A04   
Mechanism of action

Doxazosin is a potent and selective post-junctional alpha-1-adrenoceptor antagonist. This action results in a decrease in systemic blood pressure. Doxazosin is appropriate for oral administration in a once daily regimen in patients with essential hypertension.

Pharmacodynamic effects

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with co­existent diabetes mellitus, gout and insulin resistance.

Doxazosin is suitable for use in patients with coexistent asthma, left ventricular hypertrophy and in elderly patients. Treatment with Doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator. Additionally, Doxazosin improves insulin sensitivity in patients with impairment.

Doxazosin, in addition to its antihypertensive effect, has in long term studies produced a modest reduction in plasma total cholesterol, LDL-cholesterol and triglyceride concentrations and therefore may be of particular benefit to hypertensive patients with concomitant hyperlipidaemia.

Administration of Doxazosin to patients with symptomatic BPH results in a significant improvement in urodynamics and symptoms. The effect in **BPH** is thought to result from selective blockade of the alpha-adrenoceptors located in the muscular stroma and capsule of the prostate, and in the bladder neck.

**5.2 Pharmacokinetic properties**

***Absorption:*** Following oral administration in humans (young male adults or the elderly of either sex), Doxazosin is well absorbed and approximately two thirds of the dose is bioavailable.

***Biotransformation/Elimination:*** Approximately 98% of doxazosin is protein-bound in plasma. Doxazosin is extensively metabolised in man and in the animal species tested, with the faeces being the predominant route of excretion.

The mean plasma elimination half-life is 22 hours thus making the drug suitable for once daily administration.

After oral administration of doxazosin the plasma concentrations of the metabolites are low. The most active (6' hydroxy) metabolite is present in man at one fortieth of the plasma concentration of the parent compound which suggests that the antihypertensive activity is in the main due to doxazosin.

There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 subjects with moderate hepatic impairment, single dose administration of doxazosin resulted in an increase in AUC of 43% and a decrease in apparent oral clearance of 40%. As with any drug wholly metabolised by the liver, doxazosin should be administered with caution to patients with impaired liver function (see section 4.4).

Doxazosin is extensively metabolized in the liver. *In vitro* studies suggest that the primary pathway for elimination is via CYP 3A4; however CYP 2D6 and CYP 2C9 metabolic pathways are also involved for elimination, but to a lesser extent.

**5.3 Preclinical safety data**

<https://www.medicines.org.uk/emc/product/2664/smpc/print> 5/7

28/10/2022, 13:40 Doxazosin 2 mg Tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

Preclinical data reveal no special hazard for humans based on conventional animal studies in safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at doses approximately 300 times greater than the maximum human recommended dose.

Studies in lactating rats given a single oral dose of radioactive doxazosin indicate that doxazosin accumulates in rat milk with a maximum of concentration about 20 times greater than the maternal plasma concentration.

1. **Pharmaceutical particulars   
   6.1 List of excipients**

lactose monohydrate   
magnesium stearate   
microcrystalline cellulose   
sodium lauryl sulphate   
sodium starch glycolate (type A)

colloidal anhydrous silica

**6.2 Incompatibilities**

None.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Store below 25°C.

**6.5 Nature and contents of container**

Aluminium PVC/PVDC blister:   
28 tablets in a calendar pack.

**6.6 Special precautions for disposal and other handling**No special requirements.

1. **Marketing authorisation holder**

Dexcel-Pharma Ltd.

7 Sopwith Way

Drayton Fields, Daventry

Northamptonshire NN11 8PB

UK

1. **Marketing authorisation number(s)**PL 14017/0033
2. **Date of first authorisation/renewal of the authorisation**

03/05/2002

02/03/2009

**0. Date of revision of the text**

07/05/2020

**Company Contact Details**

Dexcel Pharma Ltd

**Address VVWW**

7, Sopwith Way, Drayton Fields, Daventry, [http://www.dexcelpharma.com](http://www.dexcelpharma.com/)

Northamptonshire, NN11 8PB, UK

**Fax**

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28/10/2022, 13:40 Doxazosin 2 mg Tablets - Summary of Product Characteristics (SmPC) - print friendly - (emc)

|  |  |
| --- | --- |
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**SUMMARY OF PRODUCT CHARACTERISTICS**

**1 NAME OF THE MEDICINAL PRODUCT**

Losartan Potassium 12.5 mg Film-coated Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 12.5 mg of losartan potassium equivalent to 11.4 mg of losartan.

Excipient:

16.75 mg lactose monohydrate/tablet.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated tablet

Losartan potassium 12.5 mg

White, round film-coated tablets.

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

* Treatment of essential hypertension in adults and in children and adolescents 6 - 18 years of age.
* Treatment of renal disease in adult patients with hypertension and type 2 diabetes

mellitus with proteinuria 0.5 g/day as part of an antihypertensive treatment (see sections 4.3, 4.4, 4.5, and 5.1).

* Treatment of chronic heart failure in adult patients when treatment with ACE inhibitors is not considered suitable due to incompatibility*, especially cough,* or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left

ventricular ejection fraction 40% and should be stabilised under the treatment of the chronic heart failure.

* Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

**4.2 Posology and method of administration**

**Posology**Hypertension

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).

Losartan potassium may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide) (see sections 4.3, 4.4, 4.5, and 5.1).

Hypertensive type II diabetic patients with proteinuria 0.5 g/day

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month onwards after initiation of therapy. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) (see sections 4.3, 4.4, 4.5, and 5.1) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Heart Failure

The usual initial dose of losartan in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily, 50 mg daily, 100 mg daily, up to a maximum dose of 150 mg once daily) as tolerated by the patient.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide should be added and/or the dose of losartan should be increased to 100 mg once daily based on blood pressure response.

*Special populations*

Use in patients with intravascular volume depletion:

For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

Use in patients with renal impairment and haemodialysis patients:

No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment:

A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Paediatric population

*6 months – less than 6 years*

The safety and efficacy of children aged 6 months to less than 6 years has not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on posology can be made.

*6 years to 18 years*

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. In exceptional cases the dose can be increased to a maximum of 50 mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in pediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.

It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m2, as no data are available (see also section 4.4).

Losartan is also not recommended in children with hepatic impairment (see also section 4.4).

Use in Elderly

Although consideration should be given to initiating therapy with 25 mg in patients

over 75 years of age, dosage adjustment is not usually necessary for the elderly.

**Method of administration**

Losartan tablets should be swallowed whole with a glass of water. Losartan tablets may be administered with or without food.

**4.3 Contraindications**

* Hypersensitivity to the active substance or to any of the excipients (see section 4.4 and 6.1).
* 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
* Severe hepatic impairment
* The concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see section 4.5 and 5.1).

**4.4 Special warnings and precautions for use**Hypersensitivity

*Angiooedema.* Patients with a history of angiooedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored (See section 4.8).

Hypotension and Electrolyte/Fluid Imbalance

Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of Losartan potassium, or a lower starting dose should be used (see section 4.2). This also applies to children 6 to 18 years of age.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with Losartan potassium as compared to the placebo group (see section 4.8, 'Hypertension and type 2 diabetes with renal disease - Investigations’ and ‘Post-marketing experience - Investigations’ Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a Creatinine Clearance between 30-50 ml/min should be closely monitored.

The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan is not recommended (see section 4.5).

Hepatic impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Losartan is not recommended in children with hepatic impairment (see section 4.2). Renal Impairment

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin angiotensin aldosterone system such as those

with severe cardiac insufficiency or pre-existing renal dysfunction). As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

*Use in pediatric patients with renal function impairment*

Losartan is not recommended in children with glomerular filtration rate < 30ml/min/1.73 m2 as no data are available (see section 4.2).

Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended (see section 4.5).

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan is not recommended.

Coronary heart disease and cerebrovascular disease

As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure

In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Excipients

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy

Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other warnings and precautions

As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents may increase the hypotensive action of Losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of matabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).

As with other medicinal products that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics:

amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non­selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre­existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4, and 5.1)

Grapefruit juice contains components that inhibit CYP450 enzymes and may lower the concentration of the active metabolite of losartan which may reduce the therapeutic effect. Consumption of grapefruit juice should be avoided while taking losartan tablets.

**4.6 Fertility, pregnancy and lactation** Pregnancy

The use of losartan is not recommended during the first trimester of pregnancy (see section 4.4). The use of losartan is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification

retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 'Preclinical safety data').

Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken losartan should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation

Because no information is available regarding the use of losartan during breastfeeding, losartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

**4.8 Undesirable effects**

Losartan has been evaluated in clinical studies as follows:

* In a controlled clinical trial in > 3,000 adult patients 18 years of age and older for essential hypertension.
* In a controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age
* In a controlled clinical trial in > 9,000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy (see LIFE Study, section 5.1)
* In controlled clinical trials in > 7,700 adult patients with chronic heart failure (see ELITE I, ELITE II, and HEAAL study, section 5.1)
* In a controlled clinical trial in > 1,500 type 2 diabetic patients 31 years of age and older with proteinuria (see RENAAL study, section 5.1)

In these clinical trials, the most common adverse event was dizziness.

The frequency of adverse events listed below is defined using the following convention:

very common ( 1/10); common ( 1/100 to < 1/10); uncommon ( 1/1,000 to < 1/100); rare ( 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.

**Hypertension**

In controlled clinical trials for essential hypertension with losartan the following adverse events were reported:

*Nervous system disorders*

Common: dizziness

Uncommon: somnolence, headache, sleep disorders

*Ear and labyrinth disorders*Common: vertigo

*Cardiac disorder*

Uncommon: palpitations, angina pectoris

*Vascular disorders*

Uncommon: (orthostatic) hypotension (dose-related orthostatic effects) ,

*Skin and subcutaneous tissue disorders*Uncommon: rash

*Gastrointestinal disorders*

Uncommon: abdominal pain, obstipation

*General disorders and administration site conditions*Uncommon: asthenia, fatigue, oedema

*Investigations*

Common: hyperkalaemia

Rare: increased alanine aminotransferase (ALT) §

**Hypertensive patients with left ventricular hypertrophy**

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

*Nervous system disorders*Common: dizziness

*Ear and labyrinth disorders*common: vertigo

*General disorders and administration site conditions*Common: asthenia, fatigue

**Chronic heart failure**

In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

*Blood and lymphatic system disorders*Common: anaemia

*Nervous system disorders*Common: dizziness

Uncommon: headache   
Rare: paraesthesia

*Cardiac disorders*

Rare: syncope, artrial fibrillation, cerebrovascular accident



*Vascular disorders*

Common: (orthostatic) hypotension (including dose- related orthostatic effects)

*Respiratory, thoracic and mediastinal disorders*Uncommon: dyspnoea, cough

*Gastrointestinal disorders*

Uncommon: diarrhoea, nausea, vomiting

*Skin and subcutanous tissue disorders*Uncommon: urticaria, pruritus, rash

*Renal and urinary disorders*

Common: renal impairment, renal failure

*General disorders and administration site conditions*Uncommon: asthenia, fatigue

*Investigations*

Uncommon: hyperkalaemia†

Common: increase in blood urea, serum creatinine, and serum potassium

**Hypertension and type 2 diabetes with renal disease**

In a controlled clinical trial in type 2 diabetic patients with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse events which were reported for losartan are as follows:

*Nervous system disorders*Common: dizziness

|  |  |
| --- | --- |
| *Vascular disorders*  Common: (orthostatic) hypotension (including dose- related orthostatic effects) |  |

*General disorders and administration site conditions*Common: asthenia, fatigue

*Investigations*

Common: hypoglycaemia, hyperkalaemia‡

**Post-marketing experience**

The following adverse events have been reported in post-marketing experience:

*Blood and lymphatic system disorders:*Not known: anaemia, thrombocytopenia

*Immune system disorders*

Rare: hypersensitivity reactions, anaphylactic reactions, angioedema\*, and vasculitis\*\*

*Psychiatric disorders*Not known: depression

*Nervous system disorders*

Not known: migraine, dysgeusia

*Ear and labyrinth disorders   
Not known: tinnitus*

*Respiratory, thoracic and mediastinal disorders*Not known: cough

*Gastrointestinal disorders*Not known: diarrhoea

*Hepatobiliary disorders*

Rare: hepatitis

Not known: liver function abnormalities, pancreatitis

*Skin and subcutaneous tissue disorders*

Not known: urticaria, pruritus, rash, photosensitivity

*Muscoskeletal and connective tissue disorders*Not known: myalgia, arthralgia, rhabdomyolysis

*Reproductive system and breast disorders*Not known: erectile dysfunction / impotence

*General disorders and administration site conditions* Not known: malaise

*Investigations*

Not known: hyponatraemia

*\*Including swelling of the larynx, glottis, face, lips, pharynx, and/or tongue (causing airway obstruction); in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors*

*\*\*Including Henoch-Schönlein purpura*

*Especially in patients with intravascular depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics*



*†Common in patients who received 150 mg losartan instead of 50 mg*

*‡In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mmol/l and 3.4% of patients treated with placebo*

*§Usually resolved upon discontinuation*

The following adverse events occurred more often in patients receiving losartan than placebo:

Renal and urinary disorders

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4)

Paediatric population

The adverse reaction profile for paediatric patients appears to be similar to that seen in adult patients. Data in the paediatric population are limited.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

**4.9 Overdose**

*Symptoms of intoxication*

Limited data are available with regard to overdose in humans. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia could occur from parasympathetic (vagal) stimulation.

*Treatment of intoxication*

If symptomatic hypotension should occur, supportive treatment should be instituted.

Measures are depending on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.

Neither Losartan nor the active metabolite can be removed by haemodialysis.

**5.1 Pharmacodynamic properties**

Losartan is a synthetic oral angiotensin-II receptor (type AT1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological

actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Losartan does not have an agonist effect, nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of Losartan, removal of the angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of Losartan, PRA and angiotensin II values fell within three days to the baseline values.

Both Losartan and its principal active metabolite have a far greater affinity for the AT1-receptor than for the AT2-receptor. The active metabolite is 10- to 40- times more active than Losartan on a weight for weight basis.

Hypertension Studies

In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5-6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70-80 % of the effect seen 5-6 hours postdose.

Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effects on heart rate.

Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

LIFE-Study

The Losartan Intervention For Endpoint Reduction in Hypertension [LIFE] study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left-ventricular hypertrophy. Patients were randomised to once daily Losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of Losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE-inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke

and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

*Race*

In the LIFE-Study black patients treated with Losartan had a higher risk of suffering the primary combined endpoint, i.e. a cardiovascular event (e.g. cardiac infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore, the results observed with losartan in comparison with atenolol in the LIFE study with regard to cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL-Study

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan RENAAL study was a controlled clinical study conducted worldwide in 1513 Type 2 diabetic patients with proteinuria, with or without hypertension. 751 Patients were treated with Losartan.

The objective of the study was to demonstrate a nephroprotective effect of Losartan potassium over and above the benefit of a blood lowering pressure.

Patients with proteinuria and a serum creatinine of 1.3-3.0 mg/dl were randomised to receive Losartan 50 mg once a day, titrated, if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE-inhibitors and angiotensin II antagonists.

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72 % of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average). The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end stage renal failure (need for dialysis or transplantation) or death.

The results showed that the treatment with Losartan (327 events) as compared with placebo (359 events) resulted in a 16.1 % risk reduction (p = 0.022) in the number of patients reaching the primary composite endpoint. For the following individual and combined components of the primary endpoint, the results showed a significant risk reduction in the group treated with Losartan: 25.3 % risk reduction for doubling of the serum creatinine (p = 0.006); 28.6 % risk reduction for end-stage renal failure (p = 0.002); 19.9 % risk reduction for end-stage renal failure or death (p = 0.009); 21.0 % risk reduction for doubling of serum creatinine or end-stage renal failure (p = 0.01).

All-cause mortality rate was not significantly different between the two treatment groups. In this study losartan was generally well tolerated, as shown by a therapy

discontinuation rate on account of adverse events that was comparable to the placebo group.

HEAAL Study

The Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) study was a controlled clinical study conducted worldwide in 3834 patients aged 18 to 98 years with heart failure (NYHA Class II-IV) who were intolerant of ACE inhibitor treatment. Patients were randomised to receive losartan 50 mg once a day or losartan 150 mg, on a background of conventional therapy excluding ACE-inhibitors.

Patients were followed for over 4 years (median 4.7 years). The primary endpoint of the study was a composite endpoint of all cause death or hospitalisation for heart failure.

The results showed that treatment with 150 mg losartan (828 events) as compared with 50 mg losartan (889 events) resulted in a 10.1% risk reduction (p=0.027 95% confidence interval 0.82-0.99) in the number of patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of hospitalisation for heart failure. Treatment with 150 mg losartan reduced the risk of hospitalisation for heart failure by 13.5% relative to 50 mg losartan (p=0.025 95% confidence interval 0.76-0.98). The rate of all cause death was not significantly different between the treatment groups. Renal impairment, hypotension, and hyperkalaemia were more common in the 150 mg group than in the 50 mg group, but these adverse events did not lead to significantly more treatment discontinuations in the 150 mg group.

ELITE I and ELITE II Study

In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with Losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE I Study that, compared with captopril, Losartan reduced the mortality risk, was not confirmed in the subsequent ELITE II Study, which is described in the following.

In the ELITE II Study Losartan 50 mg once daily (starting dose 12.5 mg, increased to 25 mg, then 50 mg once daily) was compared with captopril 50 mg three times daily (starting dose 12.5 mg, increased to 25 mg and then to 50 mg three times daily). The primary endpoint of this prospective study was the all-cause mortality.

In this study 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether Losartan is superior to captopril in reducing all-cause mortality. The primary endpoint did not show any statistically significant difference between Losartan and captopril in reducing all-cause mortality.

In both comparator-controlled (not placebo-controlled) clinical studies on patients with heart failure the tolerability of Losartan was superior to that of captopril, measured on the basis of a significantly lower rate of discontinuations of therapy on account of adverse events and a significantly lower frequency of cough.

An increased mortality was observed in ELITE II in the small subgroup (22% of all HF patients) taking beta-blockers at baseline.

Paediatric Population   
Pediatric Hypertension

The antihypertensive effect of Losartan potassium was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filration rate > 30 ml/min/1.73 m2. Patients who weighed >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg) but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.

These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increases as compared to placebo was largest in the middle dose group (6.70 mmHg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

Long-term effects of losartan on growth, puberty and general development have not been studied. The long-term efficacy of antihypertensive therapy with losartan in childhood to reduce cardiovascular morbidity and mortality has also not been established.

In hypertensive (N=60) and normotensive (N=246) children with proteinuria, the effect of losartan on proteinuria was evaluated in a 12-week placebo- and active-controlled (amlodipine) clinical study. Proteinuria was defined as urinary protein/creatinine ratio of 0.3. The hypertensive patients (ages 6 through 18 years) were randomised to receive either losartan (n=30) or amlodipine (n=30). The normotensive patients (ages 1 through 18 years) were randomised to receive either losartan (n=122) or placebo (n=124). Losartan was given at doses of 0.7 mg/kg to 1.4 mg/kg (up to maximum dose of 100 mg per day). Amlodipine was given at doses of 0.05 mg/kg to 0.2 mg/kg (up to a maximum dose of 5 mg per day).

Overall, after 12 weeks of treatment, patients receiving losartan experienced a statistically significant reduction from baseline in proteinuria of 36% versus 1% increase in placebo/amlodipine group (p 0.001). Hypertensive patients receiving losartan experienced a reduction from baseline proteinuria of -41.5% (95% CI -29.9;­51.1) versus +2.4% (95% CI -22.2; 14.1) in the amlodipine group. The decline in both systolic blood pressure and diastolic blood pressure was greater in the losartan group (-5.5/-3.8 mmHg) versus the amlodipine group (-0.1/+0.8 mmHg). In normotensive children a small decrease in blood pressure was observed in the losartan group (-3.7/­3.4 mmHg) compared to placebo. No significant correlation between the decline in proteinuria and blood pressure was noted, however it is possible that the decline in

blood pressure was responsible, in part, for the decline in proteinuria in the losartan treated group.

Long-term effects of losartan in children with proteinuria were studied for up to 3 years in the open-label safety extension phase of the same study, in which all patients completing the 12-week base study were invited to participate. A total of 268 patients entered the open-label extension phase and were re-randomized to losartan (N=134) or enalapril (N=134) and 109 patients had 3 years of follow-up (pre-specified termination point of 100 patients completing 3 years of follow-up in the extension period). The dose ranges of losartan and enalapril, given according to investigator discretion, were 0.30 to 4.42 mg/kg/day and 0.02 to 1.13 mg/kg/day, respectively. The maximum daily doses of 50 mg for <50 kg body weight and 100 mg>50 kg was not exceeded for most patients during the extension phase of the study.

In summary, the results of the safety extension show that losartan was well-tolerated and led to sustained decreases in proteinuria with no appreciable change in glomerular filtration rate (GFR) over 3 years. For normotensive patients (n=205), enalapril had a numerically greater effect compared to losartan on proteinuria (-33.0% (95%CI -47.2; -15.0) vs -16.6% (95%CI -34.9; 6.8)) and on GFR (9.4 (95%CI 0.4; 18.4) vs -4.0 (95%CI -13.1; 5.0) ml/min/1.73m2)). For hypertensive patients (n=49), losartan had a numerically greater effect on proteinuria (-44.5% (95%CI -64.8; -12.4) vs -39.5% (95%CI -62.5; -2.2)) and GFR (18.9 (95%CI 5.2; 32.5) vs -13.4 (95%CI -27.3; 0.6)) ml/min/1.73m2.

An open label, dose-ranging clinical trial was conducted to study the safety and efficacy of losartan in paediatric patients aged 6 months to 6 years with hypertension. A total of 101 patients were randomized to one of three different starting doses of open-label losartan: a low dose of 0.1 mg/kg/day (N=33), a medium dose of 0.3 mg/kg/day (N=34), or a high dose of 0.7 mg/kg/day (N=34). Of these, 27 were infants which were defined as children aged 6 months to 23 months. Study medication was titrated to the next dose level at Weeks 3, 6, and 9 for patients that were not at blood pressure goal and not yet on the maximal dose (1.4 mg/kg/day, not to exceed 100 mg/day) of losartan.

Of the 99 patients treated with study medication, 90 (90.9%) patients continued to the extension study with follow up visits every 3 months. The mean duration of therapy was 264 days.

In summary, the mean blood pressure decrease from baseline was similar across all treatment groups (change from baseline to Week 3 in SBP was -7.3, -7.6, and -6.7 mmHg for the low-, medium-, and high-dose groups, respectively; the reduction from baseline to Week 3 in DBP was -8.2, -5.1, and -6.7 mmHg for the low-, medium-, and high-dose groups.); however, there was no statistically significant dose-dependent response effect for SBP and DBP.

Losartan, at doses as high as 1.4 mg/kg, was generally well tolerated in hypertensive children aged 6 months to 6 years after 12 weeks of treatment. The overall safety profile appeared comparable between treatment groups.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes) have examined the use of combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE- inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. CV death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

**5.2 Pharmacokinetic properties**Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.

Distribution

Both losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of 14C-labeled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed. Elimination

Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6­9 hours, respectively. During once daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of 14C-labeled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58% / 50% in the faeces.

Characteristics in Patients

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.

In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers (see section 4.2 and 4.4).

Plasma concentrations of Losartan are not altered in patients with a creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for Losartan is about 2-times higher in haemodialysis dialysis patients.

The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in heamodialysis patients.

Neither Losartan nor the active metabolite can be removed by haemodialysis. Pharmacokinetics in paediatric patients

The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/ toddlers was comparatively high.

**5.3 Preclinical safety data**

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on the late foetal development, resulting in foetal death and malformations.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

**Tablet Core**

microcrystalline cellulose (E460)   
lactose monohydrate

pregelatinised maize starch   
magnesium stearate (E572)

**Film-coating**

Opadry Y-1-7000-White

* hypromellose (E464)
* titanium dioxide (E171)
* macrogol/PEG 400

**6.2 Incompatibilities**Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

Losartan potassium 12.5 mg:

Pack sizes containing 7, 10, 14, 21, 28, 30, 50, 56, 98 film-coated tablets.

Losartan potassium 25 mg/50mg/100mg:

Pack sizes containing 7, 10, 14, 28, 30, 50, 56, 98 film-coated tablets.

Alu/PVC/PE/PVDC - White opaque blister packs   
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Rudipharm Limited

Unit 6

Salbrook Road Industrial Estate

Salbrook Road

Redhill

Surrey

RH1 5GJ, UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 49565/0007

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

25/11/2022

**10 DATE OF REVISION OF THE TEXT**

22/12/2024

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1 NAME OF THE MEDICINAL PRODUCT**

Moxonidine 200 mcg film coated tablets.

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 200 micrograms of moxonidine.

Excipient with known effect

Each tablet contains 94.8 mg of lactose

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film coated tablets

Pale pink colour, round shaped, film-coated tablets, debossed with 'L' on one side and '18' on other side.

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Mild to moderate essential or primary hypertension.

**4.2 Posology and method of administration**

Posology

Adults (including the elderly):

Treatment should be started with 200 micrograms of Moxonidine in the morning. The dose may be titrated after three weeks to 400 micrograms, given as one dose or as divided doses (morning and evening) until a satisfactory response has been achieved. If the response is still unsatisfactory after a further three weeks’ treatment, the dosage can be increased up to a maximum of 600 micrograms in divided doses (morning and evening).

A single dose of 400 micrograms of Moxonidine and a daily dose of 600 micrograms in divided doses (morning and evening) should not be exceeded.

In patients with moderate renal dysfunction (GFR above 30 ml/min, but below 60 ml/min), the single dose should not exceed 200 micrograms and the daily dose should not exceed 400 micrograms of moxonidine.

Paediatric population

Moxonidine is not recommended for use in children and adolescents below 18 years due to lack of data on safety and efficacy.

Method of administration

The tablets should be taken with sufficient liquid. As the intake of food has no influence on the pharmacokinetic properties of moxonidine, the tablets may be taken before, during or after the meal.

**4.3 Contraindications**

Moxonidine should not be used in cases of:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- sick sinus syndrome or sino-atrial block

- 2nd or 3rd degree atrioventricular block

- bradycardia (below 50 beats/minute at rest)

- severe heart failure (see Section 4.4)

- severe renal dysfunction (GFR <30 ml/min, serum creatinine concentration >160 µmol/l).

**4.4 Special warnings and precautions for use**

Cases of varying degrees of AV block have been reported in the post-marketing setting in patients undergoing moxonidine treatment. Based on these case reports, the causative role of moxonidine in delaying atrioventricular conduction cannot be completely ruled out. Therefore, caution is recommended when treating patients with

a possible predisposition to developing an AV block. When moxonidine is used in patients with 1st degree AV block, special care should be exercised to avoid bradycardia. Moxonidine must not be used in higher degree AV blocks (see section 4.3)

When moxonidine is used in patients with severe coronary artery disease or unstable angina pectoris, special care should be exercised due to the fact that there is limited experience in this patient population.

Caution is advised in the administration of moxonidine to patients with renal impairment as moxonidine is excreted primarily via the kidneys. In these patients careful titration of the dose is recommended, especially at the start of therapy. Dosing should be initiated with 200 micrograms daily and can be increased to a maximum of 400 micrograms daily for patients with moderate renal impairment (GFR above 30 ml/min, but below 60 ml/min), if clinically indicated and well tolerated.

If Moxonidine is used in combination with a beta-blocker and both treatments have to be discontinued, the beta-blocker should be discontinued first and then Moxonidine after a few days.

So far, no rebound-effect has been observed on the blood pressure after discontinuing the treatment with moxonidine. However, an abrupt discontinuance of the

moxonidine treatment is not advisable; instead the dose should be reduced gradually over a period of two weeks.

Due to a lack of clinical data supporting the safety in patients with co-existing moderate heart failure, Moxonidine must be used with caution in such patients.

The elderly population may be more susceptible to the cardiovascular effects of blood pressure lowering drugs. Therefore therapy should be started with the lowest dose and dose increments should be introduced with caution to prevent the serious consequences these reactions may lead to.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

Due to a lack of data on safety and efficacy, Moxonidine should not be used in children and adolescents below 18 years of age.

**4.5 Interaction with other medicinal products and other forms of interaction**

Concurrent administration of other antihypertensive agents enhances the hypotensive effect of Moxonidine.

Since tricyclic antidepressants may reduce the effectiveness of centrally acting antihypertensive agents, it is not recommended that tricyclic antidepressants be co-administered with moxonidine.

Moxonidine can potentiate the sedative effect of tricyclic anti-depressants (avoid co-prescribing), tranquillisers, alcohol, sedatives and hypnotics.

Moxonidine moderately augmented the impaired performance in cognitive functions in subjects receiving lorazepam. Moxonidine may enhance the sedative effect of benzodiazepines when administered concomitantly.

Moxonidine is excreted through tubular excretion. Interaction with other agents that are excreted through tubular excretion cannot be excluded.

Interaction studies have only been performed in adults.

**4.6 Fertility, pregnancy and lactation**Pregnancy:

There are no adequate data from use of moxonidine in pregnant woman. Studies in animals have shown embryo-toxicological effects (see section 5.3). The potential risk for humans is unknown. Moxonidine should not be used during pregnancy unless clearly necessary.

Breast-feeding:

Moxonidine is secreted in breast milk and should therefore not be used during breast-feeding. If therapy with moxonidine is considered absolutely necessary, breast-feeding should be stopped.

**4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed.

Somnolence and dizziness have been reported. This should be borne in mind when performing these tasks.

**4.8 Undesirable effects**

Most frequent side effects reported by those taking moxonidine include dry mouth, dizziness, asthenia and somnolence. These symptoms often decrease after the first few weeks of treatment.

Undesirable Effects by System Organ Class *(observed during placebo-controlled clinical trials with n=886 patients exposed to moxonidine resulted in frequencies below):*

|  |  |  |  |
| --- | --- | --- | --- |
| **MedDRA system organ class** | **Very Common ?1/10** | **Common**  **?1/100, <1/10** | **Uncommon**  **?1/1,000, <1/100** |
| **Cardiac disorders** |  |  | Bradycardia |
| **Ear and labyrinth disorders** |  |  | Tinnitus |
| **Nervous system  disorders** |  | Headache\*,  Dizziness/Vertigo, Somnolence | Syncope\* |
| **Vascular disorders** |  |  | Hypotension\* (including orthostatic) |
| **Gastrointestinal disorders** | Dry mouth | Diarrhoea,  Nausea/Vomiting/ Dyspepsia |  |
| **Skin and subcutaneous tissue disorders** |  | Rash/ Pruritus | Angioedema |
| **General disorders and administration site reactions** |  | Asthenia | Oedema |
| **Musculoskeletal and connective tissue disorders** |  | Back pain | Neck pain |
| **Psychiatric disorders** |  | Insomnia | Nervousness |

\* there was no increase in frequency compared to placebo

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard.](http://www.mhra.gov.uk/yellowcard.)

**4.9 Overdose**

*Symptoms of overdose*

In the few cases of overdose that have been reported, a dose of 19.6mg was ingested acutely without fatality. Signs and symptoms reported included: headache, sedation, somnolence, hypotension, dizziness, asthenia, bradycardia, dry mouth, vomiting, fatigue and upper abdominal pain. In case of a severe overdose close monitoring of especially consciousness disturbances and respiratory depression is recommended.

In addition, based on a few high dose studies in animals, transient hypertension, tachycardia, and hyperglycaemia may also occur.

*Treatment of overdose*

No specific antidote is known. In case of hypotension, circulatory support such as fluids and dopamine administration may be considered. Bradycardia may be treated with atropine. -Receptor antagonists may diminish or abolish the paradoxal hypertensive effects of a moxonidine overdose.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Imidazoline receptor agonists, moxonidine, ATC code: C02AC05.

In different animal models, Moxonidine has been shown to be a potent antihypertensive agent. Available experimental data convincingly suggest that the site of the antihypertensive action of Moxonidine is the central nervous system (CNS). Within the brainstem, Moxonidine has been shown to selectively interact with I1-imidazoline receptors. These imidazoline-sensitive receptors are concentrated in the rostral ventrolateral medulla, an area critical to the central control of the peripheral sympathetic nervous system. The net effect of this interaction with the I1-imidazoline receptor appears to result in a reduced activity of sympathetic nerves (demonstrated for cardiac, splanchnic and renal sympathetic nerves).

Moxonidine differs from other available centrally acting antihypertensives by exhibiting only low affinity to central a2-adrenoceptors as compared to I1-imidazoline receptors; a2-adrenoceptors are considered the molecular target via which sedation and dry mouth, the most common undesired side effects of centrally acting antihypertensives, are mediated.

In humans, Moxonidine leads to a reduction of systemic vascular resistance and consequently in arterial blood pressure.

**5.2 Pharmacokinetic properties**

Oral moxonidine treatment of rats and dogs resulted in rapid and almost complete absorption and peak plasma levels within <0.5 hours. Average plasma concentrations were comparable in both species after p.o. and i.v. administration. The elimination half-lives of radioactivity and unchanged compound were estimated to be 1-3 hours. Moxonidine and its two main metabolites (4,5-dehydromoxonidine and a guanidine derivative) was predominantly excreted in the urine. No indication of moxonidine cumulation was observed in either species during chronic toxicity studies after 52 weeks.

In humans, about 90% of an oral dose of moxonidine is absorbed; it is not subject to first-pass metabolism and its bio-availability is 88%. Food intake does not interfere

with moxonidine pharmacokinetics. Moxonidine is 10-20% metabolised, mainly to 4,5-dehydromoxonidine and to a guanidine derivative by opening of the imidazoline ring. The hypotensive effect of 4,5-dehydromoxonidine is only 1/10, and that of the guanidine derivative is less than 1/100 of that of moxonidine. The maximum plasma levels of moxonidine are reached 30-180 minutes after the intake of a film-coated tablet.

Only about 7% of moxonidine is bound to plasma protein (VdSS = 1.8 ± 0.4 1/kg). Moxonidine and its metabolites are eliminated almost entirely via the kidneys. More than 90% of the dose is eliminated via the kidneys in the first 24 hours after administration, while only about 1% is eliminated via the faeces. The cumulative renal excretion of unchanged moxonidine is about 50-75%.

The mean plasma elimination half-life of moxonidine is 2.2-2.3 hours, and the renal elimination half-life is 2.6-2.8 hours.

**Pharmacokinetics in the elderly**

Small differences between the pharmacokinetic properties of moxonidine in the healthy elderly and younger adults are unlikely to be clinically significant. As there is no accumulation of moxonidine, dosage adjustment is unnecessary provided renal function is normal.

**Pharmacokinetics in children**

No pharmacokinetic studies have been performed in children.

**Pharmacokinetics in renal impairment**

In moderately impaired renal function (GFR 30-60ml/min), AUC increased by 85% and clearance decreased to 52%. In such patients the hypotensive effect of Moxonidine should be closely monitored, especially at the start of treatment; additionally, single doses should not exceed 200 micrograms and the daily dose should not exceed 400 micrograms.

**5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies

of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Chronic oral treatment for 52 weeks of rats (with dosages of 0.12-4mg/kg) and dogs (with dosages of 0.04-0.4mg/kg) revealed significant effects of moxonidine only at the highest doses. Slight disturbances of electrolyte balance (decrease of blood sodium and increase of potassium, urea and creatinine) were found in the high dose rats and emesis and salivation only for the high dose dogs. In addition slight increases of liver weight were obvious for both high dose species.

Reproductive toxicity studies showed no effect on fertility and no teratogenic potential. Embryo-fetal toxicity was seen at doses associated with maternal toxicity.

Increased embryo-fetal loss and delayed fetal development were seen in rats with doses above 2mg/kg/day and in rabbits with doses above 0.7mg/kg/day. In a peri- and post natal study in rats reduced pup weight, viability and delayed development was noted with doses above 1mg/kg/day.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Tablet core

Lactose Monohydrate

Crospovidone

Hydroxyl propyl cellulose

Magnesium stearate

Tablet coating

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol (E1521)

Talc (E553b)

Glycerol (E422)

Iron oxide Red (E172)

**6.2 Incompatibilities**None known

**6.3 Shelf life**

24 months

**6.4 Special precautions for storage**

Do not store above 25°C.

**6.5 Nature and contents of container**

Alu/PVC/PVdC Blister packs of 14, 28 & 84 tablets.   
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**Not applicable

**7 MARKETING AUTHORISATION HOLDER**

Noumed Life Sciences Limited,

Noumed House,

Shoppenhangers Road,   
Maidenhead, Berkshire,   
SL6 2RB, United Kingdom.

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 44041/0144

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

16/04/2024

**10 DATE OF REVISION OF THE TEXT**16/04/2024

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1 NAME OF THE MEDICINAL PRODUCT**Ramipril 1.25 mg capsules

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION** Each hard capsule contains ramipril 1.25 mg.

For the full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**Capsules, hard

Yellow/White size ‘4’ hard gelatin capsules imprinted with ‘D’ on yellow cap and ‘40’ on white body with black edible ink filled with white to almost white powder.

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**Treatment of hypertension.

- Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:

* manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or
* diabetes with at least one cardiovascular risk factor (see section 5.1). - Treatment of renal disease:
* Incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria,
* Manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor (see section 5.1),
* Manifest glomerular non diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day (see section 5.1).

- Treatment of symptomatic heart failure.

- Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction.

**4.2 Posology and method of administration**Posology

It is recommended that Ramipril is taken each day at the same time of the day. Ramipril can be taken before, with or after meals, because food intake does not modify its bioavailability (see section 5.2). Ramipril has to be swallowed with liquid. It must not be chewed or crushed.

*Adults*

Diuretic-Treated patients

Hypotension may occur following initiation of therapy with Ramipril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Ramipril (see section 4.4).

In hypertensive patients in whom the diuretic is not discontinued, therapy with Ramipril should be initiated with a 1.25 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Ramipril should be adjusted according to blood pressure target.

*Hypertension*

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control.

Ramipril may be used in monotherapy or in combination with other classes of antihypertensive medicinal products. (see Sections 4.3, 4.4, 4.5 and 5.1).

Starting dose

Ramipril should be started gradually with an initial recommended dose of 2.5 mg daily.

Patients with a strongly activated renin-angiotensin-aldosterone system may experience an excessive drop in blood pressure following the initial dose. A starting dose of 1.25 mg is recommended in such patients and the initiation of treatment should take place under medical supervision (see section 4.4).

Titration and maintenance dose

The dose can be doubled at interval of two to four weeks to progressively achieve target blood pressure; the maximum permitted dose of Ramipril is 10 mg daily. Usually the dose is administered once daily.

*Cardiovascular prevention*

Starting dose

The recommended initial dose is 2.5 mg of Ramipril once daily.

Titration and maintenance dose

Depending on the patient’s tolerability to the active substance, the dose should be gradually increased. It is recommended to double the dose after one or two weeks of treatment and - after another two to three weeks - to increase it up to the target maintenance dose of 10 mg Ramipril once daily.

See also posology on diuretic treated patients above.

*Treatment of renal disease*

*In patients with diabetes and microalbuminuria:*

Starting dose:

The recommended initial dose is 1.25 mg of Ramipril once daily. Titration and maintenance dose

Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the once daily dose to 2.5 mg after two weeks and then to 5 mg after a further two weeks is recommended.

*In patients with diabetes and at least one cardiovascular risk*

Starting dose:

The recommended initial dose is 2.5 mg of Ramipril once daily. Titration and maintenance dose

Depending on the patient’s tolerability to the active substance, the dose is subsequently increased. Doubling the daily dose to 5 mg Ramipril after one or two weeks and then to 10 mg Ramipril after a further two or three weeks is recommended. The target daily dose is 10 mg.

*In patients with non- diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day.*

Starting dose:

The recommended initial dose is 1.25 mg of Ramipril once daily. Titration and maintenance dose

Depending on the patient’s tolerability to the active substance, the dose is subsequently increased. Doubling the once daily dose to 2.5 mg after two weeks and then to 5 mg after a further two weeks is recommended.

*Symptomatic heart failure*Starting dose

In patients stabilized on diuretic therapy, the recommended initial dose is 1.25 mg daily.

Titration and maintenance dose

Ramipril should be titrated by doubling the dose every one to two weeks up to a maximum daily dose of 10 mg. Two administrations per day are preferable.

*Secondary prevention after acute myocardial infarction and with heart failure* Starting dose

After 48 hours, following myocardial infarction in a clinically and haemodynamically stable patient, the starting dose is 2.5 mg twice daily for three days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day the treatment should be withdrawn.

See also posology on diuretic treated patients above.   
Titration and maintenance dose

The daily dose is subsequently increased by doubling the dose at intervals of one to three days up to the target maintenance dose of 5 mg twice daily.

The maintenance dose is divided in 2 administrations per day where possible.

If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn. Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. Should the decision be taken to treat these patients, it is recommended that therapy be started at 1.25 mg once daily and that particular caution be exercised in any dose increase.

*Special populations*

Patients with renal impairment

Daily dose in patients with renal impairment should be based on creatinine clearance (see section 5.2):

- If creatinine clearance is ≥ 60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 10 mg;

- If creatinine clearance is between 30-60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 5 mg;

- If creatinine clearance is between 10-30 ml/min, the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg;

- In haemodialysed hypertensive patients: ramipril is slightly dialysable; the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg; the medicinal product should be administered few hours after haemodialysis is performed.

Patients with hepatic impairment (see section 5.2)

In patients with hepatic impairment, treatment with Ramipril must be initiated only under close medical supervision and the maximum daily dose is 2.5 mg Ramipril.

*Elderly* Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients. A reduced initial dose of 1.25 mg ramipril should be considered.

*Paediatric population*

The safety and efficacy of ramipril in children has not yet been established. Currently available data for Ramipril are described in sections 4.8, 5.1, 5.2 & 5.3 but no specific recommendation on posology can be made.

Method of administration   
Oral use

**4.3 Contraindications**

- Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or any other ACE (Angiotensin Converting Enzyme) inhibitors

- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)

- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)

- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney

- Second and third trimester of pregnancy (see sections 4.4 and 4.6)

- Ramipril must not be used in patients with hypotensive or haemodynamically unstable states.

- The concomitant use of Ramipril with aliskiren-containing products I s contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see Sections 4.5 and 5.1).

- Concomitant use with sacubitril/valsartan therapy. Ramipril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

**4.4 Special warnings and precautions for use***Special populations*

* *Pregnancy*: ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).
* *Patients at particular risk of hypotension*

*- Patients with strongly activated renin-angiotensin-aldosterone system*

Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.

Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:

- Patients with severe hypertension

- Patients with decompensated congestive heart failure

- Patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)

- Patients with unilateral renal artery stenosis with a second functional kidney

- Patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)

- Patients with liver cirrhosis and/or ascites

- Patients undergoing major surgery or during anaesthesia with agents that produce hypotension.

Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

*Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Section 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this

should only occur under specialist supervision and subject to frequent

close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly

in patients with diabetic nephropathy.

*- Transient or persistent heart failure post MI*

*- Patients at risk of cardiac or cerebral ischemia in case of acute hypotension*

The initial phase of treatment requires special medical supervision.

*Elderly* See section 4.2.

*Surgery*

It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

*Monitoring of renal function*

Renal function should be assessed before and during treatment and dosage adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment (see section 4.2).

There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

*/Angioedema*

Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of ramipril. Treatment with ramipril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (mammalian target of rapamycin) (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril). in a patient already taking an ACE inhibitor.

In case of angioedema, Ramipril must be discontinued.

Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms. Intestinal angioedema has been reported in patients treated with ACE inhibitors including Ramipril (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).

*Anaphylactic reactions during desensitization*

The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of Ramipril should be considered prior to desensitization.

*Serum potassium*

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

*Electrolyte Monitoring: Hyponatraemia*

Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with ramipril. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

*Neutropenia/agranulocytosis*

Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopoenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture (see sections 4.5 and 4.8).

*Ethnic differences*

ACE inhibitors cause higher rate of angioedema in black patients than in non black patients. As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black people than in non black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

*Cough*

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Excipients

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say

essentially ‘sodium-free’.

**4.5 Interaction with other medicinal products and other forms of interaction**

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see Sections 4.3, 4.4 and 5.1).

Contra-indicated combinations

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections 4.3 and 4.4). Treatment with ramipril must not be started until 36 hours after taking the last dose of sacubitril/valsartan. Sacubitril/valsartan must not be started until 36 hours after the last dose of Ramipril

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Precautions for use

Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin):

Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics)

Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of ramipril.

Blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count:

Increased likelihood of haematological reactions (see section 4.4).

*Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes*

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with ramipril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when ramipril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of ramipril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

*Ciclosporin*

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

*Heparin*

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

*Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin):* Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics)

*Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of* Ramipril: Blood pressure monitoring is recommended.

*Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count:* Increased likelihood of haematological reactions (see section 4.4).

*Lithium salts:* Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.

*Antidiabetic agents including insulin:* Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

*Non-steroidal anti-inflammatory drugs and acetylsalicylic acid:* Reduction of the antihypertensive effect of Ramipril is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.

**Medicines increasing the risk of angioedema**

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this

increases the risk of angioedema (see section 4.3 and 4.4).

*Neprilysin (NEP) inhibitors:*

An increased risk of angioedema has been reported with concomitant use of

ACE inhibitors and with NEP inhibitor such as racecadotril, (see section 4.4).

*mTOR inhibitors*

An increased risk of angioedema is possible in patients taking concomitant medications such as mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema. Caution should be used when starting therapy (see section 4.4).

**4.6 Fertility, Pregnancy and lactation   
Pregnancy:**

Ramipril is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3). d

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. ACE inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

**Breast-feeding:**

Because insufficient information is available regarding the use of ramipril during breastfeeding (see section 5.2), ramipril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

**4.7 Effects on ability to drive and use machines**

Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient’s ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

**4.8 Undesirable effects***Summary of safety profile*

The safety profile of ramipril includes persistent dry cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/ agranulocytosis.

*Tabulated list of adverse reactions*

Adverse reactions frequency is defined using the following convention: Very common (? 1/10); common (? 1/100 to < 1/10); uncommon (? 1/1,000 to < 1/100); rare (? 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Common | Uncommon | Rare | Very rare | Not known |
| *Cardiac* |  | Myocardial |  |  |  |
| *disorders* |  | ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral |  |  |  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Blood and lymphatic system disorders* |  | Eosinophilia | White blood cell count decreased (including neutropenia or agranulocyto sis) , red blood cell count decreased, haemoglobin decreased, platelet count decreased |  | Bone marrow failure, pancytopeni a, haemolytic anaemia |
| *Nervous  system  disorders* | Headache,  dizziness | Vertigo, paraesthesia, ageusia, dysgeusia, | Tremor,  balance  disorder |  | Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomoto r skills impaired, burning sensation, parosmia |
| *Eye disorders* |  | Visual disturbance including blurred vision | Conjunctiviti s |  |  |
| *Ear and  labyrinth  disorders* |  |  | Hearing impaired, tinnitus |  |  |
| *Respiratory, thoracic and mediastinal disorders* | Non-  productive  tickling  cough,  bronchitis,  sinusitis,  dyspnoea | Bronchospas m including asthma aggravated, nasal congestion |  |  |  |
| *Gastrointestin  a l disorders* | Gastrointestin al inflammation, digestive | Pancreatitis (cases of fatal outcome | Glossitis |  | Aphtous  stomatitis |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | disturbances, abdominal | have been  very |  |  |  |
|  | discomfort, dyspepsia, diarrhoea, nausea, vomiting | exceptionall y reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth |  |  |  |
| *Renal and* |  | Renal |  |  |  |
| *urinary* |  | impairment |  |  |  |
| *disorders* |  | including renal failure acute, urine output increased, worsening of a pre­existing proteinuria, blood urea increased, blood creatinine increased |  |  |  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Skin and subcutaneous tissue disorders* | Rash in  particular  maculo-  papular | Angioedema ;  very exceptionall y, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosi s | Exfoliative  dermatitis,  urticaria, onycholysis, | Photosensiti  vity reaction | Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform , pemphigoid or lichenoid exanthema or enanthema, alopecia |
| *Musculoskelet al and connective tissue disorders* | Muscle  spasms,  myalgia | Arthralgia |  |  |  |
| *Metabolism and nutrition disorders* | Blood potassium increased | Anorexia, decreased appetite, |  |  | Blood  sodium  decreased |
| *Vascular  disorders* | Hypotension, orthostatic blood pressure decreased, syncope | Flushing | Vascular stenosis, hypoperfusio n, vasculitis |  | Raynaud’s  phenomeno n |
| *General disorders and administratio n site conditions* | Chest pain, fatigue | Pyrexia | Asthenia |  |  |
| *Immune  system  disorders* |  |  |  |  | Anaphylacti  c  or  anaphylactoi  d reactions, antinuclear antibody increased |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Endocrine  disorders* |  |  |  |  | Syndrome of inappropriate antidiuretic hormone secretion (SIADH) |
| *Hepatobiliary disorders* |  | Hepatic enzymes and/or bilirubin conjugated increased, | Jaundice cholestatic, hepatocellula r damage |  | Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional) . |
| *Reproductive system and breast disorders* |  | Transient erectile impotence, libido decreased |  |  | Gynaecoma stia |
| *Psychiatric  disorders* |  | Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence | Confusional state |  | Disturbance  in attention |

Paediatric Population

The safety of ramipril was monitored in 325 children and

adolescents, aged 2-16 years old during 2 clinical trials. Whilst   
the nature and severity of the adverse events are similar to that of   
the adults, the frequency of the following is higher in the children:

* Tachycardia, nasal congestion and rhinitis, "common" (ie, ? 1/100 to < 1/10) in paediatric, and "uncommon" (i.e. ? 1/1,000 to < 1/100) in adult population.
* Conjunctivitis "common" (ie, ? 1/100 to < 1/10) in paediatric while "rare” (i.e. ? 1/10,000 to < 1/1,000) in adult population.
* Tremor and urticaria "uncommon" (.ie. ? 1/1,000 to < 1/100) in paediatric population while "rare" (i.e. ? 1/10,000 to < 1/1,000) in adult population.

The overall safety profile for ramipril in paediatric patients does

not differ significantly from the safety profile in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme

Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

**4.9 Overdose**

Symptoms

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Treatment

The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: ACE Inhibitors, plain, ATC code C09AA05. Mechanism of action

Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE

inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

Pharmacodynamic effects   
Antihypertensive properties:

Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.

The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.

Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Heart failure:

In addition to conventional therapy with diuretics and optional cardiac glycosides, ramipril has been shown to be effective in patients with functional classes II-IV of the New-York Heart Association. The drug had beneficial effects on cardiac haemodynamics (decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index). It also reduced neuroendocrine activation.

Clinical efficacy and safety

Cardiovascular prevention/Nephroprotection;

A preventive placebo-controlled study (the HOPE-study), was carried out in which ramipril was added to standard therapy in more than 9,200 patients. Patients with increased risk of cardiovascular disease following either atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral vascular disease) or diabetes mellitus with at least one additional risk factor (documented microalbuminuria, hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol level or cigarette smoking) were included in the study.

The study showed that ramipril statistically significantly decreases the incidence of myocardial infarction, death from cardiovascular causes and stroke, alone and combined (primary combined events).

**The HOPE study: Main results**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Ramipril | Placebo | relative risk (95% confidence interval) | p-value |
| % | % |
| **All patients** | **n=4,645** | **N=4,652** |  |  |
| **Primary**  **combined events** | **14.0** | **17.8** | **0.78 (0.70-0.86)** | **<0.001** |
| *Myocardial infarction* | *9.9* | *12.3* | *0.80 (0.70-0.90)* | *<0.001* |
| *Death from cardiovascular causes* | *6.1* | *8.1* | *0.74 (0.64-0.87)* | *<0.001* |
| *Stroke* | *3.4* | *4.9* | *0.68 (0.56-0.84)* | *<0.001* |
| **Secondary endpoints** |  |  |  |  |
| *Death from any cause* | 10.4 | 12.2 | *0.84 (0.75-0.95)* | *0.005* |
| *Need for*  *Revascularisation* | 16.0 | 18.3 | *0.85 (0.77-0.94)* | *0.002* |
| *Hospitalisation for unstable angina* | 12.1 | 12.3 | *0.98 (0.87-1.10)* | *NS* |
| *Hospitalisation for heart failure* | 3.2 | 3.5 | *0.88 (0.70-1.10)* | *0.25* |
| *Complications related to diabetes* | 6.4 | 7.6 | *0.84 (0.72-0.98)* | *0.03* |

The MICRO-HOPE study, a predefined substudy from HOPE, investigated the effect of the addition of ramipril 10 mg to the current medical regimen versus placebo in 3,577 patients at least ? 55 years old (with no upper limit of age), with a majority of type 2 diabetes (and at least another CV risk factor), normotensive or hypertensive.

The primary analysis showed that 117 (6.5 %) participants on ramipril and 149 (8.4 %) on placebo developed overt nephropathy, which corresponds to a RRR 24 %; 95 % CI [3-40], p = 0.027. The REIN study, a multicenter randomized, double-blind parallel group, placebo-controlled study aimed at assessing the effect of treatment with ramipril on the rate of decline of glomerular function rate (GFR) in 352 normotensive or hypertensive patients (18-70 years old) suffering from mild (i.e. mean urinary protein excretion > 1 and < 3 g/24 h) or severe proteinuria (? 3 g/24 h) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.

The main analysis of patients with the most severe proteinuria (stratum prematurely disrupted due to benefit in ramipril group) showed that the mean rate of GFR decline per month was lower with ramipril than with placebo; - 0.54 (0.66) vs. -0.88 (1.03) ml/min/month, p = 0.038. The intergroup difference was thus 0.34 [0.03-0.65] per month, and around 4 ml/min/year; 23.1 % of the patients in the ramipril group reached the combined secondary endpoint of doubling of baseline serum creatinine concentration and/or end-stage renal disease (ESRD) (need for dialysis or renal transplantation) vs. 45.5 % in the placebo group (p = 0.02).

*Dual blockade of the renin-angiotensin-aldosterone system (RAAS):*

Two large randomised, controlled trials (ONTARGET (Ongoing

Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes) have examined the use of combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy. These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed.

Given their similar pharmacodynamic properties, these results are also relevant for other ACE- inhibitors and angiotensin II receptor blockers. ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. CV death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Secondary prevention after acute myocardial infarction

The AIRE study included more than 2,000 patients with transient/persistent clinical signs of heart failure after documented myocardial infarction. The ramipril treatment was started 3 to 10 days after the acute myocardial infarction. The study showed that after an average follow-up time of 15 months the mortality in ramipril-treated patients was 16.9 % and in the

placebo treated patients was 22.6 %. This means an absolute mortality reduction of 5.7 % and a relative risk reduction of 27 % (95 % CI [11-40 %]).

*Paediatric Population*

In a randomized, double-blind, placebo-controlled clinical study involving 244 paediatric patients with hypertension (73% primary hypertension), aged 6-16 years, patients received either low dose, medium dose or high dose of ramipril to achieve plasma concentrations of ramiprilat corresponding to the adult dose range of 1.25 mg, 5 mg and 20 mg on the basis of body weight. At the end of 4 weeks, ramipril was ineffective in the endpoint of lowering systolic blood pressure but lowered diastolic blood pressure at the highest dose. Both medium and high doses of ramipril showed significant reduction of both systolic and diastolic BP in children with confirmed hypertension.

This effect was not seen in a 4 weeks dose-escalation, randomized, double-blind withdrawal study in 218 paediatric patients aged 6-16 years (75% primary hypertension), where both diastolic and systolic blood pressures demonstrated a modest rebound but not a statistically significant return to the baseline, in all three dose levels tested low dose (0.625 mg – 2.5 mg), medium dose (2.5 mg – 10 mg) or high dose (5mg – 20 mg) ramipril based on weight.. Ramipril did not have a linear dose response in the paediatric population studied.

**5.2 Pharmacokinetic properties***Pharmacokinetics and Metabolism*

Absorption

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 mg and 5 mg ramipril is 45 %.

Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake. Steady state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Distribution

The serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

Biotransformation

Ramipril is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat.

Elimination

Excretion of the metabolites is primarily renal.

Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations.

After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.

A single oral dose of ramipril produced an undetectable level of ramipril and its metabolite in breast milk. However the effect of multiple doses is not known.

*Patients with renal impairment (see section 4.2)*

Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

*Patients with hepatic impairment (see section 4.2)*

In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed, due to diminished activity of hepatic esterases, and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

*Lactation*

A single oral dose of ramipril produced an undetectable level of ramipril and its metabolite in breast milk. However the effect of multiple doses is not known.

*Paediatric Population*

The pharmacokinetic profile of ramipril was studied in 30 paediatric hypertensive patients, aged 2-16 years, weighing >10 kg. After doses of 0.05 to 0.2 mg/kg, ramipril was rapidly and extensively metabolized to ramiprilat. Peak plasma concentrations of ramiprilat occurred within 2-3 hours. Ramiprilat clearance highly correlated with the log of body weight (p<0.01) as well as dose (p<0.001).

Clearance and volume of distribution increased with increasing children age for each dose group. The dose of 0.05 mg /kg in children achieved exposure levels comparable to those in adults treated with ramipril 5mg. The dose of 0.2 mg/kg in children resulted in exposure levels higher than the maximum recommended dose of 10 mg per day in adults.

**5.3 Preclinical safety data**

Oral administration of ramipril has been found to be devoid of acute toxicity in rodents and dogs. Studies involving chronic oral administration have been conducted in rats, dogs and monkeys. Indications of plasma electrolyte shifts and changes in blood picture have been found in the 3 species. As an expression of the pharmacodynamic activity of ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d. Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects.

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties.

Fertility was not impaired either in male or in female rats.

The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.

Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties.

Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients***Capsule Fill:*

Hydrophobic colloidal anhydrous silica   
Pregelatinized starch (maize)

*Capsule Shell:*

Gelatin

Sodium lauryl sulfate

Iron oxide yellow (E172)

Titanium dioxide (E171)

*Printing Ink:*

Shellac

Propylene glycol

Black iron oxide (E172)

Potassium hydroxide

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Do not store above 25° C.

Keep the blister in the outer carton. Keep the container tightly closed. Store in the original package to protect from moisture.

**6.5 Nature and contents of container**

Ramipril capsules are available in Clear PVC/ PE/ PVdC- Aluminium blister pack and white opaque HDPE bottle pack.

*Pack size:*

Blister pack: 7, 10, 14, 20, 21, 28, 30, 42, 50, 56, 60, 90, 98 & 100 capsules

Bottle pack: 30, 100, 500 & 1000 capsules

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**No special requirements

**7 MARKETING AUTHORISATION HOLDER** Milpharm Limited

Ares, Odyssey Business Park

West End Road

South Ruislip HA4 6QD

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)** PL 16363/0355

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

23/11/2011

**10 DATE OF REVISION OF THE TEXT**

08/01/2025

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1 NAME OF THE MEDICINAL PRODUCT**

Spironolactone 25mg Tablets.

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**Each tablet contains 25mg of spironolactone.

Spironolactone 25mg Tablets contain 52.95mg of lactose

For the full list of excipients, see section 6.1

**3 PHARMACEUTICAL FORM**

Tablet.

Buff coloured biconvex film coated tablet marked 25 on one side and BL on the reverse

**4 CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Spironolactone is indicated in

1. Hepatic cirrhosis with ascites and oedema
2. Malignant ascites
3. Nephrotic syndrome
4. Diagnosis and treatment of primary aldosteronism
5. Congestive heart failure

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

**4.2 Posology and method of administration***Posology*

Spironolactone Tablets should always be administered with fluid and preferably with food to aid absorption.

**Adults**:

**Hepatic cirrhosis with ascites and oedema:**

If urinary Na+/K+ ratio is greater than 1.0, 100mg/day. If the ratio is less than 1.0,

200mg/day to 400mg/day. Maintenance dosage should be individually determined.

**Malignant ascites**

Initial dose is usually 100mg/day to200mg/day. In severe cases the dosage may be gradually increased up to 400mg/day. When oedema is controlled, maintenance dosage should be individually determined.

**Nephrotic syndrome**

Usually dose 100mg/day to 200mg/day. Spironolactone has not been shown to be anti-

inflammatory, nor to affect the basic pathological process. Its use is only advised if glucocorticoids by themselves are insufficiently effective.

**Congestive heart failure with oedema**

For management of oedema an initial daily dose of 100 mg of spironolactone administered in either single or divided doses is recommended, but may range from 25 mg to 200 mg daily. Maintenance dose should be individually determined.

**Severe heart failure (New York Heart Association Class III-IV)**

Based on the Randomized Aldactone Evaluation Study (RALES: see also section 5.1), treatment in conjunction with standard therapy should be initiated at a dose of spironolactone 25 mg once daily if serum potassium is 5.0 mEq/L and serum creatinine is 2.5 mg/dL. Patients who tolerate 25 mg once daily may have their dose increased to 50 mg once daily as clinically indicated. Patients who do not tolerate 25 mg once daily may have their dose reduced to 25 mg every other day. See section 4.4 for advice on monitoring serum potassium and serum creatinine.

**Diagnosis and treatment of primary aldosteronism**

Spironolactone may be employed as an initial diagnostic measure to provide presumptive

evidence of primary hyperaldosteronism while patients are on normal diets.

*Long Test* – Spironolactone is administered at a daily dosage of 400mg for 3 to 4 weeks. Correction of hypokalaemia and hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

*Short test* - Spironolactone is administered at a daily dosage of 400mg for 4 days. If serum potassium increases during spironolactone administration but drops when spironolactone is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

After diagnosis of hyperaldosteronism has been established by more definitive testing procedures, spironolactone may be administered in doses of 100mg/day to 400mg/day in preparation for surgery. For patients who are considered unsuitable for surgery, spironolactone may be employed for long-term maintenance therapy at lowest effective dosage determined for the individual patient.

**Elderly**

It is recommended that treatment should be started with the lowest dose and titrated upwards as required to achieve maximum benefit. Care should be taken in severe hepatic and renal impairment which may alter drug metabolism and excretion.

**Paediatric population**

Initial daily dosage should provide 1-3mg of spironolactone per kg bodyweight given in divided doses. Dosage should be adjusted on the basis of response and tolerance (see sections 4.3 and 4.4). If necessary the tablets may be crushed and taken dispersed in food or drink.

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

*Method of Administration*

For oral administration.

Administration of Spironolactone tablets once daily with a meal is recommended.

**4.3 Contraindications**

Spironolactone is contraindicated in adult and paediatric patients with the following:

* Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
* Acute renal insufficiency, significant renal compromise, anuria.
* Hyperkalaemia
* Addison’s disease.
* Concomitant use of eplerenone or other potassium sparing diuretics.

Spironolactone is contraindicated in paediatric patients with moderate to severe renal impairment.

Spironolactone tablets should not be administered concurrently with other potassium

conserving diuretics and potassium supplements should not be given routinely with Spironolactone tablets as hyperkalaemia may be induced.

**4.4 Special warnings and precautions for use   
Fluid and electrolyte balance**

Fluid and electrolyte status be regularly monitored particularly in the elderly and in those with significant renal and hepatic impairment.

Hyperkalaemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Should hyperkalaemia develop, Spironolactone should be discontinued, and if necessary, active measures taken to reduce the serum potassium to normal (section 4.3).

Reversible hyperchloraemic metabolic acidosis, usually in association with hyperkalaemia has been reported to occur in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.

Concomitant use of spironolactone with other potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin or other drugs or conditions known to cause hyperkalaemia, potassium supplements, a diet rich in potassium or salt substitutes containing potassium, may lead to severe hyperkalaemia.

**Urea**

Reversible increases in blood urea have been reported in association with Spironolactone therapy, particularly in the presence of impaired renal function.

**Hyperkalaemia in Patients with Severe Heart Failure**

Hyperkalaemia may be fatal. It is critical to monitor and manage serum potassium in patients with severe heart failure receiving spironolactone. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium >3.5 mEq/L. The recommended monitoring for potassium and creatinine is 1 week after initiation or increase in dose of spironolactone, monthly for the first 3 months,

then quarterly for a year, and then every 6 months. Discontinue or interrupt treatment for serum potassium >5 mEq/L or for serum creatinine >4 mg/dL. (see section 4.2).

Caution is required in severely ill patients and those with relatively small urine volumes who are at greater risk of developing hyperkalaemia.

Caution is required in patients with a predisposition to metabolic or respiratory acidosis. Acidosis potentiates the hyperkalaemic effects of spironolactone and spironolactone may potentiate acidosis.

Spironolactone has been shown to produce tumours in rats when administered at high doses over a long period of time. The significance of these findings with respect to clinical use is not certain. However, the long-term use of spironolactone in young patients requires careful consideration of the benefits and the potential hazard involved.

Caution should be exercised in patients diagnosed with porphyria as Spironolactone is considered unsafe in these patients.

Care should be taken in patients suffering from menstrual abnormalities or breast enlargement.

**Paediatric population**

Potassium-sparing diuretics should be used with caution in hypertensive paediatric patients with mild renal insufficiency because of the risk of hyperkalaemia. (Spironolactone is contraindicated for use in paediatric patients with moderate or severe renal impairment; see section 4.3).

**Acute Respiratory Toxicity**

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking Spironolactone. Pulmonary oedema typically develops within minutes to hours after Spironolactone intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Spironolactone should be withdrawn and appropriate treatment given. Spironolactone should not be administered to patients who previously experienced ARDS following Spironolactone intake.

**Important information regarding the ingredients of spironolactone tablet**

Lactose - Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium - This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

**4.5 Interaction with other medicinal products and other forms of interaction**

Concomitant use of drugs known to cause hyperkalaemia with spironolactone may result in severe hyperkalaemia. In addition, concomitant use of trimethoprim/ sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

**ACE inhibitors – since ACE inhibitors** decrease aldosterone production and they should not routinely be used with spironolactone, particularly in patients with marked renal impairment. Concomitant use of Spironolactone with ACE-inhibitors may lead to severe hyperkalaemia, particularly in patients with renal failure. Spironolactone may also have an enhanced hypotensive effect when administered concomitantly with ACE-inhibitors.

**Angiotensin-II receptor antagonists** - concurrent administration of angiotensin-II receptor antagonists, e.g. valsartan, losartan, and spironolactone may result in an increase in serum potassium levels. If concurrent use is necessary, monitor serum potassium levels.

**Cardiac glycosides** - Spironolactone has been reported to increase serum digoxin concentration and to interfere with certain serum digoxin assays. In patients receiving digoxin and spironolactone the digoxin response should be monitored by means other than serum digoxin concentrations, unless the digoxin assay used has been proven not to be affected by spironolactone therapy. If it proves necessary to adjust the dose of digoxin patients should be carefully monitored for evidence of enhanced or reduced digoxin effect. Spironolactone has been shown to increase the half-life of digoxin.

**Anti-hypertensive agents** - Potentiation of the effect of antihypertensive drugs occurs and their dosage may need to be reduced when Spironolactone is added to the treatment regime and then adjusted as necessary. Since ACE inhibitors decrease aldosterone production they should not routinely be used with spironolactone, particularly in patients with marked renal impairment.

**Anti-diabetics** - Administration with chlorpropamide may increase risk of hyponatraemia.

**Aspirin** may reduce the diuretic effect of Spironolactone

**Ciclosporin** – Co-administration of potassium sparing diuretics with ciclosporin may result in hyperkalaemia. Avoid concurrent use of spironolactone and ciclosporin. If concurrent therapy is necessary, monitor serum potassium levels for persistent elevations in patients.

**Potassium salts-** potassium supplements are contraindicated except in cases of initial potassium depletion. If potassium supplementation is considered essential, serum electrolytes should be monitored.

**Ulcer-healing drugs** - as carbenoxolone may cause sodium retention and thus decrease the effectiveness of Spironolactone, concurrent use should be avoided.

**Non-steroidal anti-inflammatory drugs** such as aspirin, indomethacin, and mefenamic acid may attenuate the natriuretic efficacy of diuretics, due to inhibition of intrarenal synthesis of prostaglandins and have been shown to attenuate the diuretic effect of spironolactone. There may be an increased risk of nephrotoxicity and hyperkalaemia when NSAIDs, notably/particularly Indometacin are used with Spironolactone. Indometacin and mefenamic acid inhibit the excretion of canrenone reducing the diuretic effect. Spironolactone enhances the metabolism of antipyrine.

**Sympathomimetics** - Spironolactone reduces vascular responsiveness to noradrenaline. Caution should be exercised in the management of patients subjected to regional or general anaesthesia while they are being treated with Spironolactone.

**Corticosteroids** - co-administration of Spironolactone with fludrocortisone may result in a paradoxical dose- related increase in urinary potassium excretion. If concomitant administration is necessary, closely monitor serum potassium levels.

**Diuretics** - Spironolactone should not be administered concurrently with other potassium-conserving diuretics as this may induce hyperkalaemia. Potassium canrenoate, a metabolite of Spironolactone, has been shown to cause myeloid leukaemia in rats.

**In fluorimetric assays**, spironolactone may interfere with the estimation of compounds with similar fluorescence characteristics.

**Lithium** - concurrent use of lithium and Spironolactone may result in increased lithium concentrations and lithium toxicity (weakness, tremor, excessive thirst and confusion) due to decreased lithium excretion. If concomitant therapy is necessary, monitor serum lithium levels within the first 5-7 days of adding or discontinuing Spironolactone and periodically thereafter. Lower lithium doses may be required with concomitant Spironolactone therapy.

**Tacrolimus** - Spironolactone should not be used in patients receiving tacrolimus due to risk of mild to severe hyperkalaemia.

**Liver function tests** - Spironolactone may enhance the metabolism of antipyrine used in liver functions tests.

**Cancer medication** – avoidance of Spironolactone recommended if receiving Mitotane treatment

**Colestyramine** - reports of hyperchloraemic metabolic acidosis

Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels in abiraterone-treated prostate cancer patients. Use with abiraterone is not recommended.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

Spironolactone or its metabolites may cross the placental barrier. The use of

Spironolactone in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the mother and foetus.

There are limited data from the use of spironolactone in pregnant women. Studies in animals have shown reproductive toxicity associated with the anti-androgenic effect of spironolactone (see Section 5.3).

Diuretics can lead to reduced perfusion of the placenta and thus to impairment of intrauterine growth and are therefore not recommended for the standard therapy for hypertension and oedema during pregnancy.

Spironolactone should not be used during pregnancy, unless the potential benefit justifies the potential risk.

**Breast-feeding**

Canrenone (a major and active) metabolites of spironolactone have been detected in breast milk. If use of spironolactone is considered essential, an alternative method of infant feeding should be instituted.

There is insufficient information on the effects of spironolactone in newborns/infants.

Spironolactone should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from spironolactone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

**Fertility**

Feminisation has been observed in male rat foetuses with spironolactone therapy.

Spironolactone administered to female mice reduced fertility (see Section 5.3).

**4.7 Effects on ability to drive and use machines**

Somnolence and dizziness have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

**4.8 Undesirable effects**

Gynaecomastia may develop in association with the use of spironolactone. Development appears to be related to both dosage level and duration of therapy and is normally reversible when the drug is discontinued. In rare instances some breast enlargement may persist.

The following adverse events have been reported in association with spironolactone therapy:

Leukope

n (Agranul Eosinoph Thrombo

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| System Organ  Class | Very common  ( 1/10) | Common  1/100 to  <1/10 | Uncommon 1/1000 to  <1/100 | Rare  1/10000 to  <1/1000 | Very Rare  <1/10000 | Frequenc known ( estimated available |
| ***Neoplasms benign, malignant and unspecified (including cysts and polyps)*** |  |  | Benign breast neoplasms (male) |  |  |  |
| ***Blood and***  ***lymphatic  system***  ***disorders*** |  |  |  | Elevation in  blood urea  nitrogen (BUN) |  |  |
| ***Metabolism***  ***and nutrition  disorders*** | Hyperkalaemia |  | Electrolyte imbalance | Hyponatraemia, Hyperkalaemia |  |  |
| ***Psychiatric disorders*** |  | Confusional  state |  |  |  | Lethargy disorder |
| ***Nervous system disorders:*** |  | Dizziness | Ataxia, drowsiness, headache, clumsiness |  |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***Respiratory,***  ***thoracic and  mediastinal disorder*** |  |  |  |  | Acute respiratory distress syndrome (ARDS) (see section 4.4) |  |
| ***Gastrointestinal disorders*** |  | Nausea |  |  |  | Gastroint disorders Gastritis, bleeding, gastroint disturban stomach |
| ***Hepatobiliary disorders*** |  |  | Hepatic function abnormal |  |  | Hepatoto |
| ***Skin and***  ***subcutaneous tissue disorder*** |  | Pruritus, Rash | Urticaria |  |  | Toxic necrolysi Stevens-J syndrom reaction eosinoph systemic symptom (DRESS) Alopecia Hypertric Pemphig |
| ***Musculo-  skeletal and  Connective  tissue  disorders*** |  | Muscle spasms |  |  |  | Leg cram Osteoma |
| ***Renal and  urinary  disorders*** |  | Acute Kidney  injury |  |  |  |  |
| ***Reproductive system and breast disorders*** |  | Gynaecomastia,  Breast  pain  (male)a | Menstrual disorder, Breast pain (female)b | Breast  enlargement,  Alteration in  voice pitch,  which may not  be reversible, |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | impotence and decreased sexual ability |  |  |
| ***General disorders***  ***and***  ***administration site conditions*** |  | Malaise |  |  |  |  |

Abbreviations: CDS = Core Data Sheet; F = female; LLT = lower level term;

M = male; PT = preferred term; WHO-ART = World Health Organization Adverse Drug Reaction Terminology.

a The term Breast pain is mapped from CDS and the frequency is derived from WHO-ART term Breast pain (M); however, Breast pain male is the LLT.

b Breast pain is the PT from CDS, and the frequency is derived from WHO-ART term Breast pain (F).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

**4.9 Overdose**

**Symptoms**:

Acute overdosage may be manifested by drowsiness, mental confusion, nausea, vomiting, dizziness or diarrhoea. Hyperkalaemia or hyponatraemia may be induced, but these effects are unlikely to be associated with acute overdosage.

Symptoms of hyperkalaemia may manifest as paraesthesia, muscular weakness, flaccid paralysis or muscle spasm and may be difficult to distinguish clinically from hypokalaemia. Electrocardiographic changes are the earliest specific signs of potassium disturbances.

**Treatment**: No specific antidote has been identified. Improvement may be expected on after withdrawal of the drug.

General supportive measures including replacement of fluids and electrolytes may be indicated. For hyperkalaemia, reduce potassium intake, administer potassium-excreting diuretics, intravenous glucose with regular insulin or oral ion - exchange resins.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: potassium-sparing agents, ATC code C03DA01 **Mechanism of action**

Spironolactone, as a competitive aldosterone antagonist, increases sodium excretion whilst reducing potassium loss at the distal renal tubule. It has a gradual and prolonged action.

**Clinical Efficacy and Safety**

**Severe Heart Failure**

RALES was a multinational, double-blind study in 1663 patients with an ejection fraction

of 35%, a history of NYHA Class IV heart failure within 6 months, and Class III-IV heart failure at the time of randomization. All patients were taking a loop diuretic, 97% were taking an ACE inhibitor and 78% were on digoxin (at the time this trial was conducted, b-blockers were not widely used to treat heart failure and only 15% were treated with a b-blocker). Patients with a baseline serum creatinine of >2.5 mg/dL or a recent increase of 25% or with a baseline serum potassium of >5.0 mEq/L were excluded. Patients were randomized 1:1 to spironolactone 25 mg orally once daily or matching placebo. Patients who tolerated 25 mg once daily had their dose increased to 50 mg once daily as clinically indicated. Patients who did not tolerate 25 mg once daily had their dosage reduced to 25 mg every other day. The primary endpoint for RALES was time to all-cause mortality. RALES was terminated early, after a mean follow-up of 24 months, because of significant mortality benefit detected on a planned interim analysis. Spironolactone reduced the risk of death by 30% compared to placebo (p<0.001; 95% confidence interval 18% - 40%). Spironolactone also significantly reduced the risk of cardiac death, primarily sudden death and death from progressive heart failure as well as the risk of hospitalization for cardiac causes. Changes in NYHA class were more favorable with spironolactone. Gynaecomastia or breast pain was reported in 10% of men who were treated with spironolactone, as compared with 1% of men in the placebo group (p<0.001). The incidence of serious hyperkalaemia was low in both groups of patients.

**Paediatric population**

There is a lack of substantive information from clinical studies on spironolactone in children. This is a result of several factors: the few trials that have been performed in the paediatric population, the use of spironolactone in combination with other agents, the small numbers of patients evaluated in each trial and the different indications studied. The dosage recommendations for paediatrics are based upon clinical experience and case studies documented in the scientific literature.

**5.2 Pharmacokinetic properties**

**Absorption**: Spironolactone is incompletely but fairly rapidly absorbed from the gastrointestinal tract and the extent of absorption will depend on the particle size and formulation and is improved after food. Bioavailability is estimated from 60 to 90%. Time to peak plasma concentration is approximately one hour.

**Distribution**: Although the plasma half-life of Spironolactone itself is short (1.3 hours) the half-lives of the active metabolites are longer (ranging from 2.8 to 11.2 hours). Spironolactone is estimated to be 90% protein bound. Volume of distribution, extent of tissue accumulation and ability to cross the blood brain barrier are not known. Spironolactone or its metabolites may cross the placental barrier and canrenone is secreted in breast milk. Spironolactone is known to have a slow onset of action (two to three days), and a slow diminishment of action.

**Biotransformation:** The main site of biotransformation is the liver where it is metabolised, to 80% sulphur containing metabolites such as 7 alpha-thiomethylspironolactone and canrenone (20%). Many of these metabolites also have a diuretic- activity. Canrenone, which is an active metabolite, has a biphasic plasma half-life of about 4-17 hours.

Elimination: Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (tmax), peak plasma concentration (Cmax), and elimination half-life (t1/2) for spironolactone is 2.6 hr., 80 ng/ml, and approximately 1.4 hr., respectively. For the 7-alpha-(thiomethyl) spironolactone and canrenone metabolites, tmax was 3.2 hr. and 4.3 hr., Cmax was 391 ng/ml and 181 ng/ml, and t1/2 was 13.8 hr. and 16.5 hr., respectively.

The renal action of a single dose of Spironolactone reaches its peak after 7 hours, and activity persists for at least 24-hours. Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

**Paediatric population**

There are no pharmacokinetic data available in respect of use in paediatric population. The dosage recommendations for paediatrics are based upon clinical experience and case studies documented in the scientific literature.

**5.3 Preclinical safety data**

**Carcinogenicity**: Spironolactone has been shown to produce tumours in rats when administered at high doses over a long period of time. The significance of these findings with respect to clinical use is not certain. However, the long-term use of spironolactone in young patients requires careful consideration of the benefits and potential hazards involved. Spironolactone or its metabolites may cross the placental barrier. With spironolactone, feminisation has been observed in male rat foetuses. The use of Spironolactone in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the mother and foetus.

Nonclinical data reveal no evidence of teratogenicity, but embryo-fetal toxicity has been seen in rabbits, and an anti-androgenic effect in rat offspring has raised concern about possible adverse effects on male genital development.

Endocrine disrupting effects have also been observed in female rodents at clinically relevant exposures. In adult rats, spironolactone was found to increase the length of the estrous cycle, and in female offspring exposed late in pregnancy, endocrine dysfunction persisting to adulthood was observed.

In mice spironolactone inhibited ovulation and implantation, thereby decreasing fertility. The clinical relevance of these findings is unknown.

**6.1 List of excipients   
Tablet core:**

Colloidal anhydrous silica

Sodium lauryl sulfate

Rice starch

Microcrystalline cellulose PH101

Agar

Lactose monohydrate   
Peppermint oil

Povidone K-29-32

Magnesium stearate

**Tablet coat:**

Methyl hydroxypropyl cellulose   
Polyethylene glycol 400

Opaspray M-1-6031B (E171, E464, E172)   
Talc.

Colloidal anhydrous silica, sodium lauryl sulfate, rice starch, microcrystalline cellulose

PH101, lactose monohydrate, peppermint oil, povidone K-29-32, industrial methylated

spirit, magnesium stearate, methyl hydroxypropyl cellulose, polyethylene glycol 400,

opaspray M-1-6031B (E171, E464, E172), and talc.

**6.2 Incompatibilities**

None stated.

**6.3 Shelf life**

48 months.

**6.4 Special precautions for storage**

Do not store above 25oC

Store in the original package in order to protect from light and moisture.

**6.5 Nature and contents of container**

Securitainers with white bodies, blue lids, containing 21, 28, 100, 250, 500 or 1000 tablets\*

PVC/PVdC//Al blister pack containing 28 tablets.

*For bulk supply, only packs of 5, 000 and 10,000 tablets will be available (supplied in polybags, free from additives, inside a card board outer container).*

**6.6 Special precautions for disposal**None stated.

**7 MARKETING AUTHORISATION HOLDER**Bristol Laboratories

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