1 NAME OF THE MEDICINAL PRODUCT

Olmesartan/Amlodipine 20 mg/5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg olmesartan medoxomil and 5 mg amlodipine (as amlodipine besilate).

Excipient with known effect:
Each tablet contains 5.60 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White coloured, round, plain film-coated tablets.
Tablet diameter: 6.61 mm (limits: 6.4 – 6.8 mm)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.
Olmesartan/amlodipine is indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology
Adults
The recommended dosage of olmesartan/amlodipine is 1 tablet per day.
Olmesartan/amlodipine 20 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled by 20 mg olmesartan medoxomil or 5 mg amlodipine alone.
Olmesartan/amlodipine 40 mg/5 mg may be administered in patients whose blood pressure is not adequately controlled by olmesartan/amlodipine 20 mg/5 mg.
Olmesartan/amlodipine 40 mg/10 mg may be administered in patients whose blood pressure is not adequately controlled by olmesartan/amlodipine 40 mg/5 mg.

A stepwise titration of the dosage of the individual components is recommended before changing to the fixed combination. When clinically appropriate, direct change from monotherapy to the fixed combination may be considered.
For convenience, patients receiving olmesartan medoxomil and amlodipine from separate tablets may be switched to olmesartan/amlodipine tablets containing the same component doses.
Olmesartan/amlodipine can be taken with or without food.

Elderly (age 65 years or over)
No adjustment of the recommended dose is generally required for elderly but increase of the dosage should take place with care (see sections 4.4 and 5.2).
If up-titration to the maximum dose of 40 mg olmesartan medoxomil daily is required, blood pressure should be closely monitored.

Renal impairment
The maximum dose of olmesartan medoxomil in patients with mild to moderate renal impairment (creatinine clearance of 20 – 60 mL/min) is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of olmesartan/amlodipine in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended (see sections 4.4 and 5.2).
Monitoring of potassium levels and creatinine is advised in patients with moderate renal impairment.

Hepatic impairment
Olmesartan/amlodipine should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.4 and 5.2).
In patients with moderate hepatic impairment, an initial dose of 10 mg olmesartan medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are already receiving diuretics and/or other antihypertensive agents. There is no experience of olmesartan medoxomil in patients with severe hepatic impairment.
As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. Olmesartan/amlodipine should therefore be administered with caution in these patients. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with impaired liver function. Use of olmesartan/amlodipine in patients with severe hepatic impairment is contraindicated (see section 4.3).

Paediatric population
The safety and efficacy of olmesartan/amlodipine in children and adolescents below 18 years has not been established. No data are available.

Method of administration
The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed and should be taken at the same time each day.

4.3 Contraindications

Hypersensitivity to the active substances, to dihydropyridine derivatives or to any of the excipients listed in section 6.1.
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
Severe hepatic insufficiency and biliary obstruction (see section 5.2).
The concomitant use of olmesartan/amlodipine with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2) (see sections 4.5 and 5.1).
Due to the component amlodipine, olmesartan/amlodipine is also contraindicated in patients with:

- 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

Patients with hypovolaemia or sodium depletion
Symptomatic hypotension may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting, especially after the first dose. Correction of this condition prior to administration of olmesartan/amlodipine or close medical supervision at the start of the treatment is recommended.

Other conditions with stimulation of the renin-angiotensin-aldosterone system
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system, such as angiotensin II receptor antagonists, has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure.

Renovascular hypertension
There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation
When olmesartan/amlodipine is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of olmesartan/amlodipine is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min) (see sections 4.2 and 5.2). There is no experience of the administration of olmesartan/amlodipine in patients with a recent kidney

transplant or in patients with end-stage renal impairment (i.e. creatinine clearance < 12 mL/min).

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.

Hepatic impairment
Exposure to amlodipine and olmesartan medoxomil is increased in patients with hepatic impairment (see section 5.2). Care should be taken when olmesartan/amlodipine is administered in patients with mild to moderate hepatic impairment. In moderately impaired patients, the dose of olmesartan medoxomil should not exceed 20 mg (see section 4.2). In patients with impaired hepatic function, amlodipine should be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Use of olmesartan/amlodipine in patients with severe hepatic impairment is contraindicated (see section 4.3).

Hyperkalaemia
As with other angiotensin II antagonists and ACE-inhibitors, hyperkalaemia may occur during treatment, especially in the presence of renal impairment and/or heart failure (see section 4.5). Close monitoring of serum potassium levels in at-risk patients is recommended.
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels.

Lithium
As with other angiotensin II receptor antagonists, the concomitant use of olmesartan/amlodipine and lithium is not recommended (see section 4.5).

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy
Due to the amlodipine component of olmesartan/amlodipine, as with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of olmesartan/amlodipine is not recommended in such patients.

Heart failure

As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death.

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study of amlodipine in patients with severe heart failure (NYHA III and IV), the reported incidence of pulmonary oedema was higher in the amlodipine 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.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including olmesartan (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, olmesartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Sprue-like enteropathy

In very rare cases severe, chronic diarrhoea with substantial weight loss has been reported in patients taking olmesartan few months to years after drug initiation, possibly caused by a localized delayed hypersensitivity reaction. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, and in the absence of other apparent aetiologies olmesartan treatment should be immediately discontinued and should not be restarted. If diarrhoea does not improve during the week after the discontinuation, further specialist (e.g. gastroenterologist) advice should be considered.

Ethnic differences

As with all other angiotensin II antagonists, the blood pressure lowering effect of olmesartan/amlodipine can be somewhat less in black patients than in non-black patients, possibly because of a higher prevalence of low-renin status in the black hypertensive population.

Elderly

In elderly, increase of the dosage should take place with care (see section 5.2).

Pregnancy

Angiotensin II antagonists should not be initiated during pregnancy. Unless continued angiotensin II antagonist 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 angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other
As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Warning about excipients
Olmesartan/amlodipine film-coated tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product 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

Potential interactions related to the olmesartan/amlodipine combination
To be taken into account with concomitant use
Other antihypertensive agents
The blood pressure lowering effect of olmesartan/amlodipine can be increased by concomitant use of other antihypertensive medicinal products (e.g. alpha-blockers, diuretics).

Potential interactions related to the olmesartan medoxomil component of olmesartan/amlodipine
Concomitant use not recommended
ACE-inhibitors, angiotensin II receptor blockers or aliskiren
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).

Medicinal products affecting potassium levels
Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase serum potassium levels (e.g. heparin, ACE-inhibitors) may lead to increases in serum potassium (see section 4.4). If medicinal products which affect potassium levels are to be prescribed in combination with olmesartan/amlodipine, monitoring of serum potassium levels is recommended.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and, rarely, with angiotensin II antagonists. Therefore concomitant use of olmesartan/amlodipine and lithium is not recommended (see section 4.4). If concomitant use of olmesartan/amlodipine and lithium proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may increase the risk of worsening of renal function and may lead to an increase in serum potassium. Therefore monitoring of renal function at the beginning of such concomitant therapy is recommended, as well as adequate hydration of the patient.

Bile acid sequestering agent colesevelam

Concurrent administration of the bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan and reduces $t_{1/2}$. Administration of olmesartan medoxomil at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Administering olmesartan medoxomil at least 4 hours before the colesevelam hydrochloride dose should be considered (see section 5.2).

Additional information

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed.

Olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin. Co-administration of olmesartan medoxomil with pravastatin had no clinically relevant effects on the pharmacokinetics of either component in healthy subjects.

Olmesartan had no clinically relevant inhibitory effects on human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4 *in vitro*, and had no or minimal inducing effects on rat cytochrome P450 activities. No clinically relevant interactions between olmesartan and medicinal products metabolised by the above cytochrome P450 enzymes are expected.

Potential interactions related to the amlodipine component of olmesartan/amlodipine

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. The clinical translation of these PK variations may be more pronounced in the elderly. There is an increased risk of hypotension. Close observation of patients is recommended 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 hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, 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 antihypertensive agents.
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

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.

Tacrolimus
There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. 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.

Ciclosporine
In a prospective study in renal transplant patients, an average 40% increase in trough ciclosporine levels was observed when used concomitantly with amlodipine. The co-administration of olmesartan/amlodipine with ciclosporine may increase exposure to ciclosporine. Monitor trough ciclosporine levels during concomitant use and ciclosporine dose reductions should be made as necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy (see section 4.3)
There are no data about the use of olmesartan/amlodipine in pregnant patients. Animal reproductive toxicity studies with olmesartan/amlodipine have not been performed.

Olmesartan medoxomil

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II antagonists is contraindicated during the 2nd and 3rd trimesters of pregnancy (see sections 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 antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin II antagonists 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 angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to angiotensin II antagonists 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 section 5.3).
Should exposure to angiotensin II antagonists have occurred from the second trimester on, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II antagonists should be closely observed for hypotension (see sections 4.3 and 4.4).

Amlodipine
Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the foetus. However, there may be a risk of prolonged delivery.
As a consequence, olmesartan/amlodipine is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

Breast-feeding
Olmesartan is excreted into the milk of lactating rats. However, it is not known whether olmesartan passes into human milk.

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.

During breast-feeding, olmesartan/amlodipine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant.

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

Olmesartan/amlodipine can have minor or moderate influence on the ability to drive and use machines.
Dizziness, headache, nausea or fatigue may occasionally occur in patients taking antihypertensive therapy, which may impair the ability to react. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Olmesartan medoxomil/amlodipine

The most commonly reported adverse reactions during treatment with Olmesartan medoxomil/amlodipine are peripheral oedema (11.3%), headache (5.3%) and dizziness (4.5%).

Adverse reactions from olmesartan medoxomil/amlodipine in clinical trials, post- authorisation safety studies and spontaneous reporting are summarised in the below table as well as adverse reactions from the individual components Olmesartan medoxomil and amlodipine based on the known safety profile of these substances.

The following terminologies have been used in order to classify the occurrence of adverse reactions: 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).

MedDRA System Organ Class	**Adverse reactions**	**Frequency**		
		Olmesartan/ amlodipine combination	Olmesartan	Amlodipine
Blood and lymphatic system disorders	Leukocytopenia	–	–	Very rare
	Thrombocytopenia	–	Uncommon	Very rare
Immune system disorders	Allergic reaction / Drug hypersensitivity	Rare	–	Very rare
	Anaphylactic reaction	–	Uncommon	–
Metabolism and nutrition disorders	Hyperglycaemia	–	–	Very rare
	Hyperkalaemia	Uncommon	Rare	–
	Hypertriglyceridemia	–	Common	–
	Hyperuricaemia	–	Common	–
Psychiatric disorders	Confusion	–	–	Rare
	Depression	–	–	Uncommon
	Insomnia	–	–	Uncommon
	Irritability	–	–	Uncommon
	Libido decreased	Uncommon	–	–
	Mood changes (including	–	–	Uncommon

	anxiety)			
Nervous system disorders	Dizziness	Common	Common	Common
	Dysgeusia	–	–	Uncommon
	Extrapyramidal disorder	–	–	Not known
	Headache	Common	Common	Common (especially at the beginning of treatment)
	Hypertonia	–	–	Very rare
	Hypoesthesia	Uncommon	–	Uncommon
	Lethargy	Uncommon	–	–
	Paraesthesia	Uncommon	–	Uncommon
	Peripheral neuropathy	–	–	Very rare
	Postural dizziness	Uncommon	–	–
	Sleep disorder	–	–	Uncommon
	Somnolence	–	–	Common
	Syncope	Rare	–	Uncommon
	Tremor	–	–	Uncommon
Eye disorders	Visual disturbance (including diplopia)	–	–	Common
Ear and labyrinth disorders	Tinnitus	–	–	Uncommon
	Vertigo	Uncommon	Uncommon	–
Cardiac disorders	Angina pectoris	–	Uncommon	Uncommon (incl. aggravation of angina pectoris)
	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	–	–	Uncommon
	Myocardial infarction	–	–	Very rare
	Palpitations	Uncommon	–	Common
	Tachycardia	Uncommon	–	–
Vascular disorders	Flushing	Rare	–	Common
	Hypotension	Uncommon	Rare	Uncommon
	Orthostatic hypotension	Uncommon	–	–
	Vasculitis	–	–	Very rare
Respiratory, thoracic and mediastinal disorders	Bronchitis	–	Common	–
	Cough	Uncommon	Common	Uncommon
	Dyspnoea	Uncommon	–	Common
	Pharyngitis	–	Common	–
	Rhinitis	–	Common	Uncommon
Gastrointestinal disorders	Abdominal pain	–	Common	Common
	Altered bowel habits (including diarrhoea and constipation)	–	–	Common
	Constipation	Uncommon	–	–

	Diarrhoea	Uncommon	Common	–
	Dry mouth	Uncommon	–	Uncommon
	Dyspepsia	Uncommon	Common	Common
	Gastritis	–	–	Very rare
	Gastroenteritis	–	Common	–
	Gingival hyperplasia	–	–	Very rare
	Intestinal angioedema		Rare	
	Nausea	Uncommon	Common	Common
	Pancreatitis	–	–	Very rare
	Sprue-like enteropathy (see section 4.4)	–	Very rare	–
	Upper abdominal pain	Uncommon	–	–
	Vomiting	Uncommon	Uncommon	Uncommon
Hepatobiliary disorders	Hepatic enzymes increased	–	Common	Very rare (mostly consistent with cholestasis)
	Hepatitis	–	–	Very rare
	Jaundice	–	–	Very rare
	Autoimmune hepatitis*		Not known	
Skin and subcutaneous tissue disorders	Allergic dermatitis	–	Uncommon	–
	Alopecia	–	–	Uncommon
	Angioneurotic oedema	–	Rare	Very rare
	Erythema multiforme	–	–	Very rare
	Exanthema	–	Uncommon	Uncommon
	Exfoliative dermatitis	–	–	Very rare
	Hyperhidrosis	–	–	Uncommon
	Photosensitivity	–	–	Very rare
	Pruritus	–	Uncommon	Uncommon
	Purpura	–	–	Uncommon
	Quincke oedema	–	–	Very rare
	Rash	Uncommon	Uncommon	Uncommon
	Skin discoloration	–	–	Uncommon
	Stevens-Johnson syndrome	–	–	Very rare
	Urticaria	Rare	Uncommon	Uncommon
	Toxic epidermal necrolysis	–	–	Not known
Musculoskeletal and connective tissue disorders	Ankle swelling	–	–	Common
	Arthralgia	–	–	Uncommon
	Arthritis	–	Common	–
	Back pain	Uncommon	Common	Uncommon
	Muscle spasm	Uncommon	Rare	Common
	Myalgia	–	Uncommon	Uncommon
	Pain in extremity	Uncommon	–	–
	Skeletal pain	–	Common	–

Renal and urinary disorders	Acute renal failure	–	Rare	–
	Haematuria	–	Common	–
	Increased urinary frequency	–	–	Uncommon
	Micturition disorder	–	–	Uncommon
	Nocturia	–	–	Uncommon
	Pollakiuria	Uncommon	–	–
	Renal insufficiency	–	Rare	–
	Urinary tract infection	–	Common	–
Reproductive system and breast disorders	Erectile dysfunction/impotence	Uncommon	–	Uncommon
	Gynecomastia	–	–	Uncommon
General disorders and administration site conditions	Asthenia	Uncommon	Uncommon	Common
	Chest pain	–	Common	Uncommon
	Face oedema	Rare	Uncommon	–
	Fatigue	Common	Common	Common
	Influenza-like symptoms	–	Common	–
	Lethargy	–	Rare	–
	Malaise	–	Uncommon	Uncommon
	Oedema	Common	–	Very common
	Pain	–	Common	Uncommon
	Peripheral oedema	Common	Common	–
	Pitting oedema	Common	–	–
Investigations	Blood creatinine increased	Uncommon	Rare	–
	Blood creatine phosphokinase increased	–	Common	–
	Blood potassium decreased	Uncommon	–	–
	Blood urea increased	–	Common	–
	Blood uric acid increased	Uncommon	–	–
	Gamma glutamyl transferase increased	Uncommon	–	–
	Weight decrease	–	–	Uncommon
	Weight increase	–	–	Uncommon

*Cases of autoimmune hepatitis with a latency of few months to years have been reported post-marketing, that were reversible after the withdrawal of olmesartan.

Single cases of rhabdomyolysis have been reported in temporal association with the intake of angiotensin II receptor blockers. Single cases of extrapyramidal syndrome have been reported in patients treated with amlodipine.

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 at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

There is no experience of overdose with olmesartan/amlodipine. The most likely effects of olmesartan medoxomil overdosage are hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurred. Amlodipine overdosage can be expected to lead to excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome has 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.

Management

If intake is recent, gastric lavage may be considered. In healthy subjects, the administration of activated charcoal immediately or up to 2 hours after ingestion of amlodipine has been shown to reduce substantially the absorption of amlodipine.
Clinically significant hypotension due to an overdose of olmesartan/amlodipine requires active support of the cardiovascular system, including close monitoring of heart and lung function, elevation of the 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.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit. The dialysability of olmesartan is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: agents acting on the renin-angiotensin system, angiotensin II receptor blockers (ARBs), combinations, ATC code: C09DB02.

Mechanism of action

Olmesartan/amlodipine is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a calcium channel blocker, amlodipine besilate. The combination of these active ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Clinical efficacy and safety

Olmesartan/amlodipine

In an 8-week, double-blind, randomised, placebo-controlled factorial design study in 1,940 patients (71% Caucasian and 29% non-Caucasian patients), treatment with each combination dose of olmesartan/amlodipine resulted in significantly greater reductions in diastolic and systolic blood pressures than the respective monotherapy components. The mean change in systolic/diastolic blood pressure was dose-dependent: -24/-14 mmHg (20 mg/5 mg combination), -25/-16 mmHg (40 mg/5 mg combination) and -30/-19 mmHg (40 mg/10 mg combination).

Olmesartan/amlodipine 40 mg/5 mg reduced seated systolic/diastolic blood pressure by an additional 2.5/1.7 mmHg over olmesartan/amlodipine 20 mg/5 mg. Similarly olmesartan/amlodipine 40 mg/10 mg reduced seated systolic/diastolic blood pressure by an additional 4.7/3.5 mmHg over olmesartan/amlodipine 40 mg/5 mg.

The proportions of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) were 42.5%, 51.0% and 49.1% for olmesartan/amlodipine 20 mg/5 mg, 40 mg/5 mg and 40 mg/10 mg, respectively.

The majority of the antihypertensive effect of olmesartan/amlodipine was generally achieved within the first 2 weeks of therapy.

A second double-blind, randomised, placebo-controlled study evaluated the effectiveness of adding amlodipine to the treatment in Caucasian patients whose blood pressure was inadequately controlled by 8 weeks of monotherapy with 20 mg olmesartan medoxomil.

In patients who continued to receive only 20 mg olmesartan medoxomil, systolic/diastolic blood pressure was reduced by -10.6/ -7.8 mmHg after a further 8 weeks. The addition of 5 mg amlodipine for 8 weeks resulted in a reduction in systolic/diastolic blood pressure of -16.2/-10.6 mmHg ($p = 0.0006$).

The proportion of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) was 44.5% for the 20 mg/5 mg combination compared to 28.5% for 20 mg olmesartan medoxomil.

A further study evaluated the addition of various doses of olmesartan medoxomil in Caucasian patients whose blood pressure was not adequately controlled by 8 weeks of monotherapy with 5 mg amlodipine.

In patients who continued to receive only 5 mg amlodipine, systolic/diastolic blood pressure was reduced by -9.9/-5.7 mmHg after a further 8 weeks. The addition of 20 mg olmesartan medoxomil resulted in a reduction in systolic/diastolic blood pressure of -15.3/-9.3 mmHg and the addition of 40 mg olmesartan medoxomil resulted in a reduction in systolic/diastolic blood pressure of -16.7/-9.5 mmHg ($p < 0.0001$).

The proportions of patients reaching blood pressure goal (< 140/90 mmHg for non-diabetic patients and < 130/80 mmHg for diabetic patients) was 29.9% for the group who continued to receive 5 mg amlodipine alone, 53.5% for olmesartan/amlodipine 20 mg/5 mg and 50.5% for olmesartan/amlodipine 40 mg/5 mg.

Randomised data in uncontrolled hypertensive patients, comparing the use of medium dose olmesartan/amlodipine combination therapy versus escalation to top dose monotherapy of amlodipine or olmesartan, are not available.

The three studies performed confirmed that the blood pressure lowering effect of olmesartan/amlodipine once daily was maintained throughout the 24-hour dose interval, with trough-to-peak ratios of 71 – 82% for systolic and diastolic response and with 24-hour effectiveness being confirmed by ambulatory blood pressure monitoring.

The antihypertensive effect of olmesartan/amlodipine was similar irrespective of age and gender, and was similar in patients with and without diabetes.
In two open-label, non-randomised extension studies, sustained efficacy using olmesartan/amlodipine 40 mg/5 mg was demonstrated at one year for 49 – 67% of patients.
Olmesartan medoxomil
The olmesartan medoxomil component of olmesartan/amlodipine is a selective angiotensin II type 1 (AT1) receptor antagonist. Olmesartan medoxomil is rapidly converted to the pharmacologically active metabolite, olmesartan. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT1 receptor in tissues including vascular smooth muscle and the adrenal gland. The action of olmesartan is independent of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) receptors by olmesartan results in increases in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.
In hypertension, olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy.
Following once daily administration to patients with hypertension, olmesartan medoxomil produces an effective and smooth reduction in blood pressure over the 24-hour dose interval. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose.
With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment.
The effect of olmesartan medoxomil on mortality and morbidity is not yet known.
The Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study in 4,447 patients with type 2 diabetes, normo-albuminuria and at least one additional cardiovascular risk factor, investigated whether treatment with olmesartan could delay the onset of microalbuminuria. During the median follow-up duration of 3.2 years, patients received either olmesartan or placebo in addition to other antihypertensive agents, except ACE-inhibitors or ARBs.
For the primary endpoint, the study demonstrated a significant risk reduction in the time to onset of microalbuminuria, in favour of olmesartan. After adjustment for BP differences this risk reduction was no longer statistically significant. 8.2% (178 of 2,160) of the patients in the olmesartan group and 9.8% (210 of 2,139) in the placebo group developed microalbuminuria.
For the secondary endpoints, cardiovascular events occurred in 96 patients (4.3%) with olmesartan and in 94 patients (4.2%) with placebo. The incidence of cardiovascular mortality was higher with olmesartan compared to placebo treatment (15 patients (0.7%) vs. 3 patients (0.1%)), despite similar rates for non-fatal stroke (14 patients (0.6%) vs. 8 patients (0.4%)), non-fatal myocardial infarction (17 patients (0.8%) vs. 26 patients (1.2%)) and non-cardiovascular mortality (11 patients (0.5%) vs. 12 patients (0.5%)). Overall mortality with olmesartan was numerically increased

(26 patients (1.2%) vs. 15 patients (0.7%)), which was mainly driven by a higher number of fatal cardiovascular events.
The Olmesartan Reducing Incidence of End-stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) investigated the effects of olmesartan on renal and cardiovascular outcomes in 577 randomized Japanese and Chinese type 2 diabetic patients with overt nephropathy. During a median follow-up of 3.1 years, patients received either olmesartan or placebo in addition to other antihypertensive agents including ACE-inhibitors.
The primary composite endpoint (time to first event of the doubling of serum creatinine, end-stage renal disease, all-cause death) occurred in 116 patients in the olmesartan group (41.1%) and 129 patients in the placebo group (45.4%) (HR 0.97 (95% CI 0.75 to 1.24); p = 0.791). The composite secondary cardiovascular endpoint occurred in 40 olmesartan-treated patients (14.2%) and 53 placebo-treated patients (18.7%). This composite cardiovascular endpoint included cardiovascular death in 10 (3.5%) patients receiving olmesartan vs. 3 (1.1%) receiving placebo, overall mortality 19 (6.7%) vs. 20 (7.0%), non-fatal stroke 8 (2.8%) vs. 11 (3.9%) and non-fatal myocardial infarction 3 (1.1%) vs. 7 (2.5%), respectively.

Amlodipine
The amlodipine component of olmesartan/amlodipine is a calcium channel blocker that inhibits the transmembrane influx of calcium ions through the potential-dependent L-type channels into the heart and smooth muscle. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. The antihypertensive effect of amlodipine derives from a direct relaxant effect on arterial smooth muscle, which leads to a lowering of peripheral resistance and hence of blood pressure.
In hypertensive patients, amlodipine causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy.
Following administration of therapeutic doses to patients with hypertension, amlodipine produces an effective reduction in blood pressure in the supine, sitting and standing positions. Chronic use of amlodipine is not associated with significant changes in heart rate or plasma catecholamine levels. In hypertensive patients with normal renal function, therapeutic doses of amlodipine reduce renal vascular resistance and increase glomerular filtration rate and effective renal plasma flow, without changing filtration fraction or proteinuria.
In haemodynamic studies in patients with heart failure and in clinical studies based on exercise tests in patients with NYHA class II – IV heart failure, amlodipine was found not to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms.
A placebo-controlled study (PRAISE) designed to evaluate patients with NYHA class III – IV heart failure receiving digoxin, diuretics and 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 despite no significant difference in the incidence of worsening heart failure as compared to placebo.

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 enrolment) 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 (0.90 – 1.07) 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).

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the 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. Cardiovascular 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

Olmesartan/amlodipine

Following oral intake of olmesartan/amlodipine, peak plasma concentrations of olmesartan and amlodipine are reached at 1.5 – 2 hours and 6 – 8 hours, respectively. The rate and extent of absorption of olmesartan/amlodipine are equivalent to the rate and extent of absorption following intake of the two components as separate tablets. Food does not affect the bioavailability of olmesartan/amlodipine .

Olmesartan medoxomil

Absorption and distribution

Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract. No intact olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of olmesartan from a tablet formulation was 25.6%.

The mean peak plasma concentration (Cmax) of olmesartan is reached within about 2 hours after oral dosing with olmesartan medoxomil, and olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg.

Food had minimal effect on the bioavailability of olmesartan and therefore olmesartan medoxomil may be administered with or without food.

No clinically relevant gender-related differences in the pharmacokinetics of olmesartan have been observed.

Olmesartan is highly bound to plasma protein (99.7%), but the potential for clinically significant protein binding displacement interactions between olmesartan and other highly bound co-administered active substances is low (as confirmed by the lack of a clinically significant interaction between olmesartan medoxomil and warfarin). The binding of olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16 – 29 L).

Biotransformation and elimination

Total plasma clearance of olmesartan was typically 1.3 L/h (CV, 19%) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of ^{14}C-labelled olmesartan medoxomil, 10 – 16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25.6%, it can be calculated that absorbed olmesartan is cleared by both renal excretion (ca 40%) and hepatobiliary excretion (ca 60%). All recovered radioactivity was identified as olmesartan. No other significant metabolite was detected. Enterohepatic recycling of olmesartan is minimal. Since a large proportion of olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated (see section 4.3).

The terminal elimination half-life of olmesartan is between 10 and 15 hours after multiple oral dosing. Steady state is reached after the first few doses and no further accumulation is evident after 14 days of repeated dosing. Renal clearance is approximately 0.5 – 0.7 L/h and is independent of dose.

Drug interactions
Bile acid sequestering agent colesevelam: Concomitant administration of 40 mg olmesartan medoxomil and 3,750 mg colesevelam hydrochloride in healthy subjects resulted in 28% reduction in C_{max} and 39% reduction in AUC of olmesartan. Lesser effects, 4% and 15% reduction in C_{max} and AUC respectively, were observed when olmesartan medoxomil was administered 4 hours prior to colesevelam hydrochloride. Elimination half-life of olmesartan was reduced by 50 – 52% irrespectively of whether administered concomitantly or 4 hours prior to colesevelam hydrochloride (see section 4.5).

Amlodipine
Absorption and distribution
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 64 – 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 absorption of amlodipine is unaffected by the concomitant intake of food.
Biotransformation and 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.

Olmesartan medoxomil / amlodipine
Special populations
Paediatric population (age below 18 years)
No pharmacokinetic data in paediatric patients are available.

Elderly (age 65 years or over)
In hypertensive patients, the olmesartan AUC at steady state is increased by ca 35% in elderly (65 – 75 years old) and by ca 44% in very elderly people (≥ 75 years old) compared with the younger age group (see section 4.2). This may be at least in part related to a mean decrease in renal function in this group of patients. The recommended dosage regimen for elderly is, however, the same, although caution should be exercised when increasing the dosage.
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 and elimination half-life in elderly. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group in this study (see section 4.4).

Renal impairment
In renally impaired patients, the olmesartan AUC at steady state increased by 62%, 82% and 179% in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls (see sections 4.2 and 4.4).
Amlodipine is extensively metabolised to inactive metabolites. Ten percent of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients, amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

Hepatic impairment
After single oral administration, olmesartan AUC values are 6% and 65% higher in mildly and moderately hepatically-impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of olmesartan at 2 hours post-dose in healthy subjects, in patients with mild hepatic impairment and in patients with moderate hepatic impairment is 0.26%, 0.34% and 0.41%, respectively. Following repeated dosing in patients with moderate hepatic impairment, olmesartan mean AUC is again about 65% higher than in matched healthy controls. Olmesartan mean C_{max} values are similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment (see sections 4.2 and 4.4).
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. The clearance of amlodipine is decreased and the half-life is prolonged in patients with impaired hepatic function, resulting in an increase in AUC of about 40% – 60% (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Based on the non-clinical toxicity profile of each substance, no exacerbation of toxicities for the combination is expected, because each substance has different targets, i.e. the kidneys for olmesartan medoxomil and the heart for amlodipine.
In a 3-month, repeat-dose toxicity study of orally administered olmesartan medoxomil/amlodipine in combination in rats the following alterations were observed: decreases in red blood cell count-related parameters and kidney changes both of which might be induced by the olmesartan medoxomil component; alterations in the intestines (luminal dilatation and diffuse mucosal thickening of the ileum and colon), the adrenals (hypertrophy of the glomerular cortical cells and vacuolation of the fascicular cortical cells), and hypertrophy of the ducts in the mammary glands which might be induced by the amlodipine component. These alterations neither augmented any of the previously reported and existing toxicity of the individual agents nor induced any new toxicity, and no toxicologically synergistic effects were observed.

Olmesartan medoxomil
In chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT1 receptor antagonists and ACE-inhibitors: raised blood urea (BUN) and creatinine; reduction in heart weight; reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit); histological indications of renal damage (regenerative lesions of the renal epithelium, thickening of the basal membrane, dilatation of the tubules). These adverse effects caused by the pharmacological action of olmesartan medoxomil have also occurred in preclinical trials on other AT1 receptor antagonists and ACE-inhibitors and can be reduced by simultaneous oral administration of sodium chloride. In both species, increased plasma renin activity and hypertrophy/hyperplasia of the juxtaglomerular cells of the kidney were observed. These changes, which are a typical effect of the class of ACE-inhibitors and other AT1 receptor antagonists, would appear to have no clinical relevance.
Like other AT1 receptor antagonists olmesartan medoxomil was found to increase the incidence of chromosome breaks in cell cultures *in vitro*. No relevant effects were

observed in several *in vivo* studies using olmesartan medoxomil at very high oral doses of up to 2,000 mg/kg. The overall data of a comprehensive genotoxicity testing program suggest that olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use.
Olmesartan medoxomil was not carcinogenic, in a 2-year study in rats nor in two 6-month carcinogenicity studies in transgenic mice.
In reproductive studies in rats, olmesartan medoxomil did not affect fertility and there was no evidence of a teratogenic effect. In common with other angiotensin II antagonists, survival of offspring was reduced following exposure to olmesartan medoxomil and pelvic dilatation of the kidney was seen after exposure of the dams in late pregnancy and lactation. In common with other antihypertensive agents, olmesartan medoxomil was shown to be more toxic to pregnant rabbits than to pregnant rats, however, there was no indication of a fetotoxic effect.

Amlodipine
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/m^2 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/m^2 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

Tablet core:
Starch, pregelatinized (maize)
Cellulose, microcrystalline (silicified) (microcrystalline cellulose and colloidal silicon dioxide)
Croscarmellose sodium
Lactose monohydrate

Colloidal silica anhydrous
Magnesium stearate
Tablet coat:
Polyvinyl alcohol
Polyethylene glycol (macrogol 4000)
Titanium dioxide (E171)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

OPA/Alu/PVC-Alu foil blisters, paper folding box.
Pack sizes: 14, 28, 30, 56, 90, 98 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

Zentiva Pharma UK Limited
12 New Fetter Lane
London
EC4A 1JP
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17780/0802

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/05/2022

10 DATE OF REVISION OF THE TEXT

27/02/2025