Summary of Product Characteristics

1. Name of the Medicinal Product

Olmesar AM Forte 5 Tablet

2. Qualitative and Quantitative Composition

Each tablet contains:

Olmesartan Medoxomil USP 40mg

Amlodipine Besilate USP equivalent to Amlodipine ….5mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Tablet

4. Clinical Particulars

4.1 Therapeutic indications

Olmesartan + Amlodipine Tablet is indicated for the treatment of hypertension, alone or with other antihypertensive agents, to lower blood pressure.

4.2 Posology and method of administration

Olmesartan + Amlodipine Tablet may be taken with or without food. It may be administered with other antihypertensive agents.

Dosage may be increased after 2 weeks. The maximum recommended dose of Olmesartan + Amlodipine Tablet is 10/40 mg.

Replacement Therapy:

Olmesartan + Amlodipine Tablet may be substituted for its individually titrated components.

When substituting for individual components, the dose of one or both of the components can be increased if blood pressure control has not been satisfactory.

Add-on Therapy:

Olmesartan + Amlodipine Tablet may be used to provide additional blood pressure lowering for patients not adequately controlled with amlodipine (or another dihydropyridine calcium channel blocker) alone or with olmesartan medoxomil (or another angiotensin receptor blocker) alone.

Initial Therapy:

The usual starting dose of Olmesartan + Amlodipine Tablet is 5/20 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum dose of one 10/40 mg tablet once daily as needed to control blood pressure.

Initial therapy with Olmesartan + Amlodipine Tablet is not recommended in patients ≥ 75 years old or with hepatic impairment.

4.3 Contraindications

Hypersensitivity to the active substances, to dihydropyridine derivatives or to any of the excipients.

Second and third trimesters of pregnancy.

Severe hepatic insufficiency and biliary obstruction.

The concomitant use of Olmesartan + Amlodipine Tablet with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2).

Due to the component amlodipine, Olmesartan + Amlodipine Tablet 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 Tablet 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 Tablet is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of Olmesartan + Amlodipine Tablet is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min). There is no experience of the administration of Olmesartan + Amlodipine Tablet 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.

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. Care should be taken when Olmesartan + Amlodipine Tablet is administered in patients with mild to moderate hepatic impairment. In moderately impaired patients, the dose of olmesartan medoxomil should not exceed 20 mg. 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 Tablet in patients with severe hepatic impairment is contraindicated.

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. 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 Tablet and lithium is not recommended.

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy:

Due to the amlodipine component of Olmesartan + Amlodipine Tablet, 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 Tablet 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. 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.

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, exclude other etiologies. Consider discontinuation of olmesartan medoxomil in cases where no other etiology is identified. In cases where symptoms disappear and sprue-like enteropathy is confirmed by biopsy, treatment with olmesartan medoxomil should not be restarted.

Ethnic differences:

As with all other angiotensin II antagonists, the blood pressure lowering effect of Olmesartan + Amlodipine Tablet 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.

Older people:

In older people, increase of the dosage should take place with care.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions related to the Olmesartan + Amlodipine Tablet combination:

To be taken into account with concomitant use

Other antihypertensive agents: The blood pressure lowering effect of Olmesartan+ Amlodipine Tablet 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 Tablet:

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.

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. If medicinal products which affect potassium levels are to be prescribed in combination with Olmesartan + Amlodipine Tablet, 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 Tablet and lithium is not recommended. If concomitant use of Olmesartan + Amlodipine Tablet 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 t1/2. 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.

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. Coadministration 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 Tablet:

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 older people. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

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, warfarin or cyclosporin.

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.

4.6 Pregnancy and Lactation

Pregnancy:

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Olmesartan + Amlodipine as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intraamniotic environment. If oligohydramnios is observed, discontinue Olmesartan + Amlodipine Tablet, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to Olmesartan + Amlodipine Tablet for hypotension, oliguria, and hyperkalemia

Lactation:

It is not known whether the amlodipine or olmesartan medoxomil components of Olmesartan + Amlodipine Tablet are excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Olmesartan + Amlodipine Tablet 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

The most commonly reported adverse reactions during treatment with Olmesartan+ Amlodipine Tablet are peripheral oedema, headache and dizziness.

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**	**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	
	Hypertriglyceridaemia		Common	
	Hyperuricaemia		Common	
Psychiatric disorders	Confusion			Rare
	Depression			Uncommon
	Insomnia			Uncommon
	Irritability			Uncommon
	Libido decreased	Uncommon		
	Mood changes (including anxiety)			Uncommon
Nervous system disorders	Dizziness	Common	Common	Common
	Dysgeusia			Uncommon
	Headache	Common	Common	Common (especially at the beginning of treatment)
	Hypertonia			Very rare
	Hypoaesthesia	Uncommon		Uncommon
	Lethargy	Uncommon		
	Paraesthesia	Uncommon		Uncommon
	Peripheral neuropathy			Very rare
	Postural dizziness	Uncommon		

MedDRA System Organ Class	Adverse reactions	Olmesartan/Amlodipine combination	Olmesartan	Amlodipine
	Sleep disorder			Uncommon
	Somnolence			Common
	Syncope	Rare		Uncommon
	Tremor			Uncommon
Eye disorders	Visual disturbance (including diplopia)			Uncommon
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)			Very rare
	Myocardial infarction			Very rare
	Palpitations	Uncommon		Uncommon
	Tachycardia	Uncommon		
Vascular disorders	Hypotension	Uncommon	Rare	Uncommon
	Orthostatic hypotension	Uncommon		
	Flushing	Rare		Common
	Vasculitis			Very rare
Respiratory, thoracic and mediastinal disorders	Bronchitis		Common	
	Cough	Uncommon	Common	Very rare
	Dyspnoea	Uncommon		Uncommon
	Pharyngitis		Common	
	Rhinitis		Common	Uncommon
Gastrointestinal disorders	Abdominal pain		Common	Common
	Altered bowel habits (including diarrhoea and constipation)			Uncommon
	Constipation	Uncommon		
	Diarrhoea	Uncommon	Common	
	Dry mouth	Uncommon		Uncommon
	Dyspepsia	Uncommon	Common	Uncommon
	Gastritis			Very rare
	Gastroenteritis		Common	
	Gingival hyperplasia			Very rare
	Nausea	Uncommon	Common	Common
	Pancreatitis			Very rare
	Upper abdominal pain	Uncommon		
	Vomiting	Uncommon	Uncommon	Uncommon
	Sprue-like enteropathy		Very rare	
Hepato-biliary disorders	Hepatic enzymes increased		Common	Very rare (mostly consistent with cholestasis)

MedDRA System Organ Class	Adverse reactions	Olmesartan/Amlodipine combination	Olmesartan	Amlodipine
	Hepatitis			Very rare
	Jaundice			Very rare
Skin and subcutaneous tissue disorders	Alopecia			Uncommon
	Angioneurotic oedema		Rare	Very rare
	Allergic dermatitis		Uncommon	
	Erythema multiforme			Very rare
	Exanthema		Uncommon	Uncommon
	Exfoliative dermatitis			Very rare
	Hyperhydrosis			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	Very rare
Musculoskeletal and connective tissue disorders	Ankle swelling			Common
	Arthralgia			Uncommon
	Arthritis		Common	
	Back pain	Uncommon	Common	Uncommon
	Muscle spasm	Uncommon	Rare	Uncommon
	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	Uncommon
	Chest pain		Common	Uncommon
	Face oedema	Rare	Uncommon	
	Fatigue	Common	Common	Common

MedDRA System Organ Class	Adverse reactions	Olmesartan/Amlodipine combination	Olmesartan	Amlodipine
	Influenza-like symptoms		Common	
	Lethargy		Rare	
	Malaise		Uncommon	Uncommon
	Oedema	Common		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

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 the National Regulatory Authority.

4.9 Overdose

Symptoms:

There is no experience of overdose with Olmesartan + Amlodipine Tablet. 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.

Treatment:

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 Tablet 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

Olmesartan + Amlodipine Tablet: It is a combination of two antihypertensive drugs: a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker), amlodipine besylate, and an angiotensin II receptor blocker, olmesartan medoxomil. The amlodipine component of Olmesartan + Amlodipine Tablet inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, and the olmesartan medoxomil component of Olmesartan + Amlodipine Tablet blocks the vasoconstrictor effects of angiotensin II.

Amlodipine:

Experimental data suggests that amlodipine binds to both dihydropyridine and nonhydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Olmesartan Medoxomil:

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that

include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT1 receptor than for the AT2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure.

5.2 Pharmacokinetic properties

The pharmacokinetics of amlodipine and olmesartan medoxomil from Olmesartan + Amlodipine Tablet are equivalent to the pharmacokinetics of amlodipine and olmesartan medoxomil when administered separately. The bioavailability of both components is well below 100%, but neither component is affected by food. The effective half-lives of amlodipine (45±11 hours) and olmesartan (7±1 hours) result in a 2-to 3-fold accumulation for amlodipine and negligible accumulation for olmesartan with once-daily dosing.

Amlodipine:

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability is estimated as between 64% and 90%.

Olmesartan Medoxomil:

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. The absolute bioavailability of olmesartan medoxomil is approximately 26%. After oral administration, the peak plasma concentration (Cmax) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan medoxomil.

Distribution:

Amlodipine:

Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Olmesartan Medoxomil:

The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

Metabolism and Excretion:

Amlodipine:

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Ten percent of the parent compound and 60% of the metabolites are excreted in the urine.

Olmesartan Medoxomil:

Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

5.3 Preclinical safety data

Amlodipine:

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of amlodipine 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose (MRHD) of amlodipine 10 mg/day. For the rat, the highest dose was, on a mg/m^2 basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.)

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of amlodipine up to 10 mg/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m² basis).

Olmesartan Medoxomil:

Olmesartan was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m² basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan. Both olmesartan medoxomil and olmesartan tested negative in the in vitro Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells in vitro (Chinese hamster lung) and tested positive for thymidine kinase mutations in the in vitro mouse lymphoma assay. Olmesartan medoxomil tested negative in vivo for mutations in the MutaMouse intestine and kidney and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).

Fertility of rats was unaffected by administration of olmesartan at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

6. Pharmaceutical Particulars

6.1 List of Excipients

- Silicified microcrystalline cellulose ,
- Colloidal silicon dioxide ,
- Pregelatinized starch ,
- Croscarmellose sodium,
- Magnesium stearate ,
- Opadry II Yellow 85F82567@ ,
- Purified Water

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C, in a dry place protect from light.

6.5 Nature and contents of container

Alu/ Alu blister pack of 7 Tablets

6.6 Special Precaution for disposal

None.

7. Manufactured and Marketed By

Macleods Pharmaceuticals Ltd.

Block N2 Vill. Theda P.O Lodhimajra Teshil Baddi,

Dist Solan (H.P) India

Fax: +91-22-2821 6599

Off.: Atlanta Arcade, Marol Church Road, Andheri (E), Mumbai - 400 059.

8. Marketing authorization number(s)

H2019/CTD5567/1383ER/R1

9. Date of first authorization/renewal of the authorization

2025 September 26

10. Date of revision of the text

2025 September 26