AMLODIPINE/OLMESARTAN MEDOXOMIL

NORMETEC®

5 mg/20 mg, 5 mg/40 mg and 10 mg/40 mg Film-coated Tablets

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1.0 PHARMACOLOGIC CATEGORY

Angiotensin II Receptor Blockers (ARBs) and Calcium Channel Blocker

2.0 DESCRIPTION

Amlodipine 5 mg plus Olmesartan medoxomil 20 mg (5 mg/20 mg) is a white, round, film-coated tablet with C73 debossed on one side.

Amlodipine 5 mg plus Olmesartan medoxomil 40 mg (5 mg/40 mg) is a cream-colored, round, film-coated tablet with C75 debossed on one side.

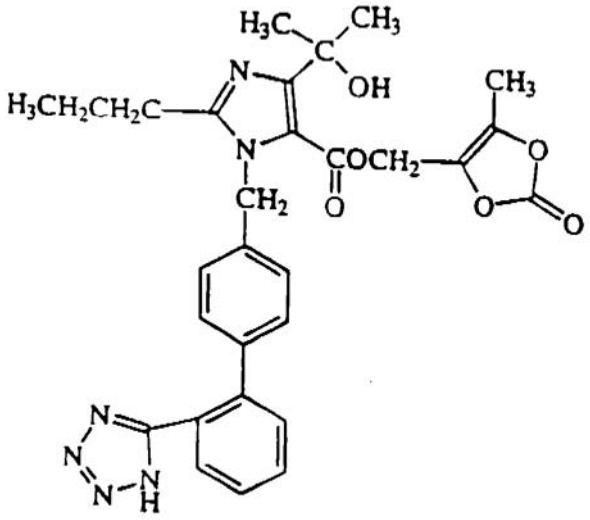
Amlodipine 10 mg plus Olmesartan medoxomil 40 mg (10 mg/40 mg) is a brownish-red, round, film-coated tablet with C77 debossed on one side.

Amlodipine/Olmesartan Medoxomil (Normetec®) is a combination of the angiotensin II receptor antagonist olmesartan medoxomil and the calcium channel blocker amlodipine.

Olmesartan medoxomil, a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract.

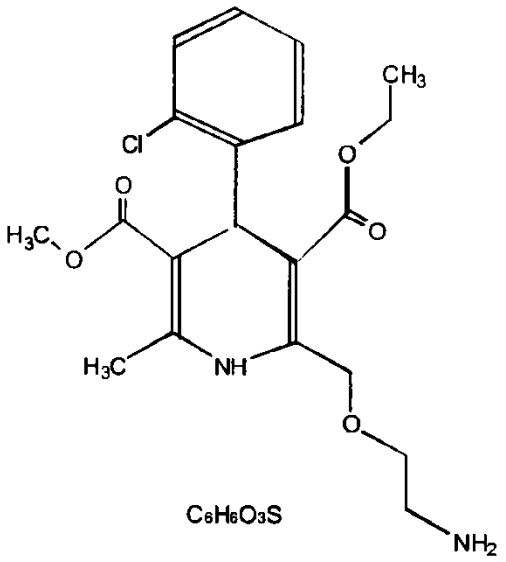
Olmesartan medoxomil is chemically described as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl) benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is $C_{29}H_{30}N_6O_6$.

The structural formula for olmesartan medoxomil is:



Amlodipine is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$.

The structural formula for amlodipine is:



3.0 FORMULATION/COMPOSITION

Amlodipine/Olmesartan Medoxomil (Normetec®) is available for oral use as film-coated tablets in the following strengths:

- Amlodipine/Olmesartan Medoxomil (Normetec® 5 mg/20 mg): Each film-coated tablet contains 6.944 mg of Amlodipine (as besilate) equivalent to 5 mg of Amlodipine Ph Eur and 20 mg of Olmesartan medoxomil equivalent to 20 mg of Olmesartan Ph Eur.
- Amlodipine/Olmesartan Medoxomil (Normetec® 5 mg/40 mg): Each film-coated tablet contains 6.944 mg of Amlodipine (as besilate) equivalent to 5 mg of Amlodipine Ph Eur and 40 mg of Olmesartan medoxomil equivalent to 40 mg of Olmesartan Ph Eur.
- Amlodipine/Olmesartan Medoxomil (Normetec® 10 mg/40 mg): Each film-coated tablet contains 13.888 mg of Amlodipine (as besilate) equivalent to 10 mg of Amlodipine Ph Eur and 40 mg of Olmesartan medoxomil equivalent to 40 mg of Olmesartan Ph Eur.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Amlodipine/Olmesartan Medoxomil (Normetec®) is indicated for the treatment of essential hypertension.

4.2 Dosage and Method of Administration

Usual Adult Dose

The recommended dosage of Amlodipine/Olmesartan Medoxomil (Normetec®) is 1 tablet daily, with or without food.

For convenience, patients receiving olmesartan medoxomil and amlodipine from separate tablets may be switched to Amlodipine/Olmesartan Medoxomil (Normetec®) tablets containing the same component doses.

When clinically appropriate, direct change from monotherapy to the fixed combination may be considered. A step-wise titration of the dosage is recommended.

When necessary, a thiazide diuretic may be added to Amlodipine/Olmesartan Medoxomil (Normetec®) therapy.

Elderly

No adjustment of the recommended dose is generally required for elderly patients.

Renal Impairment

No adjustment of the recommended dose is required for patients with mild to moderate impairment of renal function. The use of Amlodipine/Olmesartan Medoxomil (Normetec®) in patients with severe renal impairment (creatinine clearance <20 mL/min) is not recommended.

Hepatic Impairment

Amlodipine/Olmesartan Medoxomil (Normetec®) should be used with caution in patients with mild to moderate hepatic impairment. Amlodipine/Olmesartan Medoxomil (Normetec®) is not recommended in patients with severe hepatic impairment.

Children

Amlodipine/Olmesartan Medoxomil (Normetec®) is not recommended for use in children and adolescents below 18 years of age, due to a lack of data on safety and efficacy.

4.3 Contraindications

- Amlodipine/Olmesartan Medoxomil (Normetec®) is contraindicated in patients who are hypersensitive to any component of the tablet or to dihydropyridine derivatives.
- Amlodipine/Olmesartan Medoxomil (Normetec®) is contraindicated in patients who become pregnant. When pregnancy is detected, Amlodipine/Olmesartan Medoxomil (Normetec®) should be discontinued as soon as possible (see Section **4.6 Fertility, Pregnancy and Lactation**).

- Do not co-administer aliskiren with Amlodipine/Olmesartan Medoxomil (Normetec®) in patients with diabetes (see Section **4.5. Interaction with Other Medicinal Products and Other forms of Interaction**).

4.4 Special Warnings and Precautions for Use

Pregnancy and Lactation

See Section 4.6 regarding use in pregnancy and lactation.

Patients with Hypovolemia or Sodium Depletion

Symptomatic hypotension may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhea, or vomiting, especially after receiving the first dose. Correction of this condition prior to administration of Amlodipine/Olmesartan Medoxomil (Normetec®), or close medical supervision at the start of 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, azotemia, 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.

Electrolyte Imbalance

Amlodipine/Olmesartan Medoxomil (Normetec®) contains olmesartan, a drug that inhibits the renin-angiotensin system (RAS). Drugs that inhibit the RAS can cause hyperkalaemia. Monitor serum electrolytes periodically.

Sprue-like Enteropathy

Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan medoxomil months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan medoxomil, exclude other etiologies. Consider discontinuation of Amlodipine/Olmesartan Medoxomil (Normetec®) in cases where no other etiology is identified.

Renal Impairment and Kidney Transplantation

There is no experience of the administration of Amlodipine/Olmesartan Medoxomil (Normetec®) in patients with a recent kidney transplant or in patients with end-stage renal impairment (i.e. creatinine clearance <12 mL/min).

Hepatic Impairment

Since amlodipine is extensively metabolized by the liver, exposure to amlodipine and olmesartan medoxomil is increased in patients with hepatic impairment. Care should be taken when Amlodipine/Olmesartan Medoxomil (Normetec®) is administered in patients with mild to moderate hepatic impairment. Use of Amlodipine/Olmesartan Medoxomil (Normetec®) in patients with severe hepatic impairment is not recommended.

Severe Obstructive Coronary Disease

As with all vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Amlodipine/Olmesartan Medoxomil (Normetec®)

The blood pressure lowering effect of Amlodipine/Olmesartan Medoxomil (Normetec®) can be increased by concomitant use of other antihypertensive medicinal products (e.g. alpha blockers, diuretics).

No drug interaction studies have been conducted with Amlodipine/Olmesartan Medoxomil (Normetec®) and other drugs; although, studies have been conducted with the individual olmesartan medoxomil and amlodipine components of Amlodipine/Olmesartan Medoxomil (Normetec®), as described below.

Olmesartan Medoxomil

Use with Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including olmesartan. Monitor serum lithium levels during concomitant use.

Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin receptor antagonists, ACE inhibitors or aliskiren is associated with increased risks of hypotension, hyperkalemia and changes in renal function (including acute renal failure) compared to monotherapy. Monitor blood pressure, renal function and electrolytes in patients on olmesartan and other agents that affect the RAS.

Use with Aliskiren

Do not co-administer aliskiren with olmesartan medoxomil in patients with diabetes (see Section **5.0 PHARMACOLOGICAL PROPERTIES**) because dual use is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

Use with Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs and angiotensin receptor blockers (ARBs) may act synergistically by decreasing glomerular filtration. The concomitant use of NSAIDs and ARBs may increase the risk of worsening renal function.

Additionally, the antihypertensive effect of ARBs, including olmesartan, may be attenuated by NSAIDs, including selective cox2 inhibitors.

Use with Colesevelam Hydrochloride

Concurrent administration of bile acid sequestering agent colesevelam hydrochloride reduces the systemic exposure and peak plasma concentration of olmesartan. Administration of olmesartan at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect (see Section **5.0 PHARMACOLOGICAL PROPERTIES**).

Amlodipine (as Besilate)

Concomitant Use Requiring Caution

- *CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir):* A study in elderly patients showed that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4, since plasma concentrations of amlodipine increased by approximately 50% and its effect was therefore increased. The possibility that more potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.
- *CYP3A4 inducers (e.g. anticonvulsants [such as carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)*: Concomitant administration of CYP3A4 may decrease the plasma concentration of amlodipine. Clinical monitoring is indicated, with possible adjustment of amlodipine dosage during treatment with the CYP3A4 inducer and after its withdrawal.
- *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 to 20 mg daily in patients on amlodipine.
- *Tacrolimus*: The co-administration of amlodipine with tacrolimus may increase exposure of tacrolimus. Because Amlodipine/Olmesartan Medoxomil (Normetec®) contains amlodipine, monitor tacrolimus blood levels during concomitant use.
- *Cyclosporine*: In a prospective study in renal transplant patients, an average 40% increase in trough cyclosporine levels was observed in the presence of amlodipine. The co-administration of amlodipine with cyclosporine may increase exposure to cyclosporine. Because Amlodipine/Olmesartan Medoxomil (Normetec®) contains amlodipine, monitor trough cyclosporine levels during concomitant use.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Amlodipine/Olmesartan Medoxomil (Normetec®) can cause fetal harm when administered to a pregnant woman. As a precaution, Amlodipine/Olmesartan Medoxomil (Normetec®) must not be used during the first trimester of pregnancy. The patient should change to an appropriate alternative form of medication before

a planned pregnancy. If pregnancy occurs during therapy, Amlodipine/Olmesartan Medoxomil (Normetec®) must be discontinued as soon as possible. There is no experience of the use of Amlodipine/Olmesartan Medoxomil (Normetec®) in pregnant women.

Olmesartan medoxomil is contraindicated in the second and third trimesters of pregnancy. During the second and third trimesters of pregnancy, substances that act on the renin-angiotensin system may cause damage (hypotension, impairment of renal function, oliguria and/or anuria, oligohydramnia, cranial hypoplasia, intrauterine growth retardation) and death in fetuses and neonates. Cases of pulmonary hypoplasia, facial anomalies and contractions of limbs were also reported. Animal experimental studies with olmesartan medoxomil have shown furthermore that renal damage may occur in the late fetal and neonatal phase.

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 fetus. However, there may be a risk of prolonged delivery.

If Amlodipine/Olmesartan Medoxomil (Normetec®) is used during pregnancy, or if the patient becomes pregnant while taking Amlodipine/Olmesartan Medoxomil (Normetec®), the patient should be apprised of the potential hazard to a fetus. Should exposure to Amlodipine/Olmesartan Medoxomil (Normetec®) occurred from the second trimester forward, ultrasound examinations of the renal function and of the skull are recommended. Newborns exposed to angiotensin II antagonists *in utero* must be closely monitored for the occurrence of hypotension, oliguria, and hyperkalemia.

Lactation

It is not known whether olmesartan medoxomil is excreted in human milk, but olmesartan is secreted at low concentration in the milk of lactating rats. Limited available data from a published clinical lactation study report that amlodipine is present in human milk at an estimated median relative infant dose of 4.2%. No adverse effects of amlodipine on the breastfed infant have been observed. There is no available information on the effects of amlodipine on milk production. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug.

4.7 Effects on Ability to Drive and Use Machines

No data available

4.8 Undesirable Effects

Amlodipine/Olmesartan Medoxomil (Normetec®)

The overall incidence of adverse events on therapy with Amlodipine/Olmesartan Medoxomil (Normetec®) was not different from that seen with placebo. Most adverse events were mild.

The most common undesirable effects were dizziness, headache, edema, and fatigue.

Edema is a known dose-dependent undesirable effect of amlodipine. The incidence of edema was significantly lower in patients receiving Amlodipine/Olmesartan Medoxomil (Normetec®) than in those who received amlodipine 10 mg alone. Across all treatment groups, the frequency of edema was generally higher in women than in men.

The less common undesirable effects included hypotension, orthostatic hypotension, rash, palpitation, and pollakiuria.

Adverse events previously reported with one of the individual components may be potential adverse events with Amlodipine/Olmesartan Medoxomil (Normetec®), even if not observed in clinical trials with this product.

Olmesartan Medoxomil

In clinical trials, treatment with olmesartan medoxomil was well tolerated, with an incidence of adverse events similar to that seen with placebo. Events were generally mild, transient, and without relationship to the dose of olmesartan medoxomil. The overall frequency of adverse events was not dose-related. Analysis of gender, age, and racial groups demonstrated no differences between olmesartan medoxomil and placebo-treated patients. Dizziness has been reported commonly (≥1% to <10% incidence) in clinical trials with olmesartan medoxomil.

In post-launch experience, adverse drug reactions that have been reported very rarely (<0.01% incidence) were peripheral edema, headache, cough, abdominal pain, nausea, vomiting, diarrhea, sprue-like enteropathy, anaphylactic reaction, rash, pruritus, angioedema, acute renal failure, increased hepatic enzymes, increased blood creatinine, hyperkalemia, myalgia and asthenic conditions such as asthenia, fatigue, lethargy, malaise.

Amlodipine (as Besilate)

Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. The most common undesirable effects were headache, edema, dizziness, facial flushing, and palpitation.

In post-launch experience, gynecomastia has been infrequently reported as an adverse reaction where a causal relationship is uncertain. In post-marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

4.9 Overdose and Treatment

Symptoms

The maximum dose of Amlodipine/Olmesartan Medoxomil (Normetec®) is 10 mg/40 mg once daily. There is no information on overdosage with Amlodipine/Olmesartan Medoxomil (Normetec®) in humans. The most likely effect of olmesartan medoxomil overdosage is hypotension. 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

In the event of overdosage with Amlodipine/Olmesartan Medoxomil (Normetec®), treatment should be supportive.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit. The dialysability of olmesartan is unknown.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Amlodipine/Olmesartan Medoxomil (Normetec®)

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

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours.

The antihypertensive effect of Amlodipine/Olmesartan Medoxomil (Normetec®) was similar irrespective of age and gender, and was similar in patients with and without diabetes.

In follow-up studies, the antihypertensive effect of Amlodipine/Olmesartan Medoxomil (Normetec®) was sustained during long-term therapy. When required, addition of a diuretic (hydrochlorothiazide) increased the blood pressure lowering effect of Amlodipine/Olmesartan Medoxomil (Normetec®).

Olmesartan Medoxomil

The olmesartan medoxomil component of Amlodipine/Olmesartan Medoxomil (Normetec®) 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 it's 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.

Amlodipine (as Besilate)

The amlodipine component of Amlodipine/Olmesartan Medoxomil (Normetec®) 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.

Epidemiological studies have shown that long-term treatment with amlodipine monotherapy reduces the risk of cardiovascular mortality and morbidity.

5.2 Pharmacokinetic Properties

Following oral intake of Amlodipine/Olmesartan Medoxomil (Normetec®), peak plasma concentrations of olmesartan and amlodipine are reached at 1.5 hours to 2 hours and 6 to 8 hours, respectively. The rate and extent of absorption of the two active substances from Amlodipine/Olmesartan Medoxomil (Normetec®) 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 and amlodipine from Amlodipine/Olmesartan Medoxomil (Normetec®).

Absorption and Distribution

Amlodipine/Olmesartan Medoxomil (Normetec®): The pharmacokinetics of amlodipine and olmesartan from Amlodipine/Olmesartan Medoxomil (Normetec®) are equivalent to the pharmacokinetics of amlodipine and olmesartan when administered separately. Food did not affect the pharmacokinetics of amlodipine or

olmesartan when administered as Amlodipine/Olmesartan Medoxomil (Normetec®) in healthy subjects.

Olmesartan medoxomil: 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 (C_{max}) of olmesartan is reached within approximately 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; 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 L to 29 L).

Amlodipine (as besilate): After oral administration of therapeutic doses, amlodipine is slowly absorbed from the gastrointestinal tract. The absorption of amlodipine is unaffected by the concomitant intake of food. The absolute bioavailability of the unchanged compound is estimated to be 64% to 80%. Peak plasma levels are reached 6 hours to 12 hours post-dose. The volume of distribution is about 20 L/kg. The pK_a of amlodipine is 8.6. Plasma protein binding *in vitro* is approximately 98%.

Metabolism and Excretion

Olmesartan medoxomil: 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). Based on the systemic availability of 25.6%, it can be calculated that absorbed olmesartan is cleared by both renal excretion and hepato-biliary excretion. The terminal elimination half-life of olmesartan is between 10 hours 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 L/h– 0.7 L/h and is independent of dose.

Amlodipine: The plasma elimination half-life ($t_{1/2}$) varies from 35 hours to 50 hours. Steady-state plasma levels are reached after 7 to 8 consecutive days. Amlodipine is extensively metabolized to inactive metabolites. About 60% of the administered dose is excreted in the urine, about 10% of which is in the form of unchanged amlodipine.

Pharmacokinetics in Special Populations

Elderly

Analysis indicated that age is not a significant predictor of olmesartan clearance. As age is correlated with creatinine clearance, any apparent effects of age on olmesartan clearance can be explained by changes in creatinine clearance. However, elderly patients have decreased clearance of amlodipine. In hypertensive patients, the olmesartan drug concentration in plasma area under the curve (AUC) is increased in elderly patients (65 years to 75 years old) and in very elderly patients (≥75 years old) compared with the younger age group. Following oral intake of amlodipine, the time to peak plasma concentration is comparable in young and in elderly patients. In elderly patients, the clearance of amlodipine tends to decline, resulting in increases in AUC and in elimination $t_{1/2}$.

Pediatric

No pharmacokinetic data in pediatric patients (below 18 years old) are available for olmesartan medoxomil.

Renal Impairment

In renally impaired patients, at steady state the olmesartan AUC was approximately tripled in patients with severe renal impairment, compared to healthy controls. 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

Increases in olmesartan AUC values are higher in hepatically impaired patients than in their corresponding 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.

The clearance of amlodipine is decreased and the $t_{1/2}$ is prolonged in patients with impaired hepatic function, resulting in an increase in AUC of about 60%.

Olmesartan Pharmacokinetic Interactions

Drug Interaction with 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 (see Section **4.5 Interaction with Other Medicinal Products and Other forms of Interaction**).

5.3 Preclinical Safety Data

Carcinogenicity, Mutagenesis, Impairment of Fertility

The mode of antihypertensive action of amlodipine (a direct relaxant effect on vascular smooth muscle) differs from, and is complementary to, that of olmesartan medoxomil (a long-acting angiotensin II receptor antagonist). Furthermore, 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. A 3-month repeated dose toxicity study in rats demonstrated that the combined administration

of olmesartan medoxomil and amlodipine neither augmented any of the previously reported and existing toxicities of the individual agents, nor induced any new toxicities, and no toxicologically synergistic effects were observed.

No additional mutagenicity, carcinogenicity, and reproductive toxicity studies for Amlodipine/Olmesartan Medoxomil (Normetec®) have been conducted based on the well-understood safety profile of the individual compounds.

5.4 Clinical Trials

The Randomized Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) clinical study included 4447 patients with type 2 diabetes, normoalbuminuria and at least one additional cardiovascular risk factor. Patients were randomized to olmesartan 40 mg daily or placebo. The trial met its primary endpoint, delayed onset of microalbuminuria. For the secondary endpoints, which the study was not designed to formally assess, 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 [0.67%] vs. 3 patients [0.14%] [HR=4.94, 95% CI=1.43-17.06]), but the risk of non-fatal myocardial infarction was lower with olmesartan (HR 0.64, 95% CI 0.35, 1.18).

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date of the product.

6.2 Storage Condition

Store at temperatures not exceeding 25°C

6.3 Availability

- Amlodipine 5 mg plus Olmesartan medoxomil 20 mg (5 mg/20 mg): Box of 30’s in blister packs of 10’s.
- Amlodipine 5 mg plus Olmesartan medoxomil 40 mg (5 mg/40 mg): Box of 30’s in blister packs of 10’s.
- Amlodipine 10 mg plus Olmesartan medoxomil 40 mg (10 mg/40 mg): Box of 30’s in blister packs of 10’s.

7.0 FDA REGISTRATION NUMBER

5 mg/20 mg film-coated tablet : DR-XY37885

5 mg/40 mg film-coated tablet : DR-XY37884

10 mg/40 mg film-coated tablet : DR-XY37883

8.0 DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

5 mg/20 mg film-coated tablet : 29 April 2010

5 mg/40 mg film-coated tablet : 29 April 2010

10 mg/40 mg film-coated tablet: 29 April 2010

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by: Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1 D-85276 Pfaffenhofen, Germany

Packed by: Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1,
79108 Freiburg Im Breisgau, Germany

Marketing Authorization Holder: PFIZER, INC.
19F-20F, 8 Rockwell Building,
Hidalgo Drive, Rockwell Center, Poblacion,
Makati City 1210 Metro Manila, Philippines

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Reference: CDS ver. 9.1/ BOH comments/Freiburg address and administrative update

Reference Date: May 2020