NORMETEC™

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product name

Normetec™

1.2 Strength

5 mg/20 mg

5 mg/40 mg

10 mg/40 mg

1.3 Pharmaceutical dosage form

Film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Amlodipine (as amlodipine besylate) and Olmesartan medoxomil.

2.2 Quantitative Declaration

Normetec 5 mg/20 mg film-coated tablets: Each film-coated tablet of Normetec contains 5 mg of amlodipine (as amlodipine besylate) and 20 mg of olmesartan medoxomil.

Normetec 5 mg/40 mg film-coated tablets: Each film-coated tablet of Normetec contains 5 mg of amlodipine (as amlodipine besylate) and 40 mg of olmesartan medoxomil.

Normetec 10 mg/40 mg film-coated tablets: Each film-coated tablet of Normetec contains 10 mg of amlodipine (as amlodipine besylate) and 40 mg of olmesartan medoxomil.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Normetec 5 mg/20 mg film-coated tablets: White, round, film-coated tablet with C73 debossed on one side.

Normetec 5 mg/40 mg film-coated tablets: Cream, round, film-coated tablet with C75 debossed on one side.

Normetec 10 mg/40 mg film-coated tablets: Brownish-red, round, film-coated tablet with C77 debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Treatment of essential hypertension.

Normetec is indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy (see section 4.2, 5.1).

4.2 Posology and method of administration

Adults

The recommended dosage of Normetec is 1 tablet per day.

Normetec 5 mg/20 mg may be administered in patients whose blood pressure is not adequately controlled by 5 mg amlodipine or 20 mg olmesartan medoxomil alone.

Normetec 5 mg/40 mg may be administered in patients whose blood pressure is not adequately controlled by Normetec 5 mg/20 mg.

Normetec 10 mg/40 mg may be administered in patients whose blood pressure is not adequately controlled by Normetec 5 mg/40 mg.

A step-wise 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 Normetec tablets containing the same component doses.

Normetec can be taken with or without food.

Elderly (age 65 years or over)

No adjustment of the recommended dose is generally required for elderly patients (see section 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 Normetec in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended (see sections 4.4, 5.2).

Monitoring of potassium levels and creatinine is advised in patients with moderate renal impairment.

Hepatic impairment

Normetec should be used with caution in patients with mild to moderate hepatic impairment (see sections 4.4, 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. Normetec should therefore be administered with caution in these patients.

Paediatric population

The safety and efficacy of Normetec 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 (see section 6.1).

Patients who become pregnant. When pregnancy is detected, Normetec should be discontinued as soon as possible. (see section 4.4, 4.6).

Severe hepatic insufficiency and biliary obstruction (see section 5.2).

Due to the component amlodipine, Normetec 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.

Do not co-administer aliskiren with Normetec in patients with diabetes (see section 4.5).

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 Normetec 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.

Electrolyte imbalance:

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 diarrhoea 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 Normetec in cases where no other etiology is identified.

Renal impairment and kidney transplantation:

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

Exposure to amlodipine and olmesartan medoxomil is increased in patients with hepatic impairment (see section 5.2). Care should be taken when Normetec 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). Use of Normetec in patients with severe hepatic impairment is contraindicated (see section 4.3).

Hyperkalaemia:

As with other angiotensin II antagonists and angiotensin converting enzyme (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 Normetec and lithium is not recommended (see section 4.5).

Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy:
Due to the amlodipine component of Normetec, 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 Normetec 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 ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see section 5.1).

Ethnic differences:

As with all other angiotensin II antagonists, the blood pressure lowering effect of Normetec 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 patients:

In the 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 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 (see section 4.3, 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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions related to the Normetec combination:

To be taken into account with concomitant use.

Other antihypertensive agents:

The blood pressure lowering effect of Normetec 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 Normetec:

Concomitant use not recommended

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 Normetec, monitoring of serum potassium levels is recommended.

Lithium:

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

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.

Aliskiren:

Do not co-administer aliskiren with olmesartan medoxomil in patients with diabetes (see section 4.3) because dual use is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

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, NSAIDs and ARBs (angiotensin receptor blockers) may act synergistically by decreasing glomerular filtration. The 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.

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 5.2).

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 Normetec:

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors:
With concomitant use of CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively, the plasma concentrations of amlodipine increased by 22% and 50% respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

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.

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 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 Normetec contains amlodipine, monitor trough cyclosporine levels during concomitant use.

Additional information:

In clinical interaction studies, grapefruit juice, cimetidine, aluminium/magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effect 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, ethanol (alcohol), warfarin or cyclosporine.

There is no effect of amlodipine on laboratory parameters.

4.6 Pregnancy and lactation

Pregnancy (see section 4.3)

Normetec can cause fetal harm when administered to a pregnant woman. As a precaution, 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, Normetec must be discontinued as soon as possible. There are no data about the

use of Normetec in pregnant patients. Animal reproductive toxicity studies with Normetec have not been performed.

If Normetec is used during pregnancy, or if the patient becomes pregnant while taking Normetec, the patient should be apprised of the potential hazard to a fetus. Should exposure to Normetec have 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 hypotension, oliguria, and hyperkalaemia (see sections 4.3, 4.4).

Olmesartan medoxomil (active ingredient of Normetec)
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 trimester 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 also section 5.3).

Amlodipine (active ingredient of Normetec)
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.

Lactation

Olmesartan is excreted into the milk of lactating rats. However, it is not known whether olmesartan passes into human milk. 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. Similar calcium channel blockers of the dihydropyridine type are excreted in breast milk.

Because no information is available regarding the use of olmesartan and amlodipine during breast-feeding, Normetec is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

Normetec 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.

4.8 Undesirable effects

Normetec:

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

Adverse reactions from Normetec in clinical trials, post-authorisation safety studies and spontaneous reporting are summarized 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	
	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	Frequency		
		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
	Abdominal pain		Common	Common

MedDRA System Organ Class	Adverse reactions	Frequency		
		Olmesartan/ Amlodipine combination	Olmesartan	Amlodipine
Gastrointestinal disorders	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)
	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

MedDRA System Organ Class	Adverse reactions	Frequency		
		Olmesartan/ Amlodipine combination	Olmesartan	Amlodipine
	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	

MedDRA System Organ Class	Adverse reactions	Frequency		
		Olmesartan/ Amlodipine combination	Olmesartan	Amlodipine
	Fatigue	Common	Common	Common
	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.

4.9 Overdose

Symptoms:

There is no experience of overdose with Normetec. 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 Normetec 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: Angiotensin II antagonists and calcium channel blockers, ATC code C09DB02.

Mechanism of action

Normetec is a combination of an angiotensin II receptor antagonist, olmesartan medoxomil, and a calcium channel blocker, amlodipine besylate. 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

Normetec

In an 8-week, double-blind, randomised, placebo-controlled factorial design study in 1940 patients (71% Caucasian and 29% non-Caucasian patients), treatment with each combination dose of

Normetec 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 (5 mg/20 mg combination), -25/-16 mmHg (5 mg/40 mg combination) and -30/-19 mmHg (10 mg/40 mg combination).

Normetec 5 mg/40 mg reduced seated systolic/diastolic blood pressure by an additional 2.5/1.7 mmHg over Normetec 5 mg/20 mg. Similarly, Normetec 10 mg/40 mg reduced seated systolic/diastolic blood pressure by an additional 4.7/3.5 mmHg over Normetec 5 mg/40 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 Normetec 5 mg/20 mg, 5 mg/40 mg and 10 mg/40 mg respectively.

The majority of the antihypertensive effect of Normetec 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 5 mg/20 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 Normetec 5 mg/20 mg and 50.5% for Normetec 5 mg/40 mg.

Randomised data in uncontrolled hypertensive patients, comparing the use of medium dose Normetec 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 Normetec once daily was maintained throughout the 24-hour dose interval, with trough-to-peak ratios of 71% to 82% for systolic and diastolic response and with 24-hour effectiveness being confirmed by ambulatory blood pressure monitoring.

The antihypertensive effect of Normetec 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 Normetec 5 mg/40 mg was demonstrated at one year for 49% - 67% of patients.

Olmesartan medoxomil (active ingredient of Normetec)

The olmesartan medoxomil component of 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 rennin-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.

Clinical trials

The Randomised 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 randomised 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).

Amlodipine (active ingredient of Normetec)

The amlodipine component of 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.

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 the 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 the 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.

5.2 Pharmacokinetic properties

Normetec

Following oral intake of Normetec, 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 the two active substances from 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 Normetec.

Olmesartan medoxomil (active ingredient of Normetec)

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 (C_{max}) 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).

Metabolism 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.

Pharmacokinetic interactions:

Drug interaction with bile acid sequestering agent colesevelam:

Concomitant administration of 40 mg olmesartan medoxomil and 3750 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).

Amlodipine (active ingredient of Normetec)

Absorption and distribution:

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% – 80%. Peak plasma levels are reached 6 to 12 hours post-dose. The volume of distribution is about 20 L/kg. The pKa of amlodipine is 8.6. Plasma protein binding *in vitro* is approximately 98%.

Metabolism and elimination:

The plasma elimination half-life varies from 35 to 50 hours. Steady-state plasma levels are reached after 7 – 8 consecutive days. Amlodipine is extensively metabolised to inactive metabolites. About 60% of the administered dose is excreted in the urine, about 10% of which in the form of unchanged amlodipine.

Olmesartan medoxomil and amlodipine (active ingredients of Normetec)

Special populations

Paediatric patients (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 patients (65 – 75 years old) and by ca 44% in very elderly patients (≥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 patients is, however, the same, although caution should be exercised when increasing the dosage.

The time to peak plasma concentration 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 patients. 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, 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, 4.4).

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, 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 (active ingredient of Normetec)

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 2000 mg/kg. The overall data of a comprehensive genotoxicity testing programme 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 (active ingredient of Normetec)

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In animal studies with respect to the reproduction in rats at high doses delayed parturition, difficult labour and impaired fetal and pup survival were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Starch, pregelatinised maize
Silicified microcrystalline cellulose (microcrystalline cellulose with colloidal silicon dioxide)
Croscarmellose sodium
Magnesium stearate

Tablet coat:

Polyvinyl alcohol
Macrogol 3350
Talc
Titanium dioxide (E171)
Iron (III) oxide yellow (E172) (Normetec 5 mg/40 mg and 10 mg/40 mg film-coated tablets only)
Iron (III) oxide red (E172) (Normetec 10 mg/40 mg film-coated tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please see details on carton.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

OPA/Aluminium/PVC-Aluminium blister.

Pack size: Carton of 30 film-coated tablets.

7. MARKETING AUTHORISATION HOLDER

Pfizer (Thailand) Limited, Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

Normetec (Tablets 5 mg/20 mg): Reg. No. 2C 9/57 (N)

Normetec (Tablets 5 mg/40 mg): Reg. No. 2C 10/57 (N)

Normetec (Tablets 10 mg/40 mg): Reg. No. 2C 11/57 (N)

9. DATE OF AUTHORISATION

22 September 2014

10. DATE OF REVISION OF THE TEXT

9 August 2024

Warnings

1. Is contraindicated in pregnant women.
2. Consult the physician if lethargy, nausea or vomiting occur.
3. Stop using this drug and consult the physician immediately if the following symptoms occur during using this drug e.g., swelling of the face, tongue, larynx or having difficulty in breathing (dyspnoea).
4. Use with caution as this drug may cause renal failure.
5. This drug may increase serum potassium level. It should not be used concomitantly with potassium supplement or sparing diuretics.

LPD Title: Amlodipine and Olmesartan medoxomil (Daiichi-WR)

LPD rev no.: 6.1

LPD Date: August 09, 2024

Country: Thailand

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