PT. PFIZER INDONESIA
Local Product Document

Product Document Title: Olmesartan medoxomil-Amlodipine besylate
Trade Name: **NORMETEC**
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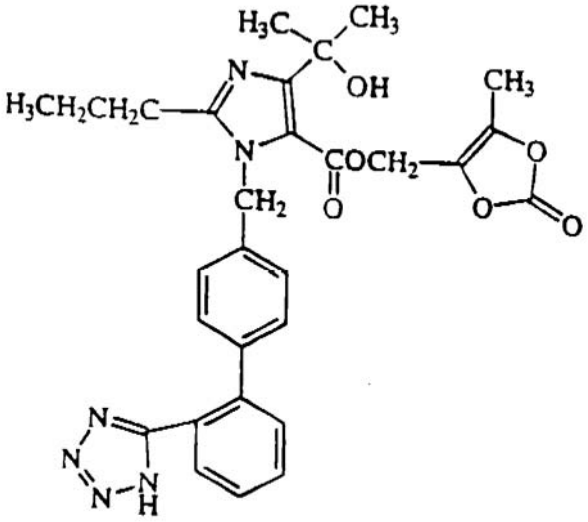
DESCRIPTION

NORMETEC is a combination of the angiotensin II receptor blocker (ARB) olmesartan medoxomil and the calcium channel receptor blocker (CCB) amlodipine besylate.

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

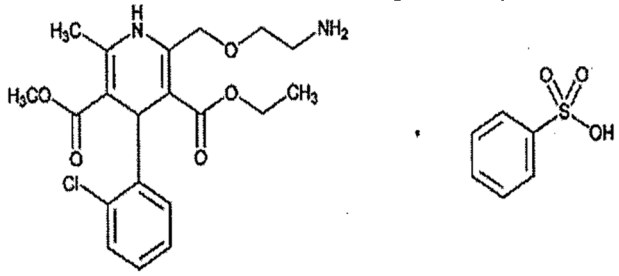
Olmesartan medoxomil is chemically described as 2,3-dihydroxy-2-butenyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-carboxylate, cyclic 2,3-carbonate. Its empirical formula is $C_{29}H_{30}N_6O_6$.

The structural formula for olmesartan medoxomil is:



Amlodipine besylate 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 besylate is:



PHARMACEUTICAL FORM

NORMETEC is available for oral use as film-coated tablets in the following strengths:
- Olmesartan medoxomil 20 mg plus amlodipine 5 mg (20/5 mg). White, round, film-coated tablet with C73 debossed on one side.
- Olmesartan medoxomil 40 mg plus amlodipine 5 mg (40/5 mg). Cream, round, film-coated tablet with C75 debossed on one side.
- Olmesartan medoxomil 40 mg plus amlodipine 10 mg (40/10 mg). Brownish-red, round, film-coated tablet with C77 debossed on one side.

LIST OF EXCIPIENTS

Pregelatinized Starch
Croscarmellose Sodium
Magnesium Stearate
Purified Water
Opadry II White 85f18422
Silicified Microcrystalline Cellulose

INDICATIONS

NORMETEC is indicated for the treatment of essential hypertension.

Replacement therapy:
Patients receiving olmesartan medoxomil and amlodipine from separate tablets may instead receive NORMETEC containing the same component doses.

Add-on therapy:
NORMETEC is indicated in patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy.

NORMETEC should not be used as initial therapy.

DOSAGE AND ADMINISTRATION

Usual Adult Dose
The recommended dosage of NORMETEC is one tablet daily, with or without food. Treatment should not be initiated with this combination.

Replacement Therapy
For convenience, patients receiving olmesartan medoxomil and amlodipine from separate tablets may be switched to NORMETEC tablets containing the same component doses.

Add-on Therapy
For patients whose blood pressure is not adequately controlled on either olmesartan or amlodipine monotherapy, they may be switched to combination therapy with NORMETEC.

Titration of dosage is recommended. For patients whose blood pressure is not adequately controlled on NORMETEC 20/5, then titration to NORMETEC 40/5 is recommended.

Subsequently, if the patient's blood pressure is not adequately controlled on NORMETEC 40/5, then titration to NORMETEC 40/10 is recommended.

Elderly
Olmesartan medoxomil
The maximum dose in elderly patients is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosage in this patient group.

Amlodipine besylate
Normal dosage regimens are recommended. Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated.

Renal Impairment
Olmesartan medoxomil
The maximum dose in patients with mild-to-moderate renal impairment (creatinine clearance of 20-60 mL/min) is 20 mg olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of olmesartan medoxomil in patients with severe renal impairment (creatinine clearance <20 mL/min is not recommended, since there is only limited experience in this patient group.

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

Hepatic Impairment
Olmesartan medoxomil
The use of olmesartan medoxomil is not recommended in patients with hepatic impairment, since there is only limited experience in this patient group.

Amlodipine besylate
As with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established in these patients. The drug should therefore be administered with caution in these patients.

Children and Adolescents
NORMETEC is not recommended for use in children and adolescents below 18 years of age, due to lack of data on safety and efficacy.

Olmesartan medoxomil
The safety and efficacy of olmesartan medoxomil have not been established in children and adolescents up to 18 years of age.

Amlodipine besylate
The recommended antihypertensive oral dose in pediatric patients aged 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

CONTRAINDICATIONS

NORMETEC is contraindicated in:
- Patients who are hypersensitive to any component of the tablet or to dihydropyridines.
- Pregnancy (see section **Warnings and Precautions - Use in pregnancy**)
- Patients with severe renal impairment (see section **Warnings and Precautions - Renal impairment**)
- Patients with severe hepatic impairment or biliary obstruction (see section **Warnings and Precautions – Hepatic impairment**)

Due to the component amlodipine, NORMETEC is also contraindicated in:
- Cardiogenic shock
- Acute myocardial infarction (within the first 4 weeks)
- Unstable angina pectoris.

Do not co-administer aliskiren with NORMETEC in patients with diabetes (see section **Interactions**).

WARNINGS AND PRECAUTIONS

Pregnancy and Lactation
See section **Pregnancy and Lactation** regarding use in pregnancy and lactation.

Intramuscular Volume 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 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
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 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 section **Contraindications**). 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
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 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 **Dosage and Administration**). Use of NORMETEC in patients with severe hepatic impairment is contraindicated (see section **Contraindications**).

Severe Obstructive Coronary Disease
Due to the amlodipine component of NORMETEC, as with all 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 drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of olmesartan medoxomil is not recommended in such patients.

Increased Angina and/or Myocardial Infarction
Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Congestive 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.

Ethnic Differences
As with all other angiotensin receptor antagonists, the blood pressure lowering effect of olmesartan medoxomil is 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.

Concomitant use of ACE Inhibitors or Angiotensin Receptor Antagonist and Anti-inflammatory Drugs and Thiazide Diuretics
The use of ACE-inhibitors or angiotensin receptor antagonist, and an anti-inflammatory drug (NSAID or COX-2 inhibitor), and a thiazide diuretic at the same time increase the risk of renal impairment. This includes use with fixed-combination products containing more than one class of drug. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the treatment. The concomitant use of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Lithium
As with other angiotensin receptor antagonists, the combination of lithium and olmesartan medoxomil is not recommended (see section **Interactions**).

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.

PREGNANCY AND LACTATION

Pregnancy
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 is no experience of the use of 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 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 the occurrence of hypotension, oliguria, and hyperkalaemia.

No animal reproductive toxicity studies have been performed with the combination of olmesartan medoxomil and amlodipine.

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.

Paediatric Use
NORMETEC is not recommended for use in children and adolescents below 18 years of age, due to lack of data on safety and efficacy.

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed. However, it should be borne in mind that dizziness or fatigue may occasionally occur in patients taking

antihypertensive therapy.

INTERACTIONS

NORMETEC

The blood pressure lowering effect of 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 NORMETEC and other drugs, although studies have been conducted with the individual olmesartan medoxomil and amlodipine components of NORMETEC, as described below.

Olmesartan medoxomil

Effects of other medicinal products on olmesartan medoxomil:

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 **Contraindications**) 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 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 **Clinical Pharmacology**).

Potassium supplements and potassium sparing diuretics:

Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g., heparin) may lead to increases in serum potassium (see section **Warnings and Precautions**). Such concomitant use is therefore, not recommended.

Other antihypertensive medications:

The blood pressure lowering effect of olmesartan medoxomil can be increased by concomitant use of other antihypertensive medications.

Non-steroidal anti-inflammatory drugs (NSAIDs):
NSAIDs (including acetylsalicylic acid at doses >3 g/day and also COX-2 inhibitors) and angiotensin-II receptor antagonists may act synergistically by decreasing glomerular filtration. The risk of the concomitant use of NSAIDs and angiotensin II antagonists is the occurrence of acute renal failure. Monitoring of renal function at the beginning of treatment should be recommended as well as regular hydration of the patient.

Additionally, concomitant treatment can reduce the antihypertensive effect of angiotensin II receptor antagonists, leading to their partial loss of efficacy.

Other compounds:
After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of olmesartan was observed. Co-administration of warfarin and digoxin had no effect on the pharmacokinetics of olmesartan.

Effects of olmesartan medoxomil on other medicinal products:
Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and angiotensin II antagonists. Therefore, use of olmesartan medoxomil and lithium in combination is not recommended (see section **Warnings and Precautions**). If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other compounds:
Compounds which have been investigated in specific clinical studies in healthy volunteers include warfarin, digoxin, an antacid (magnesium aluminum hydroxide), hydrochlorothiazide and pravastatin. No clinically relevant interactions were observed and in particular olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.

Olmesartan had no clinically relevant inhibitory effects on *in vitro* human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4, and had no or minimal inducing effects on rat cytochrome P450 activities. Therefore, *in vivo* interaction studies with known cytochrome P450 enzyme inhibitors and inducers were not conducted, and no clinically relevant interactions between olmesartan and drugs metabolised by the above cytochrome P450 enzymes are expected.

Amlodipine besylate
Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

In vitro data from studies with human-plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin, or indomethacin).

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.

In the following studies listed below, there were no significant changes in the pharmacokinetics of either amlodipine or another drug within the study, when co-administered.

Special Studies: Effect of other agents on amlodipine.
CIMETIDINE: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

ALUMINUM/MAGNESIUM (antacid): Co-administration of an aluminum/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

SILDENAFIL: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

CYP3A4 INHIBITORS: With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients, the plasma concentration of amlodipine increased by 22% and 50% respectively. The clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations 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 (e.g. rifampicin, *Hypericum perforatum*) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

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.

Special Studies: Effect of amlodipine on other agents.
ATORVASTATIN: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

CYCLOSPORINE: Pharmacokinetic studies with cyclosporine have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporine.

Drug/Laboratory Test Interactions: None known.

UNDESIRABLE EFFECTS

NORMETEC

The safety of NORMETEC was investigated in controlled clinical trials in 2892 patients receiving olmesartan medoxomil in combination with amlodipine.

Table 1 summarises the most common (≥1% in any group) drug-related adverse events by System Organ Class and preferred term. The profile of drug-related adverse events was similar across the treatments; most commonly general disorders and administrations site conditions, nervous system or vascular adverse events.

Table 1: Drug-related adverse events with ≥1% incidence in any combined treatment group Phase III all patients cohort.

Number of patients with (%)	OM/AML (N=2892)	OM (N=663)	AML (N=512)	Placebo (N=162)
General Disorders and Administration Site Conditions				
Oedema peripheral	252 (8.7)	35 (5.3)	45 (8.8)	9 (5.6)
Oedema	82 (2.8)	9 (1.4)	15 (2.9)	2 (1.2)
Fatigue	46 (1.6)	13 (2.0)	5 (1.0)	5 (3.1)
Pitting oedema	37 (1.3)	6 (0.9)	4 (0.8)	2 (1.2)
Nervous System Disorders				
Dizziness	80 (2.8)	19 (2.9)	6 (1.2)	6 (3.7)
Headache	68 (2.4)	26 (3.9)	8 (1.6)	11 (6.8)
Vascular Disorders				
Hypertension	2 (0.1)	5 (0.8)	0 (0.0)	7 (4.3)
Gastrointestinal Disorders				
Nausea	12 (0.4)	2 (0.3)	2 (0.4)	3 (1.9)

Adverse events are listed below by system organ class. Frequencies are defined as: 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).

Cardiac disorders
Uncommon : Palpitations, tachycardia.

Ear and labyrinth disorders
Uncommon : Vertigo.

Gastro-intestinal disorders
Uncommon : Nausea, vomiting, dyspepsia, diarrhoea, constipation, dry mouth, upper abdominal pain.

General disorders and administration site conditions
Uncommon : Asthenia.
Rare : Face oedema.

Immune system disorders
Rare : Drug hypersensitivity.

Investigations
Uncommon : Blood potassium decreased, blood creatinine increased, blood uric acid increased, gamma-glutamyl transferase increased.

Metabolism and nutrition disorders
Uncommon : Hyperkalaemia.

Musculoskeletal and connective tissue disorders
Uncommon : Muscle spasm, pain in extremity, back pain.

Nervous system disorders
Uncommon : Postural dizziness, lethargy, paraesthesia, hypoaesthesia.
Rare : Syncope.

Psychiatric disorders
Uncommon : Libido decreased.

Renal and urinary disorders
Uncommon : Pollakiuria.

Reproductive system and breast disorders
Uncommon : Erectile dysfunction.

Respiratory, thoracic and mediastinal disorders.
Uncommon : Dyspnoea, cough.

Skin and subcutaneous tissue disorders
Uncommon : Rash.
Rare : Urticaria.

Vascular disorders
Uncommon : Hypotension, orthostatic hypotension.

Oedema
Edema is a known dose-dependent undesirable effect of amlodipine but not of olmesartan medoxomil. The incidence of oedema was significantly lower in patients receiving 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.

Olmesartan Medoxomil
In double-blind, placebo-controlled monotherapy studies, the overall incidence of treatment-emergent adverse events was 42.4% on olmesartan medoxomil and 40.9% on placebo. In long-term (2-year) treatment, the incidence of withdrawals due to adverse events on olmesartan medoxomil 10 - 20 mg once daily was 3.7%.

In placebo-controlled monotherapy studies, the only adverse drug reaction that was unequivocally related to treatment was dizziness (2.5% incidence on olmesartan medoxomil and 0.9% on placebo).

Adverse events reported across all clinical trials with olmesartan medoxomil (including trials with active as well as placebo control), irrespective of causality or incidence relative to placebo, included those events listed below. Frequencies are defined as: common (≥1/100, <1/10); uncommon (≥1/1, 000, <1/100); rare (≥1/10, 000, <1/1, 000), very rare (<1/10, 000).

The adverse events listed include all adverse events reported commonly and other adverse events of potential clinical relevance.

Central nervous system disorders:
Common: Dizziness.
Uncommon: Vertigo.

Cardiovascular disorders:
Rare: Hypotension.

Myo/endo/pericardial and valve disorders:
Uncommon: Angina pectoris.

Respiratory system disorders:
Common: Bronchitis, cough, pharyngitis, rhinitis.

Gastro-intestinal disorders:

Common: Abdominal pain, diarrhoea, dyspepsia, gastroenteritis, nausea.

Skin and appendages disorders:
Uncommon: Rash.

Musculoskeletal disorders:
Common: Arthritis, back pain, skeletal pain.

Urinary system disorders:
Common: Haematuria, urinary tract infection.

General disorders:
Common: Chest pain, fatigue, influenza-like symptoms, peripheral oedema, pain.

Post-launch experience:
In addition, as with other angiotensin II antagonists, headache has been observed, in very rare cases hypersensitivity reactions (pruritis, urticaria, angio odema), peripheral oedema, vomiting, sprue-like enteropathy, diarrhea, anaphylactic reaction, acute renal failure, myalgia and asthenic condition, such as asthenia, fatigue, lethargy, malaise have been reported.

Laboratory parameters
In placebo-controlled monotherapy studies the incidence was somewhat higher on olmesartan medoxomil compared with placebo for hypertriglyceridaemia (2.0% vs. 1.1%) and for raised creatine phosphokinase (1.3% vs. 0.7%).

Laboratory adverse events reported across all clinical trials with olmesartan medoxomil (including trials without a placebo control), irrespective of causality or incidence relative to placebo, included:

Metabolic and nutritional disorders:
Common: Increased creatine phosphokinase, hypertriglyceridaemia, hyperuricaemia.
Rare: Hyperkalaemia

Liver and biliary disorders:
Common: Liver enzyme elevations.

Amlodipine Besylate
Amlodipine is well tolerated. In placebo-controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects were:

MedDRA System Organ Class	**Undesirable Effects**
Nervous System Disorders	headache, dizziness, somnolence
Cardiac Disorders	palpitations
Vascular Disorders	flushing
Gastrointestinal Disorders	abdominal pain, nausea
General Disorders and Administration Site Conditions	edema, fatigue

In these clinical trials, no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed.

Less commonly observed side effects in marketing experience include:

MedDRA System Organ Class	**Undesirable Effects**
Blood and Lymphatic System Disorders	leucopenia, thrombocytopenia
Metabolism and Nutrition Disorders	hyperglycemia
Psychiatric Disorders	insomnia, mood changes
Nervous System Disorders	hypertonia, hypoesthesia/paresthesia , peripheral neuropathy, syncope, taste perversion, tremor
Eye Disorders	visual disturbances
Ear and Labyrinth Disorders	tinnitus
Vascular Disorders	hypotension, vasculitis
Respiratory, Thoracic, and Mediastinal Disorders	cough, dyspnea, rhinitis
Gastrointestinal Disorders	altered bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting
Skin and Subcutaneous Tissue Disorders	alopecia, increased sweating, purpura, skin discoloration, urticaria
Musculoskeletal and Connective Tissue Disorders	arthralgia, back pain, muscle cramps, myalgia
Renal and Urinary Disorders	increased urinary frequency, micturition disorder, nocturia
Reproductive System and Breast Disorders	gynecomastia, impotence
General Disorders and Administration Site Conditions	asthenia, malaise, pain
Investigations	weight increase/decrease

Rarely, allergic reaction including pruritus, rash, angioedema, and erythema multiforme.

Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

Pediatric Patients (ages 6-17 years)
Amlodipine is well tolerated in children. Adverse events were similar to those seen in adults. In a study of 268 children, the most frequently reported adverse events were:

MedDRA System Organ Class	Undesirable Effects
Nervous System Disorders	headache, dizziness
Vascular Disorders	vasodilatation
Respiratory, Thoracic, and Mediastinal Disorders	epistaxis
Gastrointestinal Disorders	abdominal pain
General Disorders and Administration Site Conditions	asthenia

The majority of adverse events were mild or moderate. Severe adverse events (predominantly headache) were experienced by 7.2% with amlodipine 2.5 mg, 4.5% with amlodipine 5 mg, and 4.6% with placebo. The most common cause of discontinuation from the study was uncontrolled hypertension. There were no discontinuations due to laboratory abnormalities. There was no significant change in heart rate.

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:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

OVERDOSAGE

Symptoms
The maximum dose of NORMETEC is 40/10 mg once daily. There is no information on overdosage with 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

If intake is recent, gastric lavage or induction of emesis 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.

CLINICAL PHARMACOLOGY

Pharmacodynamic Properties

Pharmacotherapeutic group: Angiotensin II antagonists and calcium channel blockers, ATC code C09DB02.

NORMETEC

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.

The olmesartan medoxomil component of NORMETEC blocks the vasoconstrictor effects of angiotensin II and the amlodipine component of NORMETEC inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

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 40 mg/5 mg was demonstrated at one year for 49%–67% of patients.

Olmesartan Medoxomil

The olmesartan medoxomil component of NORMETEC is a selective angiotensin II type 1 (AT_1) receptor antagonist. Olmesartan medoxomil is rapidly converted to the pharmacologically active metabolite, olmesartan. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system, and plays a significant role in the pathophysiology of hypertension. The effects of angiotensin II include vasoconstriction, stimulation of the synthesis

and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by blocking its binding to the AT_1 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 (AT_1) 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 Besylate
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.

Pharmacokinetics
Following oral intake of 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 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.

Absorption and Distribution
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 besylate*:* 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 postdose. 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 Excretion
Olmesartan medoxomil*:* Total plasma clearance was typically 1.3 L/h (CV, 19%) and was relatively slow compared to hepatic blood flow (ca 30 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 hepato-biliary 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 **Contraindications**).

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

Amlodipine besylate*:* 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 by ca 35% in elderly patients (65 years to 75 years old) and by ca 44% 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 $t_{½}$.

Pediatric and Adolescents

No pharmacokinetic data in paediatric patients for NORMETEC are available.

The pharmacokinetics of olmesartan medoxomil have not been investigated in patients <18 years of age.

No pharmacokinetic data for amlodipine in paediatric patients are available.

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.

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

Olmesartan medoxomil*:* After single oral administration, olmesartan AUC values were 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 was 0.26%, 0.34% and 0.41%, respectively. Olmesartan medoxomil has not been

evaluated in patients with severe hepatic impairment (see sections **Dosage and Administration** and **Warnings and Precautions**).

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

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 **Interactions**).

PRECLINICAL SAFETY DATA

Carcinogenicity, Mutagenesis, Impairment of Fertility
Olmesartan medoxomil*:* In chronic toxicity studies in rats and dogs, olmesartan medoxomil showed similar effects to other AT_1 receptor antagonists and ACE inhibitors: raised blood urea (BUN) and creatinine (through functional changes to the kidneys caused by blocking AT_1 receptors); reduction in heart weight; a 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 AT_1 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 AT_1 receptor antagonists, would appear to have no clinical relevance.

Like other AT_1 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 suggest that olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use.

Olmesartan medoxomil was not carcinogenic, neither in rats in a 2-year study nor in mice when tested in two 6 month carcinogenicity studies using transgenic models.

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 besylate*:*
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

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

*Based on patient weight of 50 kg

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 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).

PRESENTATION

NORMETEC® 5/20 mg, box contains of 3 blister @ 10 tablet; Reg. No. DKI1890701617A1
NORMETEC® 5/40 mg, box contains of 3 blister @ 10 tablet; Reg. No. DKI1890701617B1
NORMETEC® 10/40 mg, box contains of 3 blister @ 10 tablet; Reg. No. DKI1890701617C1

STORAGE
Store below 30°C.

HARUS DENGAN RESEP DOKTER

Manufactured by:
Daiichi Sankyo Europe GmbH, Pfaffenhofen, Germany

Packed and Released by:
Pfizer Manufacturing Deutschland GmbH, Freiburg Im Breisgau, Germany

Imported by:
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