SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Logimax 5 mg/50 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 prolonged-release tablet contains: 5 mg felodipine and metoprolol succinate equivalent to 50 mg metoprolol tartrate.

Excipients with known effect: polyoxyl 40 hydrogenated castor, lactose and sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Logimax prolonged-release tablets contain metoprolol succinate in the form of granules, which each form an individual depot unit, and which together with felodipine are embedded in a polymer. In contact with fluid a gel layer is formed, which permits continuous release of both felodipine and metoprolol.

Appearance
Logimax: apricot-coloured, round, biconvex, marked A/FG, diameter 10 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension. Logimax can be used when treatment with beta-blockers or calcium antagonists of the dihydropyridine type in monotherapy has not produced an adequate effect.

4.2 Posology and method of administration

Adults
One Logimax 5/50 tablet once daily, if needed the dose may be doubled to two Logimax 5/50 tablets once daily.

Patients with renal impairment
Dose adjustment is not needed in patients with impaired renal function.

Patients with hepatic impairment
Dose adjustment is normally not needed in patients suffering from liver cirrhosis because metoprolol has a low protein binding (5-10%). When there are signs of serious impairment of liver function (e.g. shunt-operated patients) doses higher than Logimax 5/50 mg should not be given.

Elderly
One Logimax prolonged-release tablet once dailyis usually sufficient. If required, the dose may be increased to two Logimax prolonged-release tablets per day.

Paediatric population
Logimax should not be used in children due to lack of clinical experience.

Advice for discontinuation
Abrupt interruption of the medication is to be avoided. If possible, a dose reduction of Logimax should be performed and/or administration every second day over a period of 10-14 days. During this period, in particular, patients with known ischaemic disease should be closely monitored since the risk for myocardial infarction and sudden death may be increased during withdrawal of Logimax or other medicinal products containing a βeta-blocker.

Specific advice on action to take if doses are missed
Due to the properties of Logimax, omission of isolated doses is without consequences.

Method of administration
The prolonged-release tablets are given once daily, in the morning. The prolonged-release tablets must be swallowed with liquid, and must not be divided, crushed or chewed. The prolonged-release tablets may be taken on an empty stomach or together with a light low fat, low carbohydrate meal.

4.3 Contraindications

Known hypersensitivity to the active substances, to any of the excipients listed in section 6 to other dihydropyridines or beta-blockers. Pregnancy. Acute myocardial infarction. Unstable angina pectoris. Degree II and III AV block. Haemodynamically significant cardiac valvular obstruction. Dynamic cardiac outflow obstruction. Patients with unstable uncompensated cardiac failure (pulmonary oedema, hypoperfusion or hypotension), and patients with continuous or intermittent inotropic therapy with beta-receptor agonists. Symptomatic bradycardia. Sick sinus syndrome (unless a permanent pacemaker is in place) Cardiogenic shock. Severe peripheral vascular disease with threat of gangrene. Obstructive cardiomyopathy.

4.4 Special warnings and precautions for use

The fixed combination of felodipine and metoprolol, can like other antihypertensives, cause hypotension. Felodipine may cause significant hypotension with subsequent tachycardia. This may in susceptible patients result in myocardial ischaemia.

In cases of bronchial asthma, adequate bronchodilator therapy (tablets or inhalation) must be given concomitantly. The dose of β_2-agonists may need to be increased when treatment with Logimax is started. The risk for interaction between Logimax and β_2-agonists is, however, less than with conventional tablet formulations of β_1-selective blockers.

Treatment with Logimax may affect carbohydrate metabolism or mask hypoglycaemia, but the risk is less than with conventional tablet formulations of β_1-selective blockers and much less than with non-selective β-receptor blockers.

Logimax should not be given to patients with latent or manifest cardiac insufficiency without concomitant treatment of this condition.

An existing moderate disturbance of AV-conduction time may be exacerbated (possibly leading to AV block).

Logimax should be given with caution to patients with severe acute states of metabolic acidosis.

Intravenous administration of calcium antagonists of the verapamil type must not be given to patients being treated with Logimax.

If patients develop pronounced bradycardia, the dose of Logimax should be reduced or gradually withdrawn.

Logimax may aggravate symptoms of worsened peripheral arterial circulation.

Logimax should not be given in combination with CYP3A4- inhibitors or- inducers, see section 4.5

If Logimax is given to patients with phaeochromocytoma, concomitant treatment with α-blockers should be given.
Prior to surgery, the anaesthetist must be informed that the patient is on Logimax. It is recommended that beta-blockade is not withdrawn in patients who are undergoing surgery. Treatment with β-blockers may aggravate the treatment of an anaphylactic reaction. Adrenaline treatment in normal doses does not always produce the expected therapeutic effect.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

β_1-selective receptor blockers should be used with caution in patients with Prinzmetal's angina.
Mild gingival enlargement has been reported in patients with pronounced gingivitis/periodontitis. The enlargement can be avoided or reversed by careful dental hygiene.
LOGIMAX contains lactose and should not be given to patients with hereditary galactose intolerance or glucose-galactose malabsorption.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

Concomitant administration of substances that influence the cytochrome P450 system can affect the plasma concentration of both felodipine and metoprolol. Felodipine and metoprolol do not interact with each other, since they utilise different isoenzymes of cytochrome P450.

Interactions with felodipine

Felodipine is metabolised in the liver by cytochrome P450 3A4 (CYP3A4)2.
Interactions leading to increased plasma concentration of felodipine
Enzyme inhibitors of the cytochrome P450 3A4 system have been shown to cause an increase in felodipine plasma concentrations.

Examples:
Strong CYP3A4-inhibitor

- Itraconazole
- Ketoconazole
- Anti-HIV/protease inhibitors (e.g. ritonavir)

Other CYP3A4-inhibitors
- Cimetidine
- Erythromycin
- Certain flavonides present in grapefruit juice

During concomitant administration of itraconazole, the felodipine C_{max} increased 8-fold and the AUC 6-fold.
During concomitant administration of erythromycin, the felodipine C_{max} and AUC increased approximately 2.5-fold.
During concomitant administration of grapefruit juice the felodipine C_{max} and AUC increased approximately 2-fold.
During concomitant administration of cimetidine the felodipine C_{max} and AUC increased by approx. 55 %.

Interactions leading to decreased plasma concentrations of felodipine
Enzyme inducers of the cytochrome P450 3A4 system may cause a decrease in felodipine plasma concentrations.

Examples:
- Phenytoin
- Carbamazepine
- Rifampicin
- Barbiturates
- Efavirenz
- Nevirapine
- *Hypericum perforatum* (Saint John's worth)

During concomitant administration of carbamazepine, phenytoin, and phenobarbital, the felodipine decreased AUC by 93 % and C_{max} by 82 %.

Additional interactions with felodipine:
Tacrolimus: Felodipine may increase the concentration of tacrolimus. When used together, the tacrolimus serum concentration should be followed and the tacrolimus dose may need to be adjusted.

Cyclosporin: During concomitant administration of cyclosporin and felodipine, Cmax for felodipine increased by 150 % and AUC by approx. 60 %. Felodipine, however, does not affect plasma concentrations of cyclosporin.

Interactions with metoprolol

Metoprolol is a substrate for cytochrome P450 isoenzyme 2D6. Drugs that act as enzyme-inducing or enzyme-inhibiting substances on CYP2D6 may exert an influence on the plasma level of metoprolol.

CYP2D6-inhibitors may cause an increase in metoprolol plasma concentration.

Examples:
- Antiarrhythmics (e.g. quinidine, propafenon)
- Antihistamines (e.g. diphenhydramine)

- Histamine-2-receptor antagonists
- Antidepressants (e.g. paroxetin, fluoxetin, sertraline)
- Antipsychotics
- COX-2-inhibitors (e.g. celecoxib)
- Antifungals (e.g. terbinafine)

When propafenone treatment was initiated in four patients who were already treated with metoprolol, the plasma concentrations of metoprolol increased 2-5-fold, and two patients experienced typical metoprolol side effects. The interaction was confirmed in tests on eight healthy subjects.

Diphenhydramine reduces (2.5-fold) clearance of metoprolol to alpha-hydroxymetoprolol in rapid hydroxylators via CYP2 D6.

The plasma concentration of metoprolol may be raised by alcohol and hydralazine.
The plasma concentration of metoprolol is lowered by rifampicin.

Additional interactions with metoprolol:
The following combinations with Logimax may require adjustment of doses:

Ganglion blocking agents, MAO-inhibitors, other β-blockers:
Patients receiving concomitant treatment with Logimax and ganglion blocking agents, other β-blockers (e.g. eye drops), or MAO-inhibitors should be kept under close supervision.

Clonidine: If concomitant treatment with clonidine must be discontinued, Logimax must be withdrawn several days before clonidine.

Calcium antagonists: Increased negative inotropic and chronotropic effects may occur when Logimax is given together with calcium antagonists of the verpamil- or diltiazem type. Intravenous administration of calcium blockers of the verapamil type should not be given together with Logimax.

Antiarrhythmic agents: Logimax may increase the negative inotropic and dromotropic effects of antiarrhythmic agents (of quinidine type and amiodarone).

Digitalis glycosides: Digitalis glycosides in association with β-blockers, may increase atrioventricular conduction time and may induce bradycardia.

Inhalation anaesthetic agents: Inhalation anaesthetic agents enhance the cardiodepressant effect in patients treated with Logimax.

Prostaglandin synthetase inhibitors: Concomitant treatment with indomethacin or other prostaglandin synthetase inhibiting drugs may decrease the antihypertensive effect of Logimax.

Adrenaline: Under certain conditions, when adrenaline is administered to patients treated with β-blockers, pronounced hypertension and bradycardia may occur. Cardioselective β-blockers interfere much less with blood pressure control than non-selective β-blockers.

Oral antidiabetics: The dosage of oral antidiabetics may have to be readjusted in patients receiving Logimax.
Phenylpropanolamine: Phenylpropanolamine (norephedrine) at single doses of 50 mg may increase diastolic blood pressure to reach pathologic levels in healthy subjects. Propranolol normally counteracts that increase of blood pressure triggered by phenylpropanolamine.

β-blockers may, however trigger paradoxical hypertensive reactions in patients who take high doses of phenylpropanolamine. Hypertensive crises during treatment with phenylpropanolamine alone have been described in a few cases.

4.6 Fertility, pregnancy and lactation

Fertility
Data on male and female fertility in patients are missing (see section 5.3).

Pregnancy
Logimax should not be given during pregnancy.

Breast-feeding
Felodipine passes into human milk. When taken in therapeutic doses by the nursing mother it is not likely to affect the infant. β-blockers may cause side effects e.g. bradycardia in the foetus and in the newborn and breast-fed infant. The amount of metoprolol ingested via human milk, however, seems to be negligible as regards β-blocking effect in the infant if the mother is treated with metoprolol in doses within the therapeutic range.

4.7 Effects on ability to drive and use machines

Since dizziness and fatigue can occur during treatment with Logimax, this should be taken into account when increased alertness is required, for instance when driving a vehicle or using a machine. The patient must evaluate for himself/herself whether the alertness changes when taking Logimax.

4.8 Undesirable effects

Logimax is well tolerated and adverse reactions have generally been mild and reversible.

The most common undesirable effects reported in clinical trials with Logimax are headache, swelling of the ankles, facial redness, dizziness, nausea and fatigue. Most of these effects are attributable to the vasodilator properties of felodipine, they are usually dose related and appear at the beginning of treatment or when the dose is increased. If they appear, they are usually transient and diminish in intensity over time.

From the clinical and marketing experience with the individual components the adverse drug reactions below have been reported.

As with other calcium antagonists, mild gingival enlargement has been reported in patients with pronounced gingivitis/periodontitis. The enlargement can be avoided or reversed by careful dental hygiene.
Very common (≥1/10)
Common (≥1/100 and <1/10),
Uncommon (≥1/1,000 and <1/100)
Rare (≥1/10,000 and <1/1,000) and
Very rare (<1/10,000)

Felodipine

System organ class	Frequency	Symptoms
Nervous system disorders	Common	Headache.

System organ class	Frequency	Symptoms
	Uncommon	Dizziness, paraesthesia.
Cardiac disorders	Common	Peripheral oedema.
	Uncommon	Tachycardia, palpitations.
	Rare	Syncope.
Gastrointestinal disorders	Uncommon	Nausea, abdominal pain.
	Rare	Vomiting.
	Very rare	Gingival hyperplasia, gingivitis.
Hepatobiliary disorders	Very rare	Increased liver enzymes.
Musculoskeletal and connective tissue disorders	Rare	Myalgia, arthralgia.
Psychiatric disorders	Rare	Impotence/sexual dysfunction.
Skin and subcutaneous tissue disorders	Common	Flushing.
	Uncommon	Rash, pruritus.
	Rare	Urticaria.
	Very rare	Photosensitivity reactions, leukocytoclastic vasculitis.
Renal and urinary disorders	Very rare	Pollakiuria.
General disorders and administration site conditions	Uncommon	Fatigue.
	Very rare	Hypersensitivity reactions e.g. angioedema, fever.

Metoprolol

System organ class	Frequency	Symptoms
Cardiac disorders	Common	Bradycardia, postural disorders (very rarely with syncope), peripheral coldness of extremities, palpitations.
	Uncommon	Transient deterioration of heart failure symptoms, AV-block I, oedema, precordial pain.

System organ class	Frequency	Symptoms
	Rare	Disturbances of cardiac conduction, cardiac arrhythmia.
	Very rare	Gangrene in patients with severe peripheral circulatory disorders.
Nervous system disorders	Very common	Fatigue.
	Common	Dizziness, headache.
	Uncommon	Paraesthesia, muscle cramps.
Gastrointestinal disorders	Common	Nausea, abdominal pain, diarrhoea, constipation.
	Uncommon	Vomiting.
	Rare	Dry mouth.
Blood and lymphatic system disorders	Very rare	Thrombocytopenia.
Hepatobiliary disorders	Rare	Liver function test abnormal.
	Very rare	Hepatitis.
Metabolism and nutrition disorders	Uncommon (≥1/1,000 to <1/100)	Weight gain.
Musculoskeletal and connective tissue disorders	Very rare (<1/10,000)	Arthralgia.
Psychiatric disorders	Uncommon (≥1/1,000 to <1/100)	Depression, concentration impaired, sleep disturbance, nightmare.
	Rare (≥1/10,000 to <1/1000)	Nervousness, anxiety, impotence/sexual dysfunction.
	Very rare (<1/10,000)	Amnesia/memory impairment, confusion, hallucinations.
Respiratory, thoracic and mediastinal disorders	Common (≥1/100 to <1/10)	Dyspnoea exertional.
	Uncommon (≥1/1,000 to <1/100)	Bronchospasm, shortness of breath.
	Rare (≥1/10,000 to <1/1000)	Rhinitis.
Eye, Ear and labyrinth disorders	Rare (≥1/10,000 to <1/1000)	Visual disturbance, dry eye and/or eye irritation,

System organ class	Frequency	Symptoms
		conjunctivitis.
	Very rare (<1/10,000)	Tinnitus, taste disturbance.
Skin and subcutaneous tissue disorders	Uncommon (≥1/1,000 to <1/100)	Hypersensitivity reactions (e.g. urticaria, psoriasiform and dystrophic skin lesion) hyperhidrosis.
	Rare (≥1/10,000 to <1/1,000)	Alopecia.
	Very rare (<1/10,000)	Photosensitivity reaction, aggravated psoriasis.

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 to Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy/phs Fax: + 357 22608649.

4.9 Overdose

Toxicity
Felodipine: 10 mg in a 2-year-old caused mild intoxication. 150-200 mg in a 17-year-old and 250 mg in an adult caused mild to moderate intoxication. Probably a more pronounced effect on the peripheral circulation than on the heart, compared with other drugs in the group.

Metoprolol: 7.5 g in an adult caused fatal intoxication. 100 mg in a 5-year-old caused no symptoms after gastric lavage. 450 mg in a 12-year-old and 1.4 g in an adult caused moderate intoxication, 2.5 g in an adult caused severe intoxication, 7.5 g in an adult caused extremely severe intoxication.

Symptoms
In cases of intoxication with prolonged-release preparations, the onset of symptoms may be delayed for 12-16 hours, and severe symptoms may occur after several days.

Felodipine: Overdose with felodipine may cause excessive peripheral vasodilatation with marked hypotension and sometimes bradycardia.
Other: AV block, AV dissociation, VES, ventricular fibrillation, asystole. Dizziness, headache, impaired consciousness, coma, convulsions. Dyspnoea, pulmonary oedema (non-cardiac) and apnoea. Possibly ARDS (Adult Respiratory Distress Syndrome). Acidosis, hypokalaemia, hyperglycaemia, possibly hypocalcaemia. Flushing, hypothermia. Nausea and vomiting.

Metoprolol: Overdose of metoprolol may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, nausea, vomiting and cyanosis. In some cases, especially in children and adolescents, CNS symptoms and respiratory depression may predominate.

Other:
Poor peripheral blood perfusion, respiratory depression, apnoea. Fine tremors, convulsions, perspiration, paraesthesia, possibly oesophageal spasm, hypoglycaemia (especially in children),

or hyperglycaemia, hyperkalaemia. Effects on the kidneys. Transient myasthenic syndrome. Concomitant ingestion of alcohol, antihypertensive drugs, quinidine or barbiturates may aggravate the patient's condition.

The first signs of overdose may be seen 20 minutes to 2 hours after ingestion.

Treatment

Felodipine: Charcoal, if necessary gastric lavage, in some cases even at a late stage. If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. NOTE! Atropine (0.25-0.5 mg intravenously for adults, 10-20 micrograms/kg for children) should be given *before* gastric lavage (owing to the risk of vagal stimulation). ECG monitoring. Respirator on wide indication. Correction of acid-base and electrolyte status. In cases of concomitant bradycardia and block: Atropine 0.5-1 mg intravenously for adults (20-50 micrograms/kg for children), possibly repeated, or isoprenaline initially 0.05-0.1 micrograms/kg/minute. Pacemaker at an early stage in severe cases. If this is not enough, increase plasma volume by intravenous infusion of e.g. glucose, saline or dextran, or calcium glubionate (9 mg Ca/ml) 20(-30) ml intravenously over a period of 5 minutes for adults (3-5 mg Ca/kg for children) initially and repeated if required, or as an infusion, adrenaline or dopamine if required. In severe cases glucagon may be administered. Sympathomimetics with predominant effect on the α_1-adrenoceptor may be given if treatment as above is not sufficient.
In cases of circulatory arrest in connection with overdose, resuscitation should be instituted and may have to be continued for several hours. Diazepam for convulsions. Other symptomatic treatment.

Metoprolol: Charcoal, gastric lavage if required. NOTE! Atropine (0.25-0.5 mg intravenously for adults, 10-20 micrograms/kg for children) should be given *before* gastric lavage (on account of the risk of vagal stimulation). Intubation and respirator treatment should be carried out on very wide indication. Adequate volume expansion. Glucose infusion. ECG monitoring. Atropine 1.0-2.0 mg intravenously, possibly repeated (especially in cases of vagal symptoms). In the presence of severe hypotension, bradycardia and impending heart failure, administer a β_1-agonist intravenously at 2-5 minutes intervals or as continuous infusion until the desired effect is achieved. Where a selective β_1-agonist is not available, dopamine or atropine sulphate i.v. may be used in order to block the vagus nerve. If a satisfactory effect is not achieved, other sympathomimetic agents such as dobutamine or noradrenaline may be given.

For myocardial depression: infusion of dobutamine or dopamine and calcium glubionate 9 mg/ml, 10-20 ml. Glucagon 50-150 micrograms/kg intravenously over a period of 1 minute followed by infusion may also be administered, as may amrinone. In some cases, the addition of epinephrine (adrenaline) has been effective. Infusion of sodium (chloride or bicarbonate) in cases of widening QRS-complex and arrhythmias. Possibly pacemaker.

To combat bronchospasm, a β-agonist can be given intravenously.

In cases of circulatory arrest in connection with overdose, resuscitation for several hours may be justified. For bronchospasms, possibly terbutaline (via injection or inhalation). Symptomatic therapy.

Observe that the dosages of drugs (antidotes) needed to treat overdose of b-blockade are much higher than the recommended therapeutic dosages, because the b-receptors are occupied by the b-blockade.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium antagonists and beta-blockers.
ATC code: C07FB02

Logimax is an antihypertensive preparation consisting of a combination of felodipine, which is a calcium antagonist with a selective effect on pre-capillary resistance vessels, and metoprolol, which is a $beta_1$-selective receptor blocker.
As a result of the complementary mechanisms of action of the two substances (felodipine reduces peripheral vascular resistance and metoprolol reduces cardiac output), a more pronounced antihypertensive effect is obtained than with either of the two drugs in monotherapy. With Logimax an even and effective lowering of blood pressure over the entire interval between doses (24 hours) is achieved.

Felodipine
Felodipine is a vascular selective calcium antagonist for the treatment of hypertension and stable angina pectoris.
Felodipine is a dihydropyridine derivative and a racemate.
Felodipine acts by reducing peripheral vascular resistance, especially in arterioles. The electrical and contractile activity in the smooth muscle cells in the vessels is inhibited via an effect on the calcium channels in the cell membrane.
As a result of felodipine having a selective effect on smooth muscle in the arterioles, in therapeutic doses it has neither negative inotropic effect on the heart and nor clinically significant electrophysiological effect in the heart. Felodipine relaxes smooth muscle in the respiratory tract. Clinical experience has shown that felodipine has little effect on gastrointestinal motoricity. No clinically significant effect of felodipine on blood lipid values has been observed during long-term treatment. Nor has any clinically significant effect on metabolic control (HbA1c) been observed in patients with type II diabetes during 6 months of treatment.
Felodipine can generally also be given to patients who additionally have reduced left ventricular function and are being treated with conventional therapy, and to patients with asthma, diabetes, gout or hyperlipidaemia.

Antihypertensive effect: Felodipine lowers arterial blood pressure by reducing peripheral vascular resistance. Treatment of hypertensive patients with felodipine produces a lowering of blood pressure in supine, seated and standing positions, at rest and during exercise. Felodipine does not cause orthostatic hypotension, as the substance does not affect smooth muscle in the veins or adrenergic control mechanisms. The lowered blood pressure may initially result in a transient, reflectory increase in heart rate and cardiac output. The increase in heart rate is counteracted if felodipine is given in combination with beta-blockers. The effect on blood pressure and total peripheral vascular resistance is correlated to the plasma concentration of felodipine. At steady state the effect lasts for the entire interval between doses, and produces a lowering of blood pressure throughout the entire 24-hour period.

Treatment with felodipine produces a regression of left ventricular hypertrophy.
Felodipine has a natriuretic and diuretic but no kaliuretic effect. Tubular reabsorption of sodium and water is reduced, which may explain the absence of salt and fluid retention in patients. Felodipine reduces renal vascular resistance and increases renal perfusion. Glomerular filtration is not affected. Felodipine does not affect albumin excretion.

Metoprolol
Metoprolol is a $beta_1$-selective receptor blocker, which means that it influences the cardiac $beta_1$-receptors at lower doses than those required to influence $beta_2$-receptors in peripheral vessels and bronchi.
Metoprolol is devoid of beta-stimulant effects and has little membrane-stimulating effect. Beta-receptor blockers have negative inotropic and chronotropic effects.
Treatment with metoprolol reduces the effects of catecholamines associated with physical and psychological stress, and results in a lower heart rate, lower cardiac output and lower blood pressure. In stress states with increased secretion of adrenaline from the adrenal glands, metoprolol does not prevent normal physiological vasodilation. In therapeutic doses, metoprolol has less contractile effect on the bronchial musculature than non-selective beta-blockers. This property makes it possible to treat patients with bronchial asthma or other pronounced obstructive pulmonary disease with metoprolol in combination with $beta_2$-receptor stimulants.
Metoprolol influences insulin secretion and carbohydrate metabolism to a lesser extent than non-selective beta-blockers, and can therefore also be given to patients with diabetes mellitus. The cardiovascular reaction in hypoglycaemia, e.g. tachycardia, is less affected by metoprolol, and the return of the blood sugar level to normal takes place more rapidly than with non-selective beta-receptor blockers.
In hypertension, metoprolol produces a marked lowering of blood pressure in both supine and standing position and during physical effort. Initially, treatment with metoprolol causes an increase in peripheral vascular resistance. During long-term treatment, however, the achieved lowering of blood pressure is attributed to reduced peripheral vascular resistance and unchanged cardiac output. Metoprolol reduces the risk of cardiovascular death in men with moderate/severe hypertension. The electrolyte balance is not disturbed.

5.2 Pharmacokinetic properties

Felodipine
Bioavailability is approx. 15 % and is not influenced by concomitant food intake. The rate –but not the extent– of absorption is affected by concomitant food intake, which is why the maximum plasma concentration increases by approx. 65 %. The peak plasma concentration is reached after 3-5 hours. Binding to plasma proteins is approximately 99 %. The volume of distribution at steady state is 10 l/kg. The half-life of felodipine in the elimination phase is approx. 25 hours, and steady state is reached after 5 days. There is no risk of accumulation during long-term treatment. Clearance is on average 1200 ml/min. Reduced clearance in elderly patients and patients with impaired hepatic function leads to these patients having higher plasma concentrations of felodipine than younger patients. However, age only partially explains the interindividual variations in plasma concentration. Felodipine is metabolised in the liver, and all identified metabolites are devoid of vasodilator effects. Approx. 70 % of a given dose is excreted as metabolites via the urine, the remainder in the faeces. Less than 0.5 % of a given dose is excreted in unchanged form in the urine. Impaired renal function does not affect the plasma concentration of felodipine, but accumulation of inactive metabolites occurs. Felodipine is not eliminated by haemodialysis.

Metoprolol
Absorption after oral administration is complete, and the substance is absorbed along the entire gastrointestinal tract, including the colon. The bioavailability of Seloken ZOC is 30-40 %. Metoprolol is metabolised in the liver mainly by CYP2D6. Three main metabolites have been identified, but none with a beta-blocking effect of clinical significance. Approx. 5 % of metoprolol is excreted via the kidneys in unchanged form, the remainder of the dose in the form of metabolites.

Characteristics of combination products
On administration of Logimax the bioavailability of neither metoprolol nor felodipine is altered, compared with concomitant administration of metoprolol and felodipine only. Absorption is not influenced by concomitant intake of food.

5.3 Preclinical safety data

Available studies concerning general toxicity, genotoxicity and carcinogenicity did not reveal any special risks for humans. In animal studies beta-receptor blockers caused bradycardia in the foetuses. In several species, calcium antagonists have caused embryotoxic and/or teratogenic effects, mainly in the form of distal skeletal malformations. In reproduction toxicology studies with felodipine, prolonged pregnancy and difficult parturition were observed in rats, and in rabbits poorer development of distal phalanges was seen (probably caused by reduced uteroplacental perfusion). These observations do not indicate direct teratogenic effects, but suggest secondary consequences of the pharmacodynamic effects of felodipine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colouring agents (titanium dioxide E171, iron oxide E172), lactose anhydrous 42 mg, propyl gallate, silicon dioxide, paraffin, hypromellose, cellulose microcrystalline, ethylcellulose, hydroxypropylcellulose, aluminium sodium silicate, macrogol, sodium stearyl fumarate, polyoxyl 40 hydrogenated castor oil.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVDC blister packs.
28 tablets

6.6 Special precautions for disposal and other handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

16252

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