SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fortipine LA 40mg Modified-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient

Each film-coated tablet contains Nifedipine 40mg.

Each film-coated tablet contains 30 mg Lactose
For the full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM

Modified release tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the prophylaxis of chronic stable angina pectoris and the treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Posology

The following recommendations for dosing in adults are applicable:

In general, one modified release tablet of Fortipine LA 40 (40mg) once daily should be adequate. If necessary, this dose can be increased to 80 mg given once daily, or 40 mg twice daily.

Elderly:

Patients should be treated individually depending on the severity of the disease and the therapeutic response. The pharmacokinetics of nifedipine are altered in the elderly, so that a maintenance dose should be once daily modified release tablet of 40mg. Regular assessment of the medical regime should be performed to minimise unwanted effects.

Renal Impairment:

In patients with renal dysfunction, a slight alteration of the pharmacokinetics of nifedipine may be seen. However, dose adjustment in these patients is not usually required.

Hepatic Impairment:

In patients with liver cirrhosis and chronic liver failure, significant alterations of the pharmacokinetics of nifedipine is usually seen. These patients should usually be carefully monitored when initiating therapy and during maintenance treatment with a dose that should not exceed one modified release tablet of 40mg.

Paediatric population:

The safety and efficacy of nifedipine in children and adolescents under the age of 18 years have not been established.
Currently available data for the use of nifedipine in hypertension are described in section 5.1.

Method of administration

For oral administration.
The modified release tablets are to be taken after meals, e.g. breakfast. The modified release tablets should be swallowed whole with half a glass of water and must not be broken or chewed. Nifedipine should not be taken with Grapefruit juice (see Section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
Fortipine LA 40 should not be administered to patients with hypersensitivity to other dihydropyridines because of the theoretical risk of cross-reactivity, nor to patients with a cardiogenic shock. It is contra-indicated in women with child-bearing potential and those breastfeeding their babies. Fortipine LA 40

is contra-indicated in patients with cardiac failure, with those with markedly severe hypotension with less than 90mm Hg systolic and with porphyria.

Fortipine LA 40 should not be used in clinically significant aortic stenosis, patients who develop unstable angina, or during or within 1 month of a myocardial infarction.

Fortipine LA 40 should not be used for secondary prevention of myocardial infarction.

Fortipine LA 40 should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction.

4.4 Special warnings and precautions for use

Patients at risk of hypotensive crisis should begin any therapy under close medical supervision.

Ischaemic pain has been reported in a small proportion of patients following the introduction of nifedipine therapy. Although a 'steal' effect has not been demonstrated, patients experiencing this effect should discontinue nifedipine therapy.

Fortipine LA 40 is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be a gradual reduction of the dose of beta-blocker preferably over 8 - 10 days.

Fortipine LA 40 may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Fortipine LA will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm Hg.

Fortipine LA 40 should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Fortipine LA 40 should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.6).

Fortipine LA 40 is not recommended for use during breastfeeding because nifedipine has been reported to be excreted in human milk and the effects of oral absorption of small amounts of nifedipine are not known (see section 4.6).

Careful monitoring of blood pressure must be exercised when administering nifedipine with I.V. magnesium sulphate, owing to the possibility of an

excessive fall in blood pressure, which could harm both mother and foetus. For further information regarding use in pregnancy, refer to section 4.6.

In patients with impaired liver function, careful monitoring, and in severe cases, a dose reduction may be necessary.

Fortipine LA 40 should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

The use of Fortipine LA 40 in diabetic patients may require adjustment of their control.

In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur.

Nifedipine is metabolised via the cytochrome P450 3A4 system. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass or the clearance of nifedipine (see Section 4.5).

Drugs that are known inhibitors of the cytochrome P450 3A4 system, and which may therefore lead to increased plasma concentrations of nifedipine include, for example:

- macrolide antibiotics (e.g., erythromycin)
- anti-HIV protease inhibitors (e.g., ritonavir)
- azole antimycotics (e.g., ketoconazole)
- the antidepressants, nefazodone and fluoxetine
- quinupristin/dalfopristin
- valproic acid
- cimetidine

Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered. (see Section 4.5)

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of Interaction

Antihypertensives

Fortipine LA 40 can be administered concomitantly with other antihypertensives including beta-receptor blockers. These may have additive antihypertensive or potentiating effects and postural hypotension may therefore occur. Concomitant treatment of nifedipine with a beta-blocker occasionally results in the occurrence of heart failure. For this reason, a

combination with a beta-blocker is only recommended in patients that are not suffering from any degree of heart failure or ventricular strain. After discontinuation of the beta-blocker, a deterioration with regard to the symptoms of angina pectoris may occasionally occur, due to the abrupt withdrawal of the beta-blocker. Therefore, it is not recommended to switch abruptly from a beta-blocker to nifedipine.

Fortipine LA 40 will not prevent the possibility that there might be a rebound effect when other antihypertensive treatment is stopped.

Cimetidine

Concomitant therapy with cimetidine may potentiate the antihypertensive action of nifedipine.

Antiarrhythmics

Fortipine LA 40 administration may suppress serum levels of quinidine and may increase plasma digoxin levels due to reduced drug clearance. Therefore, on combination therapy monitoring of quinidine levels, as well as digoxin levels is recommended.

Antidiabetics

Fortipine LA 40 may modify insulin and glucose responses, requiring adjustment in therapy of treated diabetics.

Grapefruit juice

Grapefruit juice inhibits the oxidative metabolism of nifedipine; this may be potentially significant in some patients.

Antimycobacterials

Nifedipine should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see contra-indications).

Anti-psychotics

An enhanced hypotensive effect may be seen when nifedipine is co-administered with anti-psychotics and possibly ciclosporin.

Calcium-channel blockers

Nifedipine clearance can be reduced when co-administered with diltiazem.

Antiepileptics

Nifedipine effect may be reduced when co-administered with carbamazepine.

Nifedipine increases the plasma concentration of phenytoin.

Muscle relaxants

Nifedipine enhances the effect of non-depolarising muscle relaxants.

4.6 Fertility, pregnancy and lactation

Fortipine LA 40 is contraindicated in pregnancy before week 20.

Pregnancy

Fortipine LA 40 should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.4).
There are no adequate and well controlled studies in pregnant women.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as tocolytic during pregnancy (see section 4.8), especially in cases of multiple pregnancy (twins or more), with the intravenous route and/or concomitant use of beta-2 agonists.

In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity (see Section 5.3 Preclinical safety data).

From the clinical evidence available a specific prenatal risk has not been identified, although an increase in perinatal asphyxia, caesarean delivery, as well as prematurity and intrauterine growth retardation have been reported.

It is unclear whether these reports are due to the underlying hypertension, its treatment, or to a specific drug effect.

The available information is inadequate to rule out adverse drug effects on the unborn and newborn child. Therefore any use in pregnancy after week 20 requires a very

careful individual risk benefit assessment and should only be considered if all other treatment options are either not indicated or have failed to be efficacious.

Breast-feeding
Nifedipine passes into the breast milk. The nifedipine concentration in the milk is almost comparable with mother serum concentration. For immediate release formulations, it is proposed to delay breastfeeding or milk expression for 3 to 4 hours after drug administration to decrease the nifedipine exposure to the infant (see section 4.4).

Fertility
In single cases of in-vitro fertilisation calcium antagonists like nifedipine have been associated with reversible biochemical changes in the spermatozoa's head section that may result in impaired sperm function. In those men who are repeatedly unsuccessful in fathering a child by in vitro fertilisation, and where no other explanation can be found, calcium antagonists like nifedipine should be considered as possible causes.

4.7 Effects on ability to drive and use machines

Fortipine LA 40 may cause headache, dizziness, nausea and tiredness to such a degree that reaction time is affected. These effects can be aggravated by concurrent consumption of alcohol. If this occurs, the patient should be advised not to drive or operate machines.

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on placebo-controlled studies with nifedipine sorted by CIOMS III categories of frequency (clinical trial data base: nifedipine n = 2,661; placebo n = 1,486; status: 22 Feb 2006 and the ACTION study: nifedipine n = 3,825; placebo n = 3,840) are listed below:

ADRs listed under "common" were observed with a frequency below 3% with the exception of oedema (9.9%) and headache (3.9%).

ADRs derived from post marketing reports are printed in bold italic.

Common > 1% to <10%	Uncommon >0.1% to <1%	Rare >0.01% to <0.1%	Frequency Not Known
Blood and lymphatic system disorders			
			Agranulocytosis Leukopenia
Immune System Disorders			
	Allergic reaction Allergic	Pruritus Urticaria	Anaphylactic/anaphylactoid reaction

	oedema/angioedema (Incl. Larynx oedema*)	Rash	
Psychiatric Disorders			
	Anxiety reactions Sleep disorders		Depression
Metabolism and nutrition disorders			
			Hyperglycaemia
Nervous System Disorders			
Headache	Vertigo Migraine Dizziness Tremor	Par-/Dys aesthesia	Hypoaesthesia Somnolence
Eye Disorders			
	Visual disturbances		Eye Pain
Cardiac Disorders			
	Tachycardia Palpitations		Chest Pain (Angina Pectoris)
Vascular Disorders			
Oedema Vasodilatation	Hypotension Syncope		
Respiratory, thoracic, and mediastinal disorders			
	Nosebleed Nasal congestion		Dyspnoea Pulmonary oedema**
Gastrointestinal Disorders			
Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Bezoar Dysphagia Intestinal obstruction Intestinal ulcer Vomiting Gastrooesophageal sphincter insufficiency
Hepatobiliary Disorders			

	Transient increase in liver enzymes		Jaundice
Skin and Subcutaneous Tissue Disorders			
	Erythema		Toxic Epidermal Necrolysis Photosensitivity allergic reaction Palpable purpura
Musculoskeletal, Connective Tissue and Bone Disorders			
	Muscle cramps Joint swelling		Arthralgia Myalgia
Renal and Urinary Disorders			
	Polyuria Dysuria		
Reproductive System and Breast Disorders			
	Erectile dysfunction		
General Disorders and Administration Site Conditions			
Feeling unwell	Unspecific pain Chills		

* may result in life-threatening outcome

**cases have been reported when used as tocolytic during pregnancy (see section 4.6)

In dialysis patients with malignant hypertension and hypovolaemia a distinct fall in blood pressure can occur as a result of vasodilation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Toxic effects arise from the three main actions of nifedipine in overdose: dilatation of vascular smooth muscles (predominant effect); decreased myocardial contractility; and depression of AV nodal conduction. Hypotension and tachycardia or bradycardia are the most likely manifestations of overdose. Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, coma and convulsions. Cardiac effects may include heart block, AV dissociation and asystole; metabolic disturbances include hyperglycaemia, acidosis, hypo- or hyperkalaemia and hypocalcaemia; pulmonary oedema has been reported.

Treatment

Primary treatment involves removal of nifedipine by gastric lavage or ipecacuanha and administration of activated charcoal (50 g adults; 10 - 15 g children). Fortipine LA 40 is a modified release matrix tablet, therefore activated charcoal should be repeated at 4 hourly intervals (25 g adults; 10 g children). The patient should be closely monitored and treated according to predominating signs: for hypotension: the feet should be raised and plasma expanders given. If this is not effective, 10 % calcium gluconate or chloride can be given intravenously (calcium chloride should not be given to acidotic patients). If this fails, dopamine may be tried (large doses may be needed). Glucagon may be also of value; for bradycardia: treatment with atropine, isoprenaline and cardiac pacing should be given as required.

The value of extracorporeal methods of removal of nifedipine have not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with mainly vascular effects dihydropyridine derivatives.

ATC code: C08CA05

Mechanism of action

Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.

Pharmacodynamic effects

In hypertension, the main action of Fortipine LA 40 is to cause peripheral vasodilatation and thus reduce peripheral resistance.

In angina, Fortipine LA 40 reduces peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume, whilst decreasing after-load.

Additionally, nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

Nifedipine reduces the frequency of painful attacks and the ischaemic ECG changes irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

Clinical efficacy and safety

Fortipine LA 40 administered twice-daily provides 24-hour control of raised blood pressure. It causes reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, Fortipine LA 40 has little or no effect on blood pressure.

Paediatric population:
Limited information on comparison of nifedipine with other antihypertensives is available for both acute hypertension and long-term hypertension with different formulations in different dosages. Antihypertensive effects of nifedipine have been demonstrated but dose recommendations, long term safety and effect on cardiovascular outcome remain unestablished. Pediatric dosing forms are lacking.

5.2 Pharmacokinetic properties

Absorption:
Fortipine LA 40 is absorbed rapidly and almost completely following oral administration. Fortipine LA 40 reaches maximal concentrations (29.4 ± 12.0) X ± SD) ng/ml) 5.0 ± 2.7 hours after drug intake at steady state.

The release of nifedipine from the Fortipine LA 40 modified release tablet is almost linear, this means that the drug is delivered at a constant rate. The relative bioavailability of the modified release form compared to the slow release forms of nifedipine is not statistically different in steady state.

Trough levels after Fortipine LA 40 (24 h post-dose) in steady state (12.0 ± 6.5 ng/ml) are achieved already after the first dose.

Based on its pharmacokinetic profile, an effect due to Fortipine LA 40 is expected over 24 hours.

Concomitant intake of food results in higher maximum plasma concentrations of nifedipine, which occurs earlier compared to administration in the fasted state, but the concentrations at the end of the dose interval are similar.

Distribution:

The protein binding of nifedipine amounts to 94 - 99 %. Animal studies with labelled nifedipine have shown that distribution of the fraction not protein bound is throughout all organs and tissues, with higher concentrations in myocardium than in skeletal muscle. Neither nifedipine nor its metabolites are stored selectively in any tissue.

Biotransformation
Nifedipine is almost completely metabolised to inactive metabolites.

Elimination:
An apparent half-life of 14.9 ± 6.0 hours was found. The apparent half-life of Fortipine LA 40 did not change after repeated dosing. Only < 1 % of the dose is excreted in the urine as the parent compound. 70 - 80 % of the dose is excreted in the urine as metabolites. The remainder is excreted as metabolites in the faeces. Elimination may be retarded by renal failure or insufficiency.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproduction toxicology

Nifedipine has been shown to produce teratogenic findings in rats, mice and rabbits, including digital anomalies, malformation of the extremities, cleft palates, cleft sternum, and malformation of the ribs. Digital anomalies and malformation of the extremities are possibly a result of compromised uterine blood flow, but have also been observed in animals treated with nifedipine solely after the end of the organogenesis period.

Nifedipine administration was associated with a variety of embryotoxic, placentotoxic and foetotoxic effects, including stunted foetuses (rats, mice, rabbits), small placentas and underdeveloped chorionic villi (monkeys), embryonic and foetal deaths (rats, mice, rabbits) and prolonged pregnancy/decreased neonatal survival (rats; not evaluated in other species). The risk to humans cannot be ruled out if a sufficiently high systemic exposure is achieved, however, all of the doses associated with the teratogenic, embryotoxic or foetotoxic effects in animals were maternally toxic and were several times the recommended maximum dose for humans (see Section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

- Microcrystalline Cellulose
- Cellulose
- Methylhydroxypropylcellulose (Hypromellose 2208/4000 mPas)
- Lactose
- Magnesium Stearate
- Colloidal Anhydrous Silica

Film-coat
- Methylhydroxypropylcellulose Hypromellose 15 mPas)
- Macrogol 400 (Polyethyleneglycol 400)
- Macrogol 6000 (Polyethyleneglycol 6000)
- Ferric Oxide Red (E172)
- Titanium Dioxide (E171)
- Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Three years

6.4 Special Precautions for Storage

Do not store above 25°C.
Store in a dry place. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Thermoformed blister packs of red transparent, light protective PVC/PVDC film/aluminium in boxes of 28, 30, 56, 60 or 100 tablets.

6.6 Special precautions for disposal

None.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd.
Dashwood House,
69 Old Broad Street,
London, EC2M 1QS,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 12762/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 June 1998
Date of latest renewal: 14 October 2010

10 DATE OF REVISION OF THE TEXT

28/02/2025