

## **Summary of Product Characteristics**

### **1. NAME OF THE MEDICINAL PRODUCT**

Fortipine LA 40mg Modified Release Tablets

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Active Ingredient

Nifedipine (international non-proprietary name): 40mg chemical name: Dimethyl 1, 4 dihydro-2, 6-dimethyl-6 (2-nitrophenyl) pyridine-3, 5-dicarboxylate.

### **3. PHARMACEUTICAL FORM**

Modified release tablets (matrix tablets) for oral administration.

### **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**

*Adults:*

Patients should be treated individually depending on the severity of the disease and the therapeutic response. Nifedipine should not be taken with Grapefruit juice (see Section 4.5).

The following recommendations for dosing in adults and adolescents over 14 years 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.

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.

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.

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.

*Elderly Patients:*

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.

*Children:*

Not recommended for children under 14 years of age.

**4.3. Contraindications**

FORTIPINE LA 40 should not be administered to patients with hypersensitivity to nifedipine or 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.

Nifedipine 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.

Nifedipine 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 Special Precautions for Use**

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

The safety of nifedipine in malignant hypertension has not been established.

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.

**4.5. Interactions with other Medicaments and other forms of Interaction**

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.

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

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

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

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

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

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

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

Nifedipine increases the plasma concentration of phenytoin.

Nifedipine enhances the effect of non-depolarising muscle relaxants.

#### **4.6. Pregnancy and Lactation**

FORTIPINE LA 40 is contra-indicated in pregnant women and women of child-bearing potential because foetal risks, observed in animal experiments and during human use, far outweigh the potential benefits. Pregnancy category: B3

Nifedipine is secreted into breast milk, so FORTIPINE LA 40 should not be administered during lactation.

#### **4.7. Effects on Ability to Drive and Use Machines**

Nifedipine 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**

Undesirable effects, usually mild and transient in nature, may occur and are more frequent at the beginning of therapy. Frequently, headache, flush (facial reddening), dizziness, as well as oedema, due to vasodilatation, may occur. Less common side effects include rash, nausea, lethargy and urinary frequency. In rare cases, in acute studies, a transient increase in glucose has been observed. This should be considered particularly in patients with diabetes mellitus. Nifedipine has no diabetogenic effect. Rarely gingival hyperplasia has been observed which was reversible after discontinuation of therapy. In elderly patients, very rarely gynaecomastia has been observed which was reversible after discontinuation of therapy. Chest pain due to myocardial

ischaemia may occur 1-4 hours after ingestion of nifedipine. Cases of hypersensitivity to nifedipine resulting in jaundice have been reported.

List of undesirable effects according to body systems:

Cardiovascular System:

Tachycardia, hypotension. As with other vasodilators coronary ischaemia (steal phenomenon) resulting in retrosternal pain, may occur.

As with other sustained released dihydropyridines, exacerbation of angina pectoris may occur rarely at the start of treatment with sustained release formulations of nifedipine. The occurrence of myocardial infarction has been described although it is not possible to distinguish such an event from the natural course of ischaemic heart disease.

Central Nervous System:

Dizziness, tiredness, paraesthesia, tremor

Eyes:

Transient change in optical perception

Gastro-Intestinal Tract:

Nausea, Gastro-intestinal upsets

Skin:

Redness, itching, urticaria, exanthema, and exceptionally exfoliate dermatitis

Urinary Tract:

An increase in the daily amount of urine so that nocturia may occur.

Legs:

Myalgia

Liver:

Very rarely liver function disturbances (intrahepatic cholestasis, or increases in transaminases) have occurred which were reversible after discontinuation of therapy.

Miscellaneous:

Gingival hyperplasia, gynaecomastia, increase in glucose in particular in patients with diabetes mellitus

#### **4.9. Overdose**

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.

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**

Nifedipine is a Ca-antagonist of the 1,4-dihydropyridine type that has been shown to exhibit anti-anginal properties. Ca-antagonists inhibit the slow Ca-channel flux into the myocardial cells, the smooth muscle cells of the coronary arteries and the peripheral capillaries. It dilates mainly the large coronary arteries and reduces their muscle tone. Hence, it brings about a substantial improvement in the oxygen supply of the myocardium while reducing the oxygen demands. High blood pressure is normalised due to reduction in the peripheral resistance (vasodilation), which also leads to less work for the myocardium.

### **5.2. Pharmacokinetic Properties**

Absorption: FORTIPINE LA 40 is absorbed rapidly and almost completely following oral administration. FORTIPINE LA 40 reaches maximal concentrations ( $29.4 \pm 12.0$ ) X  $\pm$  SD) ng/ml)  $5.0 \pm 2.7$  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 ( $12.0 \pm 6.5$  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.

Metabolism: Nifedipine is almost completely metabolised to inactive metabolites.

Elimination: An apparent half-life of  $14.9 \pm 6.0$  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. Pre-clinical Safety Data

Different animals were investigated. Studies in mice, rats and rabbits demonstrated a low intraperitoneal, sub-cutaneous and oral acute toxicity. No significant susceptibility was detected: LD50 in mice p.o. was found to be 421 - 572 mg/kg, in rats p.o. 950 - 1087 mg/kg, in rabbits p.o. 250 - 500 mg/kg, in cats p.o. 100 mg/kg. Toxic symptoms were rapidly and completely reversible in surviving animals. No major differences have been observed between male and female animals.

Subacute, subchronic and chronic oral toxicity studies in rats demonstrated a low toxicity of high doses of nifedipine. With the exception of a dose-dependent increase in heart and liver phospholipids in the subchronic study, a no-effect dose has been evaluated to be equivalent to 75 times the human therapeutic dose. Only doses of 800 (1200 HTD) and to some extent 400 mg/kg/day, were found to be clearly toxic.

Teratogenicity studies of nifedipine in rats and rabbits demonstrated a teratogenic potential which justify it to be contra-indicated in women who are, or may become pregnant.

Extensive mutagenicity studies in Ames Salmonella mutagenicity testing systems were all negative.

No carcinogenic potential has occurred during the long clinical experience with the compound and in the negative Ames.

Nifedipine seems to have a low interaction profile toward other drugs. The possible interaction between ethanol and nifedipine, causing increased plasma levels of nifedipine, should, however, be noted.

The pharmacokinetics of nifedipine are well documented, especially in rats, with a fast absorption, dose independence and a low accumulation potential by repeated dosing. The ability to cross the blood-brain and placental barriers should be noted.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of Excipients

- Microcrystalline Cellulose
- Cellulose
- Methylhydroxypropylcellulose
- Lactose
- Magnesium Stearate
- Colloidal Anhydrous Silica
- Macrogol 400 (Polyethyleneglycol 400)
- Macrogol 6000 (Polyethyleneglycol 6000)
- Ferric Oxide Red (E172)

- Titanium Dioxide (E171)
- Talc

**6.2. Incompatibilities**

None Known.

**6.3. Shelf Life**

Three years

**6.4. Special Precautions for Storage**

FORTIPINE LA40 should be stored in the original pack below 25°C, in a dry place and protected from light.

Nifedipine is highly sensitive to light and is therefore protected both by materials in the tablet and in the packaging. Nonetheless tablets should not be exposed to direct sunlight and should only be removed from the blister pack when about to be taken.

**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. Instructions for Use/Handling**

None.

**ADMINISTRATIVE DATA**

**7. MARKETING AUTHORISATION HOLDER**

Goldshield Pharmaceuticals Ltd  
NLA Tower  
12-16 Addiscombe Road  
Croydon  
CR0 0XT

**8. MARKETING AUTHORISATION NUMBER**

PL 12762/0014

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

June 1998

**10. DATE OF (PARTIAL) REVISION OF THE TEXT**

29 June 2009