FENAMON

1. NAME OF THE MEDICINAL PRODUCT

FENAMON 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each immediate release tablet contains 10mg of nifedipine.
Excipient with known effect: lactose monohydrate. Each tablet contains 141 mg lactose as lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Yellow, round, flat scored, embossed "MC", 8 mm tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of coronary heart disease
  - **Chronic stable angina pectoris** (angina of effort)
  - **Vasospastic angina pectoris** (Prinzmetal's angina, variant angina)
- Treatment of **essential hypertension**
- Treatment of **hypertensive crisis**
- Treatment of **Raynaud's syndrome** (primary and secondary Raynaud's syndrome)

For patients suffering from essential hypertension or chronic stable angina pectoris and treated with fast release forms of nifedipine, a dose dependent increase in the risk of cardiovascular complications (e.g. myocardial infarction) and mortality may occur. Due to this, nifedipine should only be used for treatment of patients with essential hypertension or chronic stable angina pectoris if no other treatment is appropriate.

4.2. Posology and method of administration

Method of administration
Oral use

Posology
The recommended starting dose is 5mg. Unless otherwise prescribed, the following dosage guidelines apply for adults:

1. In **coronary heart disease**:	1 FENAMON 10mg tablet 3 times daily (3 x 10mg/day).
Chronic stable angina pectoris: (angina of effort)	If higher dosages are necessary, the dose can be increased in stages up to maximum 60mg daily
Vasospastic angina pectoris:	1 FENAMON tablet 3 times daily (Prinzmetal's angina, variant angina) (3 x 10mg/day) If higher dosages are necessary, the dose can be increased in stages up to maximum 60mg daily
2. In essential **hypertension**:	1 FENAMON 10mg tablet 3 times daily (3 x 10mg/day) If higher dosages are necessary, the dose can be increased in stages up to maximum 60mg daily.
3. In **hypertensive crisis**:	1 FENAMON tablet as a single oral dose (1 x 10mg)

For established diagnosis of hypertensive urgency (=without target organ damage): 1 FENAMON tablet as a single oral dose (1 x 10mg)

For established diagnosis of hypertensive emergency (=with target organ damage):

Primary care:	1 FENAMON tablet as a single oral dose (1 x 10mg)
Secondary care:	1 FENAMON tablet as a single oral dose (1 x 10mg) followed by i.v. infusion with nifedipine or nitroglycerine, clonidine, dihydralazine as secondary treatment and i.v. sodium nitroprusside as tertiary treatment

If the effect is insufficient, depending on the reaction of the blood pressure, a further 5mg or 10mg dose can be administered after at least 30 minutes. If the dosage intervals are shorter and/or the dose higher, dangerous hypotensive states can occur.

For hypertension, the dose used should not exceed 60mg daily.

4. In **Raynaud's syndrome**: 1 FENAMON 10mg tablet 3 times daily (3 x 10mg/day)
If higher dosages are necessary, the dose can be increased in stages up to maximum 60mg daily

Co-administration with CYP 3A4 inhibitors or CYP 3A4 inducers may result in the recommendation to adapt the nifedipine dose or not to use nifedipine at all (see *4.5 Interactions with other medicinal products and other forms of interaction*)

Duration of treatment
The attending doctor will determine the duration of use. Due to their pronounced anti-ischaemic and antihypertensive action, FENAMON tablets should be discontinued gradually, particularly when high doses are used.

Administration
As a rule, FENAMON tablets are swallowed whole with little liquid, irrespective of meal times. Grapefruit juice is to be avoided.
Patients taking unit doses of 20mg of immediate release formulations should allow an interval of at least 2 hours between doses.

Special populations
Children and adolescents
The safety and efficacy of FENAMON tablets in children below 18 years has not been established.
Geriatric patients
The pharmacokinetics of FENAMON tablets are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.
Patients with hepatic impairment
In patients with impaired liver functions, careful monitoring and, in severe cases, a dose reduction may be necessary.
Patients with renal impairment
Based on pharmacokinetic data, no dosage adjustment is required in patients with renal impairment. (see *5.2 Pharmacokinetic properties*)
Lower doses may be required in elderly patients as a result of reduced drug clearance.

4.3. Contraindications
- FENAMON must not be administered to patients with known hypersensitivity to the active substance, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients listed in sections 4.4 and 6.1.
- FENAMON must not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within 4 weeks of an acute myocardial infarction.
- FENAMON should not be used for the treatment of acute attacks of angina.
- The safety of FENAMON in malignant hypertension has not been established.
- FENAMON should not be used for secondary prevention of myocardial infarction.
- FENAMON should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see section 4.5).

4.4. Special warnings and precautions for use
Several well documented studies have described profound hypotension, myocardial infarction and death when immediate release nifedipine capsules are used sublingually for acute reduction of blood pressure.
Nifedipine is not a beta-blocker and therefore give 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.
FENAMON 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. FENAMON 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).
Treatment with short-acting nifedipine may induce an exaggerated fall in blood pressure and reflex tachycardia, which can cause cardiovascular complications such as myocardial and cerebrovascular ischaemia.
As with other vasoactive substances, angina pectoris may very rarely occur (data from spontaneous reports) with immediate release nifedipine, especially at the start of the treatment. Data from clinical studies confirm that the occurrence of angina pectoris attacks is uncommon.
In patients suffering from angina pectoris an increase in frequency, duration and severity of angina pectoris attacks may occur, especially at the start of the treatment.
The occurrence of myocardial infarction has been described in isolated cases, although it was not possible to distinguish this from the natural course of the underlying disease.
FENAMON should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. FENAMON should be reserved for women with severe hypertension who are unresponsive to standard therapy (see section 4.6).
Careful monitoring of blood pressure must be exercised when administering nifedipine with I.V. magnesium sulfate, 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.
FENAMON is not recommended for use during breast-feeding because nifedipine has been reported to be excreted in human milk and the effects of nifedipine exposure to the infant are not known (see section 4.6).
In patients with impaired liver function, careful monitoring, and in severe cases, a dose reduction may be necessary.
FENAMON should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.
At doses higher than those recommended, there is some concern about increased mortality and morbidity in the treatment of ischaemic heart disease, in particular after myocardial infarction.
The use of FENAMON 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).
FENAMON contains yellow orange S (E110) which may cause allergic reactions.
For use in special populations see section 4.2.

4.5. Interactions with other medicinal products and other forms of interaction

Drugs that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Drugs that are known to either inhibit or to induce this enzyme system may therefore alter the first pass (after oral administration) or the clearance of nifedipine (see Section 4.4).
The extent as well as the duration of interactions should be taken into account when administering nifedipine together with the following drugs:
Rifampicin: Rifampicin strongly induces the cytochrome P450 3A4 system. Upon co-administration with rifampicin, the bioavailability of nifedipine is distinctly reduced and thus its efficacy weakened. The use of nifedipine in combination with rifampicin is therefore contraindicated (see Section 4.3).
Upon co-administration of known inhibitors of the cytochrome P450 3A4 system the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered (see Sections 4.2 and 4.4). In the majority of these cases, no formal studies to assess the potential for a drug interaction between nifedipine and the drug(s) listed have been undertaken, thus far.
Drugs increasing nifedipine exposure:

- macrolide antibiotics (e.g., erythromycin)
- anti-HIV protease inhibitors (e.g., ritonavir)
- azole anti-mycotics (e.g., ketoconazole)
- fluoxetine
- nefazodone
- quinupristin/dalfopristin
- cisapride
- valproic acid
- cimetidine
- diltiazem

Upon co-administration of inducers of the cytochrome P450 3A4 system, the clinical response to nifedipine should be monitored and, if necessary, an increase in the nifedipine dose considered. If the dose of nifedipine is increased during co-administration of both drugs, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

Drugs decreasing nifedipine exposure:

- rifampicin (see above)
- phenytoin
- carbamazepine
- phenobarbital

Effects of nifedipine on other drugs

Nifedipine may increase the blood pressure lowering effect of concomitant applied antihypertensives.

When nifedipine is administered simultaneously with beta-receptor blockers the patient should be carefully monitored, since deterioration of heart failure is also known to develop in isolated cases.

Digoxin: The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and, hence, an increase in the plasma digoxin level. The patient should therefore be subjected to precautionary checks for symptoms of digoxin overdosage and, if necessary, the glycoside dose should be reduced.

Quinidine: Co-administration of nifedipine with quinidine may lower plasma quinidine levels, and after discontinuation of nifedipine, a distinct increase in plasma quinidine levels may be observed in individual cases. Consequently, when nifedipine is either additionally administered or discontinued, monitoring of the quinidine plasma concentration, and if necessary, adjustment of the quinidine dose are recommended. Blood pressure should be carefully monitored and, if necessary, the dose of nifedipine should be decreased.

Tacrolimus: Tacrolimus is metabolised via the cytochrome P450 3A4 system. Published data indicate that the dose of tacrolimus administered simultaneously with nifedipine may be reduced in individual cases. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Drug food interactions

Grapefruit juice inhibits the cytochrome P450 3A4 system. Administration of nifedipine together with grapefruit juice thus results in elevated plasma concentrations and prolonged action of nifedipine due to a decreased first pass metabolism or reduced clearance. As a consequence, the blood pressure lowering effect of nifedipine may be increased. After regular intake of grapefruit juice, this effect may last for at least three days after the last ingestion of grapefruit juice.

Ingestion of grapefruit/grapefruit juice is therefore to be avoided while taking nifedipine (see Section 4.2).

Other forms of interaction

Nifedipine may increase the spectrophotometric values of urinary vanillylmandelic acid falsely. However, HPLC measurements are unaffected.

4.6. Fertility, pregnancy and lactation

Pregnancy

FENAMON should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine (see section 4.4).

In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity (see section 5.3).

There are no adequate and well-controlled studies in pregnant women.

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 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 is excreted in 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 breast-feeding 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

Reactions to the drug, which vary in intensity from individual to individual, may impair the ability to drive or to operate machinery (see section 4.8). This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

4.8. Undesirable effects

The ADRs reported with nifedipine-containing products are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not Known
Blood and Lymphatic System Disorders				Agranulocytosis Leucopenia
Immune System Disorders		Allergic reaction Allergic oedema / angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction
Psychiatric Disorders		Anxiety reactions Sleep disorders		
Metabolism and Nutrition Disorders				Hyperglycaemia
Nervous System Disorders	Headache	Vertigo Migraine Dizziness Tremor	Par- /Dysaesthesia	Hypoaesthesia Somnolence
Eye Disorders		Visual disturbances		Eye pain
Cardiac Disorders		Tachycardia Palpitations		Chest pain (Angina Pectoris)
Vascular Disorders	Oedema (incl. peripheral oedema) Vasodilatation	Hypotension Syncope		
Respiratory, Thoracic, and Mediastinal Disorders		Nasal congestion Nosebleed		Dyspnoea
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	Vomiting Gastroesophageal 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 and Connective Tissue 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

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

4.9. Overdose

Symptoms

The following symptoms are observed in cases of severe nifedipine intoxication:

Disturbances of consciousness to the point of coma, a drop in blood pressure, tachycardia, bradycardia, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.

Treatment

As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority. Elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

The benefit of gastric decontamination is uncertain.

1. Consider activated charcoal (50 g for adults, 1 g/kg for children) if the patient presents within 1 hour of ingestion of a potentially toxic amount.

Although it may seem reasonable to assume that late administration of activated charcoal may be beneficial for sustained release (SR, MR) preparations there is no evidence to support this.

2. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose.
3. Consider further doses of activated charcoal every 4 hours if a clinically significant amount of a sustained release preparation has been ingested with a single dose of an osmotic laxative (e.g. sorbitol, lactulose or magnesium sulfate).
4. Asymptomatic patients should be observed for at least 4 hours after ingestion and for 12 hours if a sustained release preparation has been taken.

Haemodialysis serves no purpose as nifedipine is not dialysable, but plasmapheresis is advisable (high plasma protein binding, relatively low volume of distribution).

Hypotension as a result of cardiogenic shock and arterial vasodilatation can be treated with calcium (10-20 ml of a 10 % calcium gluconate solution administered intravenously over 5-10 minutes). If the effects are inadequate, the treatment can be continued, with ECG monitoring. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient's response.

Symptomatic bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required.

Additional fluids should be administered with caution to avoid cardiac overload.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives, ATC code: C08CA05

Nifedipine is a calcium antagonist of the 1, 4-dihydropyridine type. Calcium antagonists reduce the transmembranal influx of calcium ions through the slow calcium channel into the cell. As a specific and potent calcium antagonist,

nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels. The main action of FENAMON is to relax arterial smooth muscle both in the coronary and peripheral circulation.
In angina pectoris, FENAMON relax peripheral arteries so reducing the load on the left ventricle. Additionally, FENAMON dilate submaximally both clear and pre-stenotic coronary arteries, and stenotic and post-stenotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.
FENAMON reduce the frequency of painful attacks and ischaemic ECG changes, irrespective of the relative contribution from coronary artery spasm or atherosclerosis.
FENAMON cause a reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, FENAMON have 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. Paediatric dosing forms are lacking.

5.2. Pharmacokinetic properties
Absorption
After oral administration nifedipine is almost completely absorbed. The systemic availability of orally administered nifedipine immediate release formulation is 45 – 56 % owing to a first pass effect. Maximum plasma and serum concentrations are reached at 30 to 60 minutes. Simultaneous food intake leads to delayed, but not reduced absorption.
Distribution
Nifedipine is about 95% bound to plasma protein (albumin). The distribution half-life after intravenous administration has been determined to be 5 to 6 minutes.
Biotransformation
After oral administration nifedipine is metabolized in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is excreted in the form of its metabolites predominantly via the kidneys and about 5 – 15 % via the bile in the faeces. The unchanged substance is recovered only in traces (below 0.1 %) in the urine.
Elimination
The terminal elimination half-life is 1.7 to 3.4 hours. No accumulation of the substance after the usual dose was reported during long-term treatment. In cases of impaired kidney function no substantial changes have been detected in comparison with healthy volunteers. In cases of impaired liver function the elimination half-life is distinctly prolonged and the total clearance is reduced. A dose reduction may be necessary in severe cases (see Section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
The tablets also contain:
- povidone,
- lactose monohydrate,
- microcrystalline cellulose,
- sodium starch glycolate,
- silica colloidal anhydrous,
- quinoline lake yellow (E104),
- orange lake (E110) and
- magnesium stearate.

6.2. Special precautions for storage
Store below 30°C, in the original package, in order to protect from light.

6.3. Nature and contents of container
White polyvinylchloride film – aluminium foil blisters of ten tablets. Packs, with a patient information leaflet, containing 1000 tablets are available.

7. MARKETING AUTHORISATION HOLDER

Komedic Sdn Bhd, 4 Jalan PJS 11/14, Bandar Sunway, 46150 Petaling Jaya

8. MANUFACTURER

Medochemie Ltd. (Central Factory), 1-10 Constantinoupoleos Street, 3011 Limassol, Cyprus

9. DATE OF REVISION OF THE TEXT

08/2021