The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in February 2017.

1 NAME OF THE MEDICINAL PRODUCT

Pressolat 10

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 10 mg nifedipine.

Excipient with known effect: Lactose monohydrate.

For excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablets.
Grey-pink, round, modified-release tablets marked with A10 on one side and Bayer cross on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension.

4.2 Posology and method of administration

Method of administration

Oral Use.

As a rule, tablets are swallowed whole with a little liquid, either with or without food.

Pressolat should not be taken with grapefruit juice (see Section 4.5).

Dosage regimen

As far as possible the treatment must be tailored to the needs of the individual according to the severity of the disease and the patient's response.

Depending on the clinical picture in each case, the basic dose must be introduced gradually.

Pressolat 10 mg is particularly suitable for dose titration. Dose titration is particularly recommended for hypertensives with severe cerebrovascular disease and for patients, who because of low body weight or multiple therapies with other antihypertensive drugs, are likely to have an excessive reaction to nifedipine. In addition, patients in whom side effects in response to the nifedipine treatment make a finer dose adjustment desirable should be individually stabilised with Pressolat 10 mg.

Unless otherwise prescribed, the following dosage guidelines apply for adults:

- In hypertension: 1 Pressolat 10 mg tablet twice daily (2 x 10 mg/day)
  2 Pressolat 10 mg tablet twice daily (2 x 20 mg/day)

  If higher dosages are necessary, the dose can be increased in stages up to maximum 60 mg 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 section 4.5)*.

Duration of Treatment

Treatment may be continued indefinitely.

Additional information on special populations

Children and adolescents
The safety and efficacy of Pressolat in children below 18 years has not been established. Currently available data for the use of nifedipine in hypertension are described in section 5.1.

Elderly (>65 years)

The pharmacokinetics of Pressolat are altered in the elderly so that lower maintenance doses of nifedipine may be required.

Patients with hepatic impairment
Nifedipine is metabolised primarily by the liver and therefore patients with mild, moderate or severe liver dysfunction should be carefully monitored and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.4 and 5.2).

Patients with renal impairment
Based on pharmacokinetic data, no dosage adjustment is required in patients with renal impairment (*see section 5.2)*.

4.3 Contraindications

Pressolat 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).*

Pressolat must not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within 4 weeks of a myocardial infarction.

Pressolat should not be used for the treatment of acute attacks of angina.

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

Pressolat should not be used for secondary prevention of myocardial infarction.

Pressolat 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

Pressolat 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.

Pressolat 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. Pressolat 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 mmHg).

Pressolat should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Pressolat 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.

Pressolat 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 mild, moderate or severe impaired liver function, careful monitoring and a dose reduction may be necessary. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see *section 4.2* and *5.2*). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Pressolat 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 Pressolat 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 may 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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

For use in special populations see section 4.2.

4.5 Interaction 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.

<u>Drugs increasing nifedipine exposure:</u>

- *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.

<u>Drugs decreasing nifedipine exposure:</u>

- *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 3 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

Pressolat 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.

Acute pulmonary oedema has been observed when calcium channel blockers, among others nifedipine, have been used as a tocolytic agent 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.

Breastfeeding

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 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

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 the treatment, on changing the medication and in combination with alcohol.

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%).

The frequencies of 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. Frequencies are defined as common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). The ADRs identified only during the ongoing postmarketing surveillance, and for which a frequency could not be estimated, are listed under "Not known".

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				Agranulocytosis Leukopenia
Immune system disorders		Allergic reaction Allergic oedema / angioedema (incl. larynx oedema*)	Pruritus Urticaria Rash	Anaphylactic/ anaphylactoid reaction
Psychiatric disorders		Anxiety reactions Sleep disorders		

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
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		Nosebleed Nasal congestion		Dyspnoea Pulmonary oedema**
Gastrointestinal disorders	Constipation	Gastrointestinal and abdominal pain Nausea Dyspepsia Flatulence Dry mouth	Gingival hyperplasia	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 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.**

** = 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 suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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 sulphate).

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 vasodilation 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 specific and potent 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. Nifedipine acts particularly on the cells of the myocardium and the smooth muscle cells of the coronary arteries and the peripheral resistance vessels.

In hypertension, the main action of Pressolat is to cause peripheral vasodilatation and thus reduce peripheral resistance.
In angina, Pressolat 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.

Pressolat administered twice-daily provides 24-hour control of raised blood pressure. Pressolat causes reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, Pressolat 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. Paediatric dosing forms are lacking.

5.2 Pharmacokinetic Properties

Absorption

After oral administration nifedipine is rapidly and almost completely absorbed. The systemic availability of orally administered nifedipine is 45 - 56 % owing to a first pass effect. Maximum plasma and serum concentrations are reached at 1.5 to 4.2 hours with Pressolat (20 mg tablets). 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 was determined to be 5 to 6 minutes.

Biotransformation

After oral administration nifedipine is metabolised 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 6 – 11 h (Pressolat) because of delayed absorption. 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 a study comparing the pharmacokinetics of nifedipine in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with those in patients with normal liver function, oral clearance of nifedipine was reduced by on average 48% (Child Pugh A) and 72% (Child Pugh B). As a result AUC and Cmax of nifedipine increased on average by 93% and 64% (Child Pugh A) and by 253% and 171% (Child Pugh B), respectively, compared to patients with normal hepatic function. The pharmacokinetics of nifedipine has not been investigated in patients with severe hepatic impairment (see section 4.4).

5.3 Preclinical Safety Data

Preclinical data reveal no special hazard 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

Cellulose microcrystalline
Maize starch
Lactose monohydrate
Polysorbate 80
Magnesium stearate
Hypromellose 15 cP
Macrogol 4000
Ferric oxide red
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf - life

4 Years.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

30 or 50 or 100 tablets in a blister pack.

6.6 Special precautions for disposal and other handling

No additional information.

MANUFACTURER

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REGISTRATION HOLDER

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