Professional information for

DAPINELAT 30 & 60

SCHEDULING STATUS S3

1. Name of the medicinal product

DAPINELAT 30 & 60

2. Qualitative and quantitative composition

Each extended release tablet contains 30 mg nifedipine

Each extended release tablet contains 60 mg nifedipine

Sugar-free

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Extended release tablet

Description 30 mg tablets:

Brown coloured, round biconvex film coated tablet free from cracks, plain on one side & laser drilled hole on other side.

Description 60 mg tablets:

Brown coloured, round biconvex film coated tablet free from cracks, plain on one side & laser drilled hole on other side.

4. Clinical Particulars

4.1 Therapeutic indications

Treatment of mild to moderate hypertension.

Prophylaxis of chronic stable angina pectoris.

4.2 Posology and method of administration

Posology

The recommended initial dose is one 30 mg tablet once daily.

If necessary, the dosage can be increased according to individual requirements up to a maximum of 90 mg once daily.

In general, titration steps should proceed over a 7 to 14 days period so that the response to each dose level can be assessed before proceeding to higher doses.

Special populations:

Patients with renal impairment

Based on pharmacokinetic data, no dosage adjustment is required in patients with renal impairment.

Patients with hepatic impairment

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Owing to the duration of action of the formulation, DAPINELAT should not be administered to patients with hepatic impairment.

Elderly

Based on pharmacokinetic data for DAPINELAT no dose adaptation in elderly people above 65 years is necessary.

Paediatric population

The safety and efficacy of DAPINELAT in children below 18 years has not been established.

Method of administration:

Oral use.

The tablets should be swallowed whole with a glass of fluid; under no circumstances should they be bitten, chewed or broken up. Grapefruit juice is to be avoided.

The tablets should be taken at approximately 24 hour intervals, i.e. at the same time each day, preferably during the morning. DAPINELAT may be taken irrespective of meal times.

4.3 Contraindications

DAPINELAT should 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 6.1.

DAPINELAT should not be used in cases of cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.

DAPINELAT should not be used for the treatment of acute attacks of angina. The safety of DAPINELAT in malignant hypertension has not been established.

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

Owing to the duration of action of the formulation, DAPINELAT should not be administered to patients with hepatic impairment.

DAPINELAT should not be administered to patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.

DAPINELAT must not be used in patients with a kock pouch (ileostomy after proctocolectomy).

DAPINELAT is contra-indicated in patients with inflammatory bowel disease or crohn's disease.

DAPINELAT 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).

Nifedipine is contra-indicated in pregnancy and during breastfeeding (see: Pregnancy and lactation).

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm Hg), in cases of manifest heart failure and in the case of severe aortic stenosis.

4.4 Special warnings and precautions for use

- DAPINELAT tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.

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- Caution should be exercised in patients with hypotension as there is a risk of further reduction in blood pressure and care must be exercised in patients with very low blood pressure (severe hypotension with systolic blood pressure less than 90 mm Hg).
- DAPINELAT should not be used during pregnancy.
- 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,
- DAPINELAT 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.
- DAPINELAT may be used in combination with beta-blocking medicines and other antihypertensive medicines but the possibility of an additive effect resulting in postural hypotension should be borne in mind. DAPINELAT will not prevent possible rebound effects after cessation of other antihypertensive therapy.
- DAPINELAT should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.
- Diabetic patients taking DAPINELAT may require adjustment of their control.
- In dialysis patients with malignant hypertension and hypovolaemia, a marked decrease in blood pressure can occur.
- Nifedipine is metabolized via the cytochrome P450 3A4 system. Medicines 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).
- Medicines, which are known inhibitors of the cytochrome P450 3A4 system, and which may therefore lead to increased plasma concentrations of nifedipine include, for example: (see section 4.5).
  - 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
  - diltiazem

Upon co-administration with these medicines, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

- As the outer membrane of the DAPINELAT tablet is not digested, what appears to be the complete tablet may be seen in the toilet or associated with the patient's stools. As a result of this, care should be exercised when administering DAPINELAT to patients, as obstructive symptoms may occur. Bezoars can occur in very rare cases and may require surgical intervention.
- In single cases, obstructive symptoms have been described without known history of gastrointestinal disorders.
- A false positive effect may be experienced when performing a barium contrast x-ray.
- For use in special populations see section 4.2.

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- Grapefruit juice inhibits the metabolism of nifedipine. After regular intake of grapefruit juice the blood pressure lowering 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 DAPINELAT (see section 4.5).
- Safety of nifedipine as tocolytic agent and in the treatment of hypertension in pregnancy after 20 weeks has not been established. Harm to the foetus cannot be excluded.
- Although a "steal" effect has not been demonstrated, DAPINELAT therapy should be discontinued in patients experiencing this effect.
- DAPINELAT should not be switched once a patient has been stabilised, without appropriate monitoring.
- Each 30 mg tablet contains 24,2 mg sodium, equivalent to 1,21 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- Each 60 mg tablet contains 48,4 mg sodium, equivalent to 2,42 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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4.5 Interaction with other medicines and other forms of interaction

Medicines that affect nifedipine

Nifedipine is metabolised via the cytochrome P450 3A4 system, located both in the intestinal mucosa and in the liver. Medicines 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 medicines:

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 DAPINELAT 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 DAPINELAT 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.

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Medicines 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 medcicnes, a reduction of the nifedipine dose should be considered when the treatment is discontinued.

Medicines decreasing nifedipine exposure

- *rifampicin (see above)*
- *phenytoin*
- *carbamazepine*
- *phenobarbitone*

Effects of nifedipine on other medicines

Nifedipine may exacerbate the blood pressure lowering effect of concomitantly applied antihypertensive, such as:

- diuretics
- β-blockers
- ACE-inhibitors
- Angiotensin receptor blockers
- Other calcium channel blockers
- α-adrenergic blocking medicines
- PDE5 inhibitors
- α-methyldopa

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

Digoxin: The simultaneous administration of DAPINELAT 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 over dosage and, if necessary, digoxin dose should be reduced.

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

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4.6 Fertility, pregnancy and lactation

Pregnancy

Nifedipine should not be used during pregnancy.

In animal studies, nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity when administered during any stage of pregnancy and decreased neonatal survival after birth. Only a life-threatening hypertensive crisis of the mother, in the late trimester of pregnancy, who is not responding to any treatment may override this contraindication.

Co-administration of nifedipine with i.v. magnesium sulfate may cause an excessive fall in blood pressure which could harm both mother and foetus.

Breast Feeding

Nifedipine is excreted in the breast milk. DAPINELAT is contraindicated during breastfeeding (See section 4.3)

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 this medicine, 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 following Adverse Drug Reactions (ADRs) can occur:

Immune System Disorders

Less frequent: Allergic reaction, allergic oedema/angioedema (incl. larynx oedema*), pruritus, urticaria, rash

Psychiatric Disorders

Less frequent: Anxiety reactions, sleep disorders

Nervous System Disorders

Frequent: Headache

Less frequent: Vertigo, migraine, dizziness. tremor, paraesthesia, dysaesthesia, somnolence

Eye Disorders

Frequent: Eye pain

Less frequent: Visual disturbances, amblyopia

Cardiac Disorders

Less frequent: Tachycardia, palpitations, chest pain (Angina pectoris)

Vascular Disorders

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Frequent: Oedema (incl. peripheral oedema), vasodilatation

Less frequent: Hypotension, syncope

Respiratory, Thoracic, and Mediastinal Disorders

Less frequent: Nosebleed, nasal congestion

Gastrointestinal Disorders

Frequent: Constipation

Less frequent: Gastrointestinal and abdominal pain, nausea, dyspepsia, flatulence, dry mouth, gingival hyperplasia, gastroesophageal sphincter insufficiency

Hepatobiliary Disorders

Less frequent: Transient increase in liver enzymes

Skin and Subcutaneous Tissue Disorders

Less frequent: Erythema, palpable purpura

Musculoskeletal and Connective Tissue Disorders

Less frequent: Muscle cramps, joint swelling, arthralgia, myalgia

Renal and Urinary Disorders

Less frequent: Polyuria, dysuria

Reproductive System and Breast Disorders

Less frequent: Erectile dysfunction

General Disorders and Administration Site Conditions

Frequent: Feeling unwell

Less frequent: 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.

The ADRs for which a frequency could not be estimated, are listed below:

System Organ Class (MedDRA)	**Frequency unknown**
Blood and Lymphatic System Disorders	Agranulocytosis, Leucopenia
Immune System Disorders	Anaphylactic/ anaphylactoid reaction
Metabolism and Nutrition Disorders	Hyperglycaemia
Nervous System Disorders	Hypoaesthesia
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnoea, pulmonary oedema**
Gastrointestinal Disorders	Bezoar, dysphagia, intestinal obstruction,

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	intestinal ulcer,
	vomiting,
	jaundice
Hepatobiliary Disorders	Jaundice
Skin and Subcutaneous Tissue	Toxic Epidermal Necrolysis,
Disorders	photosensitivity allergic reaction
Endocrine disorders	Gynaecomastia

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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4.9 Overdose

Flushing, headaches, severe hypotension, increase or decrease in heart rate, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema and unconsciousness to the point of coma have been observed.

Particularly in cases of intoxication with slow-release products like DAPINELAT elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance.

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

Treatment is symptomatic and supportive.
Bradycardiac heart rhythm disturbances may be treated symptomatically with ß-sympathomimetics and in life- threatening bradycardiac disturbances of heart rhythm, temporary pacemaker therapy is advisable.
Hypotension as a result of cardiogenic shock and arterial vasodilation may be treated with calcium (10 - 20 ml of a 10 % calcium gluconate solution administered slowly i.v. and repeated if necessary). As a result, the serum calcium may reach the upper normal to slightly elevated levels. If an insufficient increase in blood pressure is achieved with calcium, vasoconstricting sympathomimetics such as dopamine or norepinephrine (noradrenaline) may be administered additionally. The dosage of these medicines is determined solely by the effect obtained.

Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:	Selective calcium channel blockers with mainly vascular effect, dihydropyridine derivatives
Category and class:	Vasodilators, hypotensive medicines.
ATC Code:	C08CA05

Nifedipine, a calcium channel blocker, improves oxygen supply to the myocardium with simultaneous decrease of oxygen requirements. Nifedipine has a vasodilatory effect on the peripheral arterial beds causing a fall in peripheral vascular resistance and an increase in peripheral blood flow. Ca^{2+}-channel blockers are useful in low- renin hypertension. Nifedipine dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

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5.2 Pharmacokinetic properties

General characteristics:

DAPINELAT tablets are formulated to provide nifedipine at an approximately constant rate over 24 hours. Nifedipine is released from the tablet at a zero-order rate by a membrane-controlled, osmotic push-pull process. The pharmacokinetic profile of this formulation is characterized by low peak-trough fluctuation. 0-24 hour plasma concentration versus time profiles at steady state are plateau-like, rendering the DAPINELAT tablet appropriate for once-a day administration.
The delivery rate is independent of gastrointestinal pH or motility. Upon swallowing, the biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the faeces as an insoluble shell.

Absorption

Orally administered nifedipine is almost completely absorbed in the gastro-intestinal tract. The systemic availability of orally administered nifedipine immediate release formulations (nifedipine capsules) is 45–56 % owing to a first pass effect. At steady-state, the bioavailability of DAPINELAT tablets ranges from 68-86 % relative to nifedipine capsules. Administration in the presence of food slightly alters the early rate of absorption but does not influence the extent of drug availability.

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 metabolised in the gut wall and in the liver, primarily by oxidative processes. These metabolites show no pharmacodynamic activity. Nifedipine is eliminated in the form of its metabolites, predominantly via the kidneys, with approximately 5-15 % being excreted via the bile in the faeces. Non-metabolised nifedipine can be detected only in traces (below 0,1 %) in the urine.

Elimination

The terminal elimination half-life is 1,7 to 3,4 h in conventional formulations (nifedipine capsules). The terminal half-life following DAPINELAT administration does not represent a meaningful parameter as a plateau-like plasma concentration is maintained during release from the tablets and absorption. After release and absorption of the last dose the plasma concentration finally declines with an elimination half-life as seen in conventional formulations.

Characteristics in patients:

There are no significant differences in the pharmacokinetics of nifedipine between healthy subjects and subjects with renal impairment. Therefore, dosage adjustment is not needed in these patients.
In patients with hepatic impairment, the elimination half-life is distinctly prolonged and the total clearance is reduced. Owing to the duration of action of the formulation, DAPINELAT should not be administered in these patients.

5.3 Preclinical safety data

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No non-clinical study was performed.

6. Pharmaceutical particulars

6.1 List of excipients

Polyethylene oxide (polyox),
hypromellose type 2910 (methocel premium E5LV),
potassium chloride,
magnesium stearate,
colloidal silicon dioxide,
sodium chloride,
ferric oxide red,
cellulose acetate,
polyethylene glycol 4000,
hypromellose type 2208 (Methocel E3 LV),
opadry brown 03B86636 (HPMC 2910/hypromellose, titanium dioxide, macrogol/PEG, iron oxide red, iron oxide yellow).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years for 30 mg tablets and
3 years for 60 mg tablets.

6.4 Special precautions for storage

Store at or below 25 °C.
Protect from light and moisture.
Not to be removed from the outer carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

30 tablets per carton.
10 tablets in an Aluminum PVC blister; 3 such blisters with product insert into a carton.

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6.6 Special precautions for disposal and other handling

No additional information

7. Marketing authorisation holder

Biotech Laboratories (Pty) Ltd
Ground Floor Block K West Central Park
400 16th Road, Randjespark
Halfway House
Midrand 1685
Tel. nr: 011 848 3050

8. Marketing authorisation number(s)

53/7.1/0521 & 53/7.1/0522

9. Date of first authorisation/renewal of the authorisation

29 March 2022

10. Date of revision of the text

For future use.