1.6 product information

1.6.1 Prescribing information (Summary of product characteristics)

1. Name of the medicinal product
Nicardin-SR Tablets

2. Qualitative and quantitative composition
Each film coated tablet contains: Nifedipine BP 20mg for sustained release.

3. Pharmaceutical form
Tablets

4. Clinical Particulars
4.1 Therapeutic Indications
Nicardln-SR®Tablets are used alone or in combination with other agents such as thiazide diuretics and beta-blockers in the management of hypertension. They are also used in the treatment and prophylaxis of angina pectoris, particular1y when a vasospastic element is present. as in prinzmetal's angina. Nifedipine has also been used in the treatment of Raynaud's syndrome.

4.2 Posology and method of administration
Nicardin-SR® Tablets are administered by the oral route either with or after meals as follows:

Indications	Dosage
Hypertension	10mg twice daily, increased if necessary to up to 40mg twice daily.
Prophylaxis of angina pectoris, or alternative in the treatment of hypertension	10mg three times daily, increased if necessary to 20mg three times daily, or more. A maximum daily dose of 1180mg has been recommended but doses greater than 120mg daily are reported to be necessary only rarely

Nicardin-SR Tablets is taken at the usual dose rate of one tablet twice daily for hypertension and angina prophlaxis.The usual maintenance dosage may be increased up to 40mg twice daily.in elderly patients, those on concomitant medication, or those with hepatic dysfunction; the recommended initial dose is half the above doses.

Nifedipine must not be used in cases of known hypersensitivity to Nifedipine, or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients.
Nifedipine must not be used in cases of cardiovascular shock, unstable angina, or during or within one month of a myocardial infarction. Nifedipine should not be used for the treatment of acute attacks of angina.

The safety of Nifedipine in malignant hypertension has not been established.
Nifedipine should not be used for secondary prevention of myocardial infarction.

Owing to the duration of action of the formulation, Nifedipine should not be administered to patients with hepatic impairment.
Nifedipine should not be administered to patients with a history of gastrointestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.
Nifedipine must not be used in patients with a Kock pouch (ileostomy after proctocolectomy).
Nifedipine is contra-indicated in patients with inflammatory bowel disease or Crohn's disease. Nifedipine must not be used in combination with rifampicin because no efficient plasma levels of Nifedipine may be obtained due to enzyme induction (see Section 4.5), potentially myelotoxic drugs or grapefruit juice.

4.3 Special Warnings and Precautions for Use
Nifedipine tablets must be swallowed whole; under no circumstances should they be bitten, chewed or broken up.
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), in cases of manifest heart failure and in the case of severe aortic stenosis.
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.
Nifedipine 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 4.6).
Nifedipine 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.
In patients with impaired liver function careful monitoring and, in severe cases, a dose reduction may be necessary.
Nifedipine 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. Nifedipine will not prevent possible rebound effects after cessation of other antihypertensive therapy.
Nifedipine 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 Nifedipine 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

Drugs, which are knowninhibitors of the cytochrome P450 3A4 system and therefore may lead to increased plasma concentrations of nifedipine are, e.g.:
- 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.
As the outer membrane of the Nifedipine 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 used when administering Nifedipine in patients with pre-existing severe gastrointestinal narrowing because 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.
When doing a barium contrast x-ray nifedipine may cause false positive effects (e.g. filling defects interpreted as polyp). For use in special populations see Section 4.2.
Ischaemic pain has been reported in a small proportion of patients within one to four hours of the introduction of Nifedipine Retard therapy. Patients experiencing this effect should discontinue treatment.Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 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.
The extent as well as the duration of interactions should be taken into account when administering Nifedipine together with the following drugs:
Nifedipine strongly induces the cytochrome P450 3A4 system. Upon coadministration 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.
Upon co-administration of the following weak to moderate inhibitors of the cytochrome P450 3A4 system, the blood pressure should be monitored and, if necessary, a reduction in the Nifedipine dose considered.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.

4.5 Pregnancy and Lactation

Pregnancy

Nifedipine 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).
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.

In animal studies, Nifedipine has been shown to produce embryotoxicity, foetotoxicity and teratogenicity
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.
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 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.

4.6 Effects on Ability to Drive and Use Machines

Reactions to the drug, which vary in intensity from individual to individual, can 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.

4.7 Undesirable Effects

The most common adverse effects of nifedipine are associated with the vasodilatory action, such as dizziness, flushing, headache, hypotension, and peripherial oedema. Gastro-intestinal disturbances, increased frequency of micturition, lethargy, eye pain, and mental depression have occurred. A paradoxical increase in ischemic chest pain may occur at the start of treatment and in few patients excessive fall in blood pressure has led to cerebral or myocardial ischemia or transient blindness. There have been reports of rashes, fever and abnormalities in liver function due to hypersensitivity reactions. Gingiva hyperplasia has been reported but is often reversible on drug withdrawal.

4.8 Overdose and treatment

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, tachycardiac/ bradycardiac heart rhythm disturbances, hyperglycaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema.
Management of Overdose As far as treatment is concerned, elimination of the active substance and the restoration of stable cardiovascular conditions have priority.
After oral ingestion thorough gastric lavage is indicated, if necessary in combination with irrigation of the small intestine
Particularly in cases of intoxication with slow release Nifedipine formulations,

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 vasodilatation can 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 can reach the upper normal range to slightly elevated levels. 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 (norepinephrine) are additionally administered. The dosage of these drugs should be determined by the effect obtained. Bradycardiac heart rhythm disturbances may be treated symptomatically with atropine, beta-sympathomimetics and in life-threatening bradycardiac disturbances of heart rhythm temporary pacemaker therapy can be advisable.
Additional liquid or volume must be administered with caution because of the danger of overloading the heart.

5. Pharmacological properties
5.1 Pharmacodynamic properties
ATC code: C08 CA05
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 nifedipine is to relax arterial smooth muscle, both in the coronary and peripheral circulation. The Nifedipine tablet is formulated to achieve controlled delivery of nifedipine in a release profile sufficient to enable once-daily administration to be effective in clinical use.
In hypertension, the main action of nifedipine is to cause peripheral vasodilatation and thus reduce peripheral resistance. Nifedipine administered once-daily provides 24-hour control of raised blood pressure. Nifedipine causes reduction in blood

pressure such that the percentage lowering is proportional to its initial level. In normotensive individuals, nifedipine has little or no effect on blood pressure.
In angina, Nifedipine 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.
In a multi-national, randomised, double-blind, prospective study involving 6321 hypertensive patients with at least one additional risk factor followed over 3 to 4.8 years, Nifedipine 30 and 60 (nifedipine GITS) were shown to reduce blood pressure to a comparable degree as a standard diuretic combination.
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
Nifedipine 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 Nifedipine 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 steadystate, the bioavailability of Nifedipine 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. Nonmetabolised 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 Nifedipine 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 halflife 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, Nifedipine should not be administered in these patients.

5.3 Preclinical safety data
There is no pre-clinical data of relevance to a prescriber, which is additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars
6.1 List of Excipients
METHOCELTM K100 LV
Microcrystalline Cellulose PH 101
STARCH 1500® [Pregelatinized Starch]
Purified Water
METHOCELTM K100 LV
STARCH 1500® [Pregelatinized1 Starch]
Colloidal Silicon Dioxide
Magnesium Stearate
Film Coating
Erythrosine Lake Colour
Hydroxypropyl Methylcellulose (5Cps)
Titanium Dioxide
Polyethylene Glycol -6000
Purified Talc
Ponceau 4R Lake Colour
Monopropylene Glycol
Alcohol 96%

6.2 Incompatibilities
None.

6.3 Shelf Life
36 onths

6.4 Special Precautions for Storage
Store below 30°C in a dry place.

6.5 Nature and Contents of Container
BLISTER PACKS:
Blisters of 10 x 10 tablets packed in a unit carton with a literature insert
BULK PACKS: 1000's packed in polythene bags contained in HDPE containers with a literature insert.

6.6 Special precaution for disposal and other handling

No special requirements.

7 Marketing Authorization Holder and Manufacturing Site Addresses Marketing Authorization Holder:

Company Name: LABORATORY & ALLIED LTD
Address: Plot No. 209/10349, Opposite Sameer Business Park, Next to Libra House, Mombasa road, P.O. Box 42875 GPO 00100, Nairobi,
Country : Kenya
Telephone : +254 20 8040306
Telefax : +254 20 8040309
E-Mail : info@laballied.com.

Manufacturing Site Address:
Company Name: LABORATORY & ALLIED LTD
Address: Plot No. 209/10349, Opposite Sameer Business Park, Next to Libra House, Mombasa road, P.O. Box 42875 GPO 00100, Nairobi,
Country : Kenya
Telephone : +254 20 8040306
Telefax : +254 20 8040309
E-Mail : info@laballied.com

8 Marketing Authorization Number:

KENYA: 256

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10 Date of revision of the text:

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