

Summary Product Characteristics

1.Product Name:

NIFESTAR SR

2.Qualitative / Quantitative composition of the substance (s) active (s) (in table form)

Each slow-release film coated tablet contains:

Nifedipine

BP.....20mg

For the full list of excipients, See
Section 6.1

3.Pharmaceutical form

Film coated tablet

Pinkish coloured, round shaped biconvex film coated tablet plain on both sides.

4.Clinical particulars

4.1 Therapeutic indications

NIFESTAR SR are indicated for the treatment of hypertension and the prophylaxis of chronic stable angina pectoris.

4.2 Posology and method of administration

Posology

The recommended starting dose of NIFESTAR SR is 10 mg every 12 hours swallowed with water with subsequent titration of the dosage according to response. NIFESTAR SR permit titration of initial dosage, which may be adjusted upwards to 40 mg every 12 hours, to a maximum daily dose of 80 mg.

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.

Duration of treatment

Treatment may be continued indefinitely.

Additional information on special
populations Paediatric population

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

Older people (>65 years)

The pharmacokinetics of NIFESTAR SR are altered in the older people 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).

Method of
administration Oral
use.

As a rule, tablets must be swallowed whole with a little liquid, either with or without food. NIFESTAR SR should not be taken with grapefruit juice (see Section 4.5).

The tablets should not be crushed, chewed, divided or dissolved.

4.3 Contraindications

NIFESTAR SR must not be administered to patients with known hypersensitivity to nifedipine or to other dihydropyridines because of the theoretical risk of cross-reactivity, or to any of the excipients listed in section 4.4 and 6.1.

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

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

NIFESTAR SR should not be used for the secondary prevention of myocardial infarction.

NIFESTAR SR 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

NIFESTAR SR are not beta-blockers 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.

NIFESTAR SR 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. NIFESTAR SR 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).

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

NIFESTAR SR are not recommended for use during breastfeeding 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.

NIFESTAR SR 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 NIFESTAR SR 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).

Since these medicinal products contain 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.

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

NIFESTAR SR 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 Preclinical safety data).

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.

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 head section of spermatozoa 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

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 ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ 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 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	Para-/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		Nasal congestion Nosebleed		Dyspnoea Pulmonary oedema*

Mediastinal Disorders				*
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

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

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

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions

Healthcare professional are requested to report any suspected adverse reactions

via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS)
<https://pv.pharmacyboardkenya.org>.

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 cardio-vascular 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 blocker (dihydropyridine derivative) with mainly vascular effects (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 slow calcium channels 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 NIFESTAR SR is to cause peripheral vasodilatation and thus reduce peripheral resistance.

In angina, NIFESTAR SR reduce 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.

NIFESTAR SR administered twice-daily provides 24-hour control of raised blood pressure. NIFESTAR SR cause reduction in blood pressure such that the percentage lowering is directly related to its initial level. In normotensive individuals, NIFESTAR SR 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. Pediatric 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 NIFESTAR SR (20 mg Modified-release 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 hours (NIFESTAR SR 20 mg and NIFESTAR SR 20 mg), 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 C_{max} 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).

6.0 Pharmaceutical Parameters:

6.1 List of excipients

- Maize starch
- Dicalcium Phosphate
- Purified Water
- Magnesium Stearate
- Sodium Starch Glycolate
- Colloidal Anhydrous silica
- HPMC 15 cps
- Talcum
- PEG 6000
- Colloidal Anhydrous silica
- Tween -80
- Erythrosine colour
- Iso Propyl Alcohol
- Methylene Dichloride

6.2 Incompatibilities

None Known.

6.3 Shelf life:

36 Months

6.4 Special precautions for storage

Store below 30°C in a cool & dry place.

6.5 Nature and contents of container

10 tablets are packed in one blister; such 10 blisters packed in one carton with insert coded with batch number, manufacturing date and expiry date packed in an inner carton.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7.0 Marketing Authorisation Holder:

Manufacturer:

Zain Pharma limited

Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,

Behind Nice And Lovely House, P.O. Box: 100167-00101, Nairobi, Kenya

8. Market Authorization Number

H2026/CTD8894/20487

9. Date of First Authorization: NA

10. Date of revision of text: 23.06.2021