Summary of Product Characteristics (SPC)

A. Brand Name
NIPINE-SR 20

B. International Non-Proprietary Names (INNs)
Nifedipine Extended Release Tablets USP 20 mg

C. Pharmaceutical Form, Dosage and Route of Administration

Pharmaceutical Form: Tablet

Dosage: Nipine-SR is recommended to be administered in a dose of one tablet twice a day (12 hourly). If the blood pressure is not adequately controlled, its dose may be increased to 2 tablets twice a day.
Nipine-SR is not recommended for use in children.
Discontinuation of Nipine-SR therapy has not been reported to cause withdrawal syndrome, however, it is recommended to taper the dosage of Nipine-SR when discontinuation of treatment is necessary.

Route of Administration: Oral

D. Qualitative and Quantitative Composition of active ingredients and excipients

Sr. No.	Raw Material	Specification	QTY. / TABLET MGS. / Tablet		QTY. / BATCH (KGS. / Batch.)		Category
A	**Mixing**						
1	Nifedipine	USP	20.000	mg	2.000	Kg	Active Pharmaceutical Ingredient
2	Lactose	BP	20.000	mg	2.000	Kg	Diluent
3	Laffcol - 6000	IH	8.000	mg	0.800	Kg	Plasticizer
B	**Binding**						
4	MAT SR base II	IH	40.000	mg	4.000	Kg	Polymer for
5	Povidone (Polyvinyl Pyrrolidone) (P.V.P.K – 30)	USP	18.000	mg	1.800	Kg	Binding agent
6	Iso Propyl Alcohol	BP	0.034	ml	3.400	Ltr	Solvent
C	**Lubrication**						
7	Colloidal Silicon Dioxide	USP	2.000	mg	0.2000	Kg	Glidant and / or Anticaking agent
8	Magnesium Stearate	BP	1.000	mg	0.100	Kg	Lubricant
	Total		109.00	mg	10.900	Kg	---

Where, BP- British Pharmacopoeia, USP- United States Pharmacopoeia, IHS- In-House.

NOTES:

* Active material issue quantity calculated on actual assay & L.O.D to compensate the 100 % assay.

** If issue qty. is less than standard qty. in this case active material qty. compensate by adding excipients & if issue qty. is more than standard qty. in this case active material qty. compensate by reducing excipients.

E. Therapeutic Indications

Nifedipine Extended-Release Tablets are indicated in the treatment of all grades of essential hypertension. It may be used alone or in combination with other antihypertensive agents.

F. Dosage and Method of Administration

Refer section C above in the SPC

G. Contra-indications

Nifedipine Extended-Release Tablets is contraindicated in:

1. Pregnancy
2. Cardiogenic shock
3. Hypersensitivity of Nifedipine

H. Precautions and Warnings

Nifedipine Extended-Release Tablets should be used with caution in patients having poor cardiac reserve and impaired hepatic function.

Although, in most patients Nifedipine Extended-Release Tablets does not produce excessive hypotension, but in occasional patients, particularly in those receiving other antihypertensives, it may lead to excessive hypotension, therefore blood pressure should be closely monitored specially during the initial phase of therapy.

Rarely, patients having severe obstructive coronary disease may develop increased frequency during and or severity of angina on starting treatment with Nifedipine Extended-Release Tablets. Similarly, patients abruptly withdrawn from beta-blockers and put on Nifedipine Extended-Release Tablets therapy may experience angina pectoris. Therefore, it is important to taper beta-blockers before starting treatment with Nifedipine Extended-Release Tablets.

Concomitant administration of Nifedipine Extended-Release Tablets with beta-blockers may lead to heart failure, particularly in patients having tight aortic stenosis.

I. Drug Interactions

Nifedipine is a powerful and specific blocker of slow calcium channels of smooth muscle cells. It inhibits the influx of calcium-ions into the cells of smooth muscle of coronary arteries, peripheral resistance vessels and also the myocardium. This action brings about uncoupling of excitation – contraction resulting in a decrease in the mechanical contraction of myocardium, coronary arteries and peripheral resistance vessels. In fact Nifedipine exerts a selective action on the smooth muscle of coronary and peripheral blood vessels resulting in the relief of coronary spasm, coronary vasodilation and peripheral vasodilation. The peripheral vasodilating action of Nifedipine leads to a decrease in peripheral vascular resistance and thereby a fall in blood pressure. The fall in blood pressure produced by Nifedipine is proportionate to the pre-treatment level of blood pressure. Unlike other calcium channel blocking agents. Nifedipine does not inhibit calcium influx into cells of atrioventricular node, therefore, it does not affect intracardiac impulse conduction.

The use of Nifedipine is not associated with disturbances of atrioventricular conduction, deterioration of pulmonary functions due to broncho-constriction in cases of chronic obstructive pulmonary disease (COPD) and impairment of haemodynamic adjustments. Long-term administration of Nifedipine does not produce development of tolerance to its therapeutic actions and its abrupt discontinuation does not lead to occurrence of any withdrawal reaction.

Nifedipine Extended-Release Tablets is compatible with beta-blockers, digitalis, anti-thrombotics, anti-coagulants and anti-diabetics.

Beta-adrenergic blocking agents:

Nifedipine extended-release tablet was well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.

Digitalis:

Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and nifedipine extended-release tablet, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine extended-release tablet to avoid possible over- or under-digitalization.

Coumarin Anticoagulants:

There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

J. Use during Pregnancy and Lactation

Nifedipine is contraindicated throughout pregnancy. Drugs in this class carry the potential to produce foetal hypoxia, caesarean deliveries, prematurity and intrauterine growth retardation, which may be associated with maternal hypotension.

Pregnancy Category C

In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic and fetotoxic effects, inducing stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m2 basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.

The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with*in utero* exposure to phenytoin.

There are no adequate and well-controlled studies in pregnant women. Nifedipine Extended-Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Nursing Mothers

Nifedipine is excreted in human milk. So far, insufficient evidence is available as to whether nifedipine has an effect on breastfed infants. Breastfeeding should be stopped first if nifedipine treatment becomes necessary during the breastfeeding period.

K. Side Effects

Nifedipine Extended-Release Tablets is generally well tolerated by majority of patients. The reported side effects are mild and transient in nature which tends to disappear on continuation of therapy. These side effects are mostly extension of its pharmacological effects and include headache, sensation of warmth, flushing, dizziness, light headedness, giddiness, weakness, nausea and heart burn. Sometimes it may lead to palpitation, tremor and nervousness. On very rare occasions, it may lead to angina pectoris and excessive hypotension. Ankle edema and Peripheral edema has also been reported with the use of Nifedipine Extended-Release Tablets.

L. Over dosage

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.

Experience with nifedipine overdosage is limited. Generally, overdosage with nifedipine leading to pronounced hypotension calls for active cardiovascular support including monitoring of cardiovascular and respiratory function, elevation of extremities, judicious use of calcium infusion, pressor agents and fluids. Clearance of nifedipine would be expected to be prolonged in patients with impaired liver function. Since nifedipine is highly protein bound, dialysis is not likely to be of any benefit; however, plasmapheresis may be beneficial.

There has been one reported case of massive overdosage with tablets of another extended release formulation of nifedipine. The main effects of ingestion of approximately 4800 mg of nifedipine in a young man attempting suicide as a result of cocaine-induced depression was initial dizziness, palpitations, flushing, and nervousness. Within several hours of ingestion, nausea, vomiting, and generalized edema developed. No significant hypotension was apparent at presentation, 18 hours post ingestion. Blood chemistry abnormalities consisted of a mild, transient elevation of serum creatinine and modest elevations of LDH and CPK, but normal SGOT. Vital signs remained stable, no electrocardiographic abnormalities were noted and renal function returned to normal within 24 to 48 hours with routine supportive measures alone. No prolonged sequelae were observed.

The effect of a single 900 mg ingestion of nifedipine capsules in a depressed anginal patient on tricyclic antidepressants was loss of consciousness within 30 minutes of ingestion, and profound hypotension, which responded to calcium infusion, pressor agents, and fluid replacement. A variety of ECG abnormalities were seen in this patient with a history of bundle branch block, including sinus bradycardia and varying degrees of AV block. These dictated the prophylactic placement of a temporary ventricular pacemaker, but otherwise resolved spontaneously. Significant hyperglycemia was seen initially in this patient, but plasma glucose levels rapidly normalized without further treatment.

A young hypertensive patient with advanced renal failure ingested 280 mg of nifedipine capsules at one time, with resulting marked hypotension responding to calcium infusion and fluids. No AV conduction abnormalities, arrhythmias, or pronounced changes in heart rate were noted, nor was there any further deterioration in renal function.

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. 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.

M. Pharmacodynamic Data

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 Extended-Release 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 Extended – Release Tablets 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.

N. Pharmacokinetic Data

General characteristics:

Nifedipine Extended-Release 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 Extended – Release tablet appropriate for twice-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 Nifedipine Extended-Release Tablets ranges from 68-86% other 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 Nifedipine Extended-Release Tablets 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, Nifedipine Extended – Release Tablets should not be administered in these patients.

O. Incompatibilities

Not applicable

P. Storage Conditions

Store in a cool (below 30^0C), dark place. Protect from light. Keep out of the reach of children.

Q. Instructions For Use /handling
Use as directed by a physician.

R. Effect 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 K. side effects). This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

S. Shelf Life
36 months

T. Inscription in the List of Poisonous Substance
Not applicable

U. Packaging
Available in Blister pack of 10 x 10 tablets placed in carton along with insert.

V. Name and Address of the Manufacturer
M/s. Centurion Laboratories Pvt. Ltd.
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