SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hypolar* Retard 20

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20mg nifedipine in a modified release formulation.

3 PHARMACEUTICAL FORM

Modified release tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypolar* Retard 20 tablets are indicated for the treatment of hypertension and the prophylaxis of chronic stable angina pectoris.

Hypolar* Retard 20 has no therapeutic antiarrhythmic effect.

4.2. Posology and Method of Administration

These tablets should be swallowed with a glass of water. They must be swallowed whole and not broken or chewed.

Adults:
The recommended starting dose of nifedipine is 10mg every 12 hours swallowed with water with subsequent titration of dosage according to response. The dose may be adjusted to 40mg every 12 hours.

Elderly:
The pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Nifedipine is metabolised primarily by the liver and therefore patients with liver dysfunction should be carefully monitored. Patients with renal impairment should not require adjustment of dosage.

Treatment with Hypolar* Retard 20 may be continued long term.

Children:
Nifedipine is not recommended for use in children.

Route of administration
Oral.

4.3 Contraindications

Nifedipine has been shown to be teratogenic in animals and therefore Hypolar* Retard 20 tablets should not be administered to women who are pregnant or may become pregnant and to nursing mothers.

Other contraindications:

- Patients with cardiogenic shock.
- Hypersensitivity to nifedipine or other dihydropyridines because of the theoretical risk of cross reactivity.
- Nifedipine should not be used in clinically significant aortic stenosis, 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.
- Nifedipine should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction.
- Patients with acute porphyrias. Calcium channel blockers have been shown to be porphyrinogenic.

4.4 Special warnings and precautions for use

Hypolar* Retard 20 should be used with caution in patients with severe hypotension and in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.

Cardiac ischaemic pain has been reported to have occurred in some patients within 1 to 4 hours of receiving nifedipine. In such cases treatment should be discontinued.

Care must be exercised in patients with very low blood pressure (severe hypotension with systolic pressure less than 90 mm Hg).

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. For further information regarding use in pregnancy, refer to section 4.6.

Caution should be exercised when Hypolar* Retard 20 is given to diabetic patients as they may require adjustment of their diabetic therapy.

In patients with malignant hypertension and hypovolaemia who are on dialysis, a significant decrease in blood pressure can occur.

In patients with impaired liver function, careful monitoring, and in severe cases, a dose reduction may be necessary.

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.

This medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Nifedipine is metabolized via the cytochrome P450 3A4 system. Drugs that are know to either inhibit or to induce this enzyme system may therefore alter the first pass 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:

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 if 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 of the nifedipine dose should be 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., itraconazole, ketoconazole)
- the antidepressant fluoxetine
- quinupristin/dalfopristin
- 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)
- theophylline
- phenytoin
- carbamazepine
- primidone
- phenobarbital

Effects of nifedipine on other drugs

Other antihypertensive: Hypolar* Retard 20 may be used in combined therapy with other antihypertensive agents including beta-blockers where an additive or synergistic hypotensive effect is to be expected. Withdrawal of any previous antihypertensive agents should be gradual as nifedipine will not compensate for any possible rebound effects.

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 nifepidine 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 metabolized 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.

Enhanced hypotensive effect when calcium channel blockers given with general anaesthetics and nitrates.

Hypotensive effect of calcium channel blockers antagonsied when given with corticosteroids, oestrogens, alprostadil, vadenafil,

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 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, the 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 interactions reported include:

Enhanced hypertensive effect of nifedipine when taken with alcohol.

Nifedipine may increase the spectrophotometric value of urinary vanillylmandelic acid falsely. However, HPLC measurements are unaffected.

4.6 Fertility, pregnancy and lactation

As nifedipine has been shown to be teratogenic in animals, Hypolar* Retard 20 should not be administered to women who are pregnant or may become pregnant and to nursing mothers.

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.

4.7. Effects on Ability to Drive and Use Machines

Nausea, headaches, lethargy and dizziness have been reported to occur and therefore the patient should be warned of these possible effects.

4.8 Undesirable effects

Exacerbation of angina pectoris may occur rarely at the start of treatment with modified release formulations of nifedipine. The occurrence of myocardial infarction has been described although it is not possible to distinguish such an event from the natural course of ischaemic heart disease.

The most common side effects reported are dizziness, flushing, headaches, hypotension, tachycardia and palpitations and ankle swelling. Other less common side effects include gastrointestinal disturbances, increased micturition, rash, pruritus and urticaria, nausea, lethargy, paraesthesiae, myalgia, tremor and visual disturbances.

Gingival hyperplasia has been reported to occur, and in older men gynaecomastia following long term therapy, however both these conditions are reversible on withdrawal of the drug.

There have been reports of rare cases of hypersensitivity-type jaundice. Liver function disturbances such as intra-hepatic cholestasis may also occur.

Discontinuation of therapy will result in regression of these side effects.

Respiratory, thoracic and mediastinal disorders with a frequency not known: Pulmonary oedema*

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

4.9. Overdose

This may be associated with severe hypotension, tachycardia or bradycardia and unconsciousness although there are few reports and the symptoms are not necessarily dose-related.

The metabolic disturbances which can occur include hyperglycaemia, metabolic acidosis and hypo- or hyperkalaemia. The cardiac effects which

may occur include heart block, AV dissociation and asystole and cardiogenic shock with pulmonary oedema.

Other effects include drowsiness, dizziness, confusion, nausea, vomiting, lethargy, flushing and hypoxia.

In the treatment of overdosage it is important to restore stable cardiovascular conditions as soon as possible and achieve total elimination of nifedipine.

Gastric lavage and charcoal instillation may be of assistance if the patient is found early after the overdose. Gastric lavage may be necessary in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

Activated charcoal should be given in 4 hourly doses of 25g for adults and 10g for children.
The patient should be carefully monitored.

Hypotension should be treated by placing the patient in the supine position with the feet raised and the use of plasma expanders, as appropriate. If necessary, intravenous administration of 10% calcium gluconate 10-20ml over a period of 5-10 minutes may be appropriate. Beta-sympathomimetics may be given e.g.: isoprenaline. If the blood pressure response is inadequate with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The patient's response should determine the dosage of these drugs.

If bradycardia persists the patient may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker.

It has also been reported that the use of metaraminol combined with calcium salts has been beneficial.

Care should be exercised with any additional fluids given to avoid cardiac overload.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Nifedipine is a dihydropyridine and is a potent antagonist of calcium influx through the slow channel of the cell membrane of cardiac and smooth muscle cells. Nifedipine also binds to intracellular calcium binding proteins. Calcium is normally released from the sarcoplasmic reticulum intracellularly and this combined with the influx of extracellular calcium results in enhanced binding calcium to calmodulin. Calcium channel blockers such as nifedipine act as arteriolar dilators by inhibiting this calcium entry into the channel. The effects are more pronounced on vascular

smooth muscle because depolarisation of cardiac muscle cells is dependent on both sodium ion influx and calcium ion influx and also nifedipine has little effect on the rate of recovery of the slow calcium channel.

Nifedipine is known to be an effective and relatively well tolerated treatment for angina and mild to severe hypertension.

The antihypertensive effects of nifedipine are achieved by causing peripheral vasodilation resulting in a reduction in peripheral resistance. Nifedipine reduces blood pressure in hypertension but has little or no effect in normotensive individuals.

Nifedipine produces its effects in the treatment of angina by reducing peripheral and coronary vascular resistance, leading to an increase in coronary blood flow, cardiac output and stroke volume and causing a decrease in after-load.

5.2 Pharmacokinetic Properties

Nifedipine is rapidly and almost completely absorbed from the gastro-intestinal tract after oral administration, however due to extensive hepatic first pass metabolism the resultant bioavailability lies between 45% and 75%.

Hypolar* Retard 20 is a modified release preparation designed to release Nifedipine over a period of time. Following a pharmacokinetic study in volunteers it was found that the average time to reach maximum plasma concentration was 2.2 hours and the mean peak plasma concentration was found to be 58.5ng/ml. The average elimination half-life was found to be 17.3 hours. Nifedipine is highly bound to plasma protein.

5.3 Preclinical Safety Data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose, corn starch, talc, hydroxypropyl methyl cellulose, magnesium stearate, polysorbate 80, polyethylene glycol 4000, iron oxide (E172), and titanium dioxide (E171).

6.2 Incompatibilities

None reported.

6.3 Shelf Life

3 years.

6.4 Special Precautions for Storage

Store in a dry place below 25^{o}C. Protect from light.

6.5 Nature and Contents of Container

Blister strips composed of PVC foil 250µm ± 5%, PVdC 25µm ± 5%, aluminium foil 25µm ± 8%, PVdC 20µm ± 10%.
Pack sizes: 28, 30, 56, 60, 84, 100, 250, 500 and 1,000.

6.6 Instructions for Use/Handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Woolmer Way
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Hampshire
GU35 9QE

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PL 04416/0245

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