SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Valni 20 Retard (Nifedipine).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg Nifedipine .

Excipient with known effect: Each tablet contains 11.980mg lactose (as lactose monohydrate)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified Release Tablet.

Pale red, round, biconvex tablets, marked NIF 20 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Valni 20 Retard tablets are indicated for the following:

(i) Hypertension

(ii) The prophylaxis of chronic stable angina pectoris

4.2 Posology and method of administration

Posology

Adults

The recommended dose is one tablet (20 mg) every 12 hours. The dosage may be increased up to 40 mg every 12 hours to achieve the desired effect.

Paediatric population

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

Elderly

There are no special dosage requirements for the elderly, however, the pharmacokinetics of nifedipine are altered in the elderly so that lower maintenance doses of nifedipine may be required compared to younger patients.

Hepatic Impairment

Patients with hepatic dysfunction must be carefully monitored when treatment is commenced as Nifedipine is primarily metabolised in the liver. If hepatic function is impaired, the dosage requirements of nifedipine should be established before use of Valni 20 Retard.

Renal Impairment

Dosage adjustments should not be required for patients with renal impairment. Treatment with Valni 20 Retard may be continued long term.

Method of Administration

Oral administration.

It is recommended that these tablets are swallowed with a glass of water. These tablets must be swallowed whole and not broken or chewed.

These tablets should not be taken with grapefruit juice (see section 4.5).

4.3 Contraindications

Hypersensitivity to nifedipine, any of the excipients listed in section 6.1. or other dihydropyridines because of the theoretical risk of cross reactivity.

Nifedipine 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.

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 gastro-intestinal 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 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

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 pressure less than 90 mm Hg).

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).

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, 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 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.

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 diabetic treatment.

In dialysis patients with malignant hypertension and hypovolaemia, a significant 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 which 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.

For use in special populations see section 4.2.

Excipient(s) with known effect

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

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 is 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 Pregnancy and lactation

Pregnancy

Nifedipine 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).

There are no adequate, 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 breast-feeding 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.

4.7 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 (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). The ADRs identified only during the ongoing post-marketing 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
Metabolism and Nutrition Disorders				Hyperglycaemia
Psychiatric Disorders		Anxiety reactions Sleep disorders		Depression
Nervous System Disorders	Headache	Migraine Vertigo Dizziness Tremor	Dysaesthesia Paraesthesia Lethargy	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 Mediastinal Disorders		Nasal congestion Nosebleed		Dyspnoea Pulmonary oedema**
Gastrointestinal Disorders	Constipation	Gastrointestinal and abdominal pain Dyspepsia Flatulence Dry mouth Nausea	Gingival hyperplasia	Vomiting Bezoar Dysphagia Intestinal obstruction Intestinal ulcer 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		Myalgia Arthralgia
Renal and Urinary Disorders		Dysuria Polyuria	Increased frequency of micturition	
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)

Exacerbation of angina pectoris may occur frequently at the start of treatment with short acting 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.

Gingival hyperplasia and, in older men, gynaecomastia have been reported but these are usually reversible on drug withdrawal. Hypersensitivity reactions such as skin rashes and abnormalities of liver function have occurred. These symptoms disappear upon discontinuation of nifedipine.
In dialysis patients with malignant hypertension and hypovolaemia, a distinct fall in blood pressure can occur as a result of vasodilation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 cardiovascular conditions have priority. After oral ingestion thorough gastric lavage is indicated, if necessary, in combination with irrigation of the small intestine. Particularly in the cases of intoxication with slow release nifedipine formulations such as Nifedipine Retard. 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 (alternatively ipecacuanha) 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 (10-20ml 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 blockers with mainly vascular effect, dihydropyridine derivatives

ATC Code: C08 CA05

Nifedipine is a calcium antagonist of the 1,4-dihydropyridine type. Calcium antagonists reduce the transmembrane 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 retard tablet is formulated to achieve controlled delivery of nifedipine in a release profile sufficient to enable twice-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 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 sub maximally 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 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

Absorption
Orally administered nifedipine is almost completely absorbed in the gastro-intestinal tract, however due to extensive hepatic first pass metabolism, the resultant bioavailability lies between 45% and 75%.
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 proteins (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 retard 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 retard should not be administered in these patients.

Bioavailability
Adalat Retard is a modified release formulation currently available on the UK market. A comparative bioavailability study has been carried out comparing this preparation with Valni 20 Retard. The results of the study are provided below and demonstrate that these two preparations are bioequivalent.

Mean data from the comparative bioavailability study is presented below:

Pharmacokinetic parameters measured after 6 days at steady state (mean N=24)	**Adalat Retard Tablet**	**Valni 20 Retard Tablet**
C_{MAX}	58.7ng/ml	58.5ng/ml
T½ ß	13.31 hours	17.30 hours
AUC $_{0\text{-}48\ hours}$	407 ng/ml/hour	413 ng/ml/hour
$AUC_{0\text{-}INF}$	480 ng/ml/hour	517 ng/ml/hour
T_{MAX}	2.00 hours	2.21 hours

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential.

Following acute oral and intravenous administration of nifedipine in various animal species, the following LD_{50} (mg/kg) values were obtained:

Mouse:	Oral: 494 (421-572)*;	i.v.: 4.2 (3.8-4.6)*.
Rat:	Oral: 1022 (950-1087)*;	i.v.: 15.5 (13.7-17.5)*.
Rabbit	Oral: 250-500;	i.v.: 2-3.
Cat:	Oral: ~ 100;	i.v.: 0.5-8.
Dog:	Oral: > 250;	i.v.: 2-3.
* 95% confidence interval.		

In subacute and sub-chronic toxicity studies in rats and dogs, nifedipine was tolerated without damage at doses of up to 50 mg/kg (rats) and 100 mg/kg (dogs) p.o. over periods of thirteen and four weeks, respectively. Following intravenous administration, dogs tolerated up to 0.1 mg/kg nifedipine for six days without damage. Rats tolerated daily intravenous administration of 2.5 mg/kg nifedipine over a period of three weeks without damage.

In chronic toxicity studies in dogs with treatment lasting up to one year, nifedipine was tolerated without damage at doses up to and including 100 mg/kg p.o. In rats, toxic effects occurred at concentrations above 100 ppm in the feed (approximately 5-7 mg/kg bodyweight).

In a carcinogenicity study in rats (two years), there was no evidence of a carcinogenic effect of nifedipine.

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.

In *in vitro* and *in vivo* tests, nifedipine has not been associated with mutagenic properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose, corn starch, talc, hydroxypropylmethyl 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°C. Store in the original package in order to 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 20GSM ± 10%.

Pack size: 28, 30, 56, 60, 84, 100, 250, 500, 1,000.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
220 Butterfield, Great Marlings
Luton
LU2 8DL
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8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0458

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10/10/1995

Date of renewal: 20/08/2001

10 DATE OF REVISION OF THE TEXT

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