1 NAME OF THE MEDICINAL PRODUCT
Cardilate MR® 20mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient: nifedipine (INN) 20mg
For excipients, see Section 6.1

3 PHARMACEUTICAL FORM
Modified Release Tablet for oral administration. Dissolution rate of nifedipine from Cardilate MR® 20mg Tablets are such that twice daily (12 hourly) administration is usually possible.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cardilate MR® 20mg Tablets are indicated for the treatment of hypertension and for prophylaxis of chronic stable angina pectons.

4.2 Posology and method of administration

Adult: The recommended starting dose of Cardilate MR® 20mg Tablets 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.

Cardilate MR® 10mg Tablets permit titration of initial dosage. The recommended dose is one Cardilate MR® 10mg Tablet (10mg) every 12 hours.

Nifedipine is metabolised primarily by the liver and therefore patients with liver dysfunction should be carefully monitored, and in severe cases, a dose reduction may be necessary.

Patients with renal impairment should not require adjustment of dosage. Treatment may be continued indefinitely.

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

Children: Nifedipine is not recommended for use in children.

Cardilate MR® 20mg Tablets should not be taken with grapefruit juice (see Section 4.5).
Paediatric population
The safety and efficacy of nifedipine in children under the age 18 years have not been established.

Currently available data for the use of nifedipine in hypertension are described in section 5.1

4.3 Contraindications
Cardilate MR® 20mg Tablets should not be administered to patients with known hypersensitivity to nifedipine, or other dihydropyridines because of the theoretical risk of cross-reactivity.
Cardilate MR® 20mg Tablets should not be administered to women capable of child-bearing or to nursing mothers.
Cardilate MR® 20mg Tablets should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina, or during or within one month of a myocardial infarction.
Cardilate MR® 20mg Tablets should not be used for the treatment of acute attacks of angina.
The safety of Cardilate MR® 20mg Tablets in malignant hypertension has not been established.
Cardilate MR® 20mg Tablets should not be used for secondary prevention of myocardial infarction.
Cardilate MR® 20mg Tablets 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
Cardilate MR® 20mg Tablets are not a beta-blocker and therefore give no protection against the dangers of abrupt beta-blocker withdrawal any such withdrawal should be gradual reduction of the dose of beta-blocker preferably over 8 - 10 days.
Cardilate MR® 20mg Tablets 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. Cardilate MR® 20mg Tablets will not prevent possible rebound effects after cessation of other antihypertensive therapy.
Cardilate MR® 20mg Tablets should be used with caution in patients whose cardiac reserve is poor. Deterioration of heart failure has occasionally been observed with nifedipine.
Caution should be exercised in patients with severe hypotension.
Ischaemic pain has been reported in a small proportion of patients within one to four hours of the introduction of Nifedipine therapy. Although a “steal” effect has not been demonstrated, patients experiencing this effect should discontinue Cardilate MR® 20mg Tablets.
The use of Cardilate MR® 20mg Tablets 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.

Whilst nifedipine is contra-indicated in pregnancy, particular care must be exercised when administering nifedipine in combination with i.v. magnesium sulphate to pregnant women.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Known Interactions**

As with other dihydropyridines, nifedipine should not be taken with grapefruit juice as elevated plasma concentrations occur, due to a decreased first pass metabolism. 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 ingestion of grapefruit juice.

The antihypertensive effect of Cardilate MR® 20mg Tablets may be potentiated by simultaneous administration of cimetidine.

When used in combination with nifedipine, serum quinidine levels have been shown to be suppressed regardless of dosage of quinidine. Therefore monitoring of quinidine plasma levels and if necessary adjustment of the quinidine dosage are recommended. The pharmacokinetics of nifedipine may also be altered when used in combination with quinidine. It is therefore recommended to monitor blood pressure, and if necessary reduce the nifedipine dosage.

The simultaneous administration of nifedipine and digoxin may lead to reduced digoxin clearance and hence an increase in the plasma digoxin level. Plasma digoxin levels should be monitored and, if necessary, the digoxin dose reduced.

Phenytoin induces the cytochrome P450 3A4 system. Upon co-administration with phenytoin the bioavailability of nifedipine is reduced and thus its efficacy weakened. When both drugs are concomitantly administered, the clinical response to nifedipine should be monitored and, if necessary an increase of 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 with phenytoin is discontinued.

Diltiazem decreases the clearance of nifedipine and hence increases plasma nifedipine levels. Therefore, caution should be taken when both drugs are used in combination and a reduction of the nifedipine dose may be necessary.

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

Cardilate MR® 20mg Tablets should not be administered concomitantly with rifampicin since effective plasma levels of nifedipine may not be achieved owing to enzyme induction (see Section 4.3).

Simultaneous administration of cisapride and nifedipine or ciuinupristin/dalfopristin and nifedipine may lead to increased plasma
concentrations of nifedipine. Consequently, the blood pressure should be monitored and, if necessary, the nifedipine dose reduced.

Theoretical Interactions
Nifedipine is metabolised via the cytochrome P450 3A4 system and, therefore, there are theoretical interactions for drugs which are known to inhibit this enzyme system (e.g. erythromycin, ketoconazole, itraconazole, fluconazole, fluoxetine, indinavir, nifedipine, ritonavir, amprenavir and saquinavir). Although no formal in vivo interaction studies have been performed with these drugs, co-administration can be expected to lead to an increase in plasma concentrations of nifedipine. Blood pressure should therefore be monitored and, if necessary, a reduction in the nifedipine dose considered.

A clinical study investigating the potential of a drug interaction between nifedipine and nefazodone has not yet been performed. Nefazodone is known to inhibit the cytochrome P450 3A4 mediated metabolism of other drugs. Therefore an increase in nifedipine plasma concentrations upon co-administration of both drugs cannot be excluded. When nefazodone is given together with nifedipine, the blood pressure should be monitored and, if necessary, a reduction in the nifedipine dose considered.

Tacrolimus has been shown to be metabolised via the cytochrome P450 3A4 system. Upon co-administration of both drugs, the tacrolimus plasma concentrations should be monitored and, if necessary, a reduction in the tacrolimus dose considered.

Although no formal interaction studies have been performed between nifedipine and carbamazepine, phenobarbital or valproic acid, these drugs have been shown to alter the plasma concentrations of a structurally similar calcium channel blocker. A decrease (carbamazepine, phenobarbital) or an increase (valproic acid) in nifedipine plasma concentrations and hence an alteration in efficacy cannot be excluded.

Drugs shown not to interact with nifedipine
The following drugs have been shown to have no effect on the pharmacokinetics of Nifedipine when administered concomitantly: ajmaline, aspirin, benazepril, candesartan, cilexetil, debrisoquine, doxazosin, irbesartan, omeprazole, orlistat, pantoprazole, ranitidine, rosiglitazone, talinolol and triamterene hydrochlorothiazide.

4.6 Pregnancy and lactation
Cardilate MR® 20mg Tablets are contra-indicated in women capable of childbearing or to nursing mothers.

The safety of Cardilate MR® 20mg Tablets for use in human pregnancy have not been established. Evaluation of experimental animal studies has shown reproductive toxicity consisting of embryotoxicity and teratogenic effects at maternally toxic doses.

Cardilate MR® 20mg Tablets are contra-indicated in nursing mothers, as nifedipine may be present in breast milk.
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. This applies particularly at the start of treatment, on changing the medication and in combination with alcohol.

4.8 **Undesirable effects**
Most undesirable effects are consequences of the vasodilatory effects of nifedipine and usually regress upon withdrawal of therapy.

In all clinical studies (n = 7243) the following undesirable effects were commonly reported (>1% <10% incidence): headache, vasodilatation and palpitations which occur most frequently in the early stages of treatment, lethargy, asthenia, Constipation, dizziness and oedema particularly peripheral oedema not associated with heart failure or weight gain.

Additionally, uncommon and rare undesirable effects were also reported:
- **Uncommon (>0.1% <1%)**
  - **Body as a whole:** abdominal pain, chest pain, leg pain, malaise, pain
  - **Cardiovascular:** postural hypotension, syncope, tachycardia
  - **Digestive:** constipation, diarrhoea, dry mouth, dyspepsia, vomiting
  - **Musculo-skeletal:** arthralgia, myalgia
  - **Nervous:** insomnia, nervousness, paraesthesia, somnolence, tremor, vertigo
  - **Respiratory:** dyspnoea
  - **Skin:** pruritus, rash, skin disorder, sweating
  - **Special senses:** nocturia, polyuria

As with other sustained release dihydropyridines, exacerbation of angina pectoris may occur at the start of treatment with sustained 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.

**Rare (>0.01% <0.1%)**
- **Body as a whole:** enlarged abdomen, allergic reaction, photosensitivity reactions, hypersensitivity type jaundice.
- **Cardiovascular:** hypotension
Digestive: flatulence, gastrointestinal disorder, GGTP increase, liver function test abnormalities

Haemic and Lymphatic system: purpura

Nervous: hyperaesthesia: mood changes

Skin: urticaria

Special senses: abnormal vision, ambylopia

Urogenital: impotence

For spontaneous reports the following undesirable effects were reported very rarely worldwide (0.01%): gingival hyperplasia, agranulocytosis, erythromelalgia, exfoliative dermatitis and anaphylactic reaction. There have also been reports of gynaecomastia in older men on long-term therapy, but this usually regresses upon withdrawal of therapy.

4.9 Overdose

Clinical effects
Reports of nifedipine overdosage are limited and symptoms are not necessarily dose-related. Severe hypotension, due to vasodilatation and tachycardia, or bradycardia are the most likely manifestations of overdose.

Metabolic disturbances include hyperglycaemia, metabolic acidosis and hypoor hyperkalaemia.

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

Other toxic effects include nausea, vomiting, drowsiness, dizziness, confusion, lethargy, flushing, hypoxia and unconsciousness to the point of coma.

Treatment
As far as treatment is concerned, elimination of nifedipine and the restoration of stable cardiovascular conditions have priority.

After oral ingestion gastric lavage is indicated, if necessary in combination with irrigation of the small intestine. Ipecacuanha should be given to children.

Elimination must be as complete as possible, including the small intestine, to prevent the otherwise inevitable subsequent absorption of the active substance. Activated charcoal should be given in 4-hourly doses of 25g for adults, 10g for children.

Blood pressure, ECG, central arterial pressure, pulmonary wedge pressure, urea and electrolytes should be monitored.

Hypotension as a result of cardiogenic shock and arterial vasodilatation should be treated with elevation of the feet and plasma expanders. If these measures are ineffective, hypotension may be treated with 10% calcium gluconate 10-20ml intravenously over 5-10 minutes. If the effects are inadequate, the treatment can be continued, with ECG monitoring. In addition, beta-sympathomimetics may be given, e.g. isoprenaline 0.2mg slowly i.v., or as a continuous infusion of 5μg/min. If an insufficient increase in blood pressure is achieved with calcium and isoprenaline, vasoconstricting sympathomimetics such as dopamine or noradrenaline should be administered. The dosage of these drugs should be determined by the patient’s response.
Bradycardia may be treated with atropine, beta-sympathomimetics or a temporary cardiac pacemaker, as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C08C A 05

Selective Calcium channel blocker (Dihydropyridine derivative) with mainly vascular effects

Nifedipine is a specific and potent calcium antagonist. In hypertension, the main action of Cardilate MR® 20mg Tablets are to cause peripheral vasodilatation and thus reduce peripheral resistance.

In angina Cardilate MR® 20mg Tablets 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.

Cardilate MR® 20mg Tablets administered twice-daily provide 24-hour control of raised blood pressure. Cardilate MR® 20mg Tablets cause reduction in blood pressure such that the percentage lowering are directly related to its initial level. In normotensive individuals Cardilate MR® 20mg Tablets have little or no effect on blood pressure.

Nifedipine inhibits influx into cells, the smooth muscle cells of the coronary arteries and the peripheral capillaries. Nifedipine brings a substantial improvement in the oxygen supply to the myocardium while reducing oxygen demand. It has to anti properties. High blood pressure is due to a reduction in the peripheral resistance (vasodilation).

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 is absorbed almost completely from the gastro-intestinal tract regardless of the oral formulation used and undergoes extensive metabolism in the liver to inactive metabolites with less than 1% of the parent drug appearing unchanged in the urine. The rate of absorption determines the drug’s apparent
elimination. The apparent elimination phase half-life for Cardilate MR® 20mg Tablets have been estimated as 2.2 - 2.4 + 0.8 hours. After enteral or intravenous doses 70 - 80% of activity is eliminated (primarily as metabolites) via the urine. Remaining excretion is via the faeces. After 24 hours, 90% of the administered dose is eliminated. Protein binding of nifedipine exceeds 90% in human serum.

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose (E460)
Carboxymethyl sodium starch
Mannitol (E421)
Colloidal anhydrous silica
Polyvidone U&P
Magnesium stearate (E572)
Sodium lauryl sulphate
Hyromellose (E464)
Polyoxyethylene glycol 6000
Polyoxyethylene glycol 400
Red ferric oxide (E172)
Titanium dioxide (E171)
Talc
Purified water
Alcohol (Industrial)

6.2 Incompatibilities
None known

6.3 Shelf life
Three years

6.4 Special precautions for storage
Cardilate MR® 20mg Tablets should be stored in the original pack below 25ºC, in a dry place and protected from light. Nifedipine is highly sensitive to light and is therefore protected both by materials in the tablet and in the packaging. Nonetheless tablets should not be
exposed to direct sunlight and should only be removed from the blister pack when about to be taken.

6.5 **Nature and contents of container**
Thermoformed blister packs of PVC/red transparent PVDC/aluminium in boxes of 7, 14, and 20
21, 28, 30, 56, 60, 84, 90, 100, 112 and 120 tablets

6.6 **Special precautions for disposal**
None

7 **MARKETING AUTHORISATION HOLDER**

Norton Healthcare Ltd
T/A IVAX Pharmaceuticals UK
Ridings Point,
Whistler Drive,
Castleford,
West Yorkshire,
WF10 5HX

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00530/0488

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
13/06/1995 / 10/10/2006

10 **DATE OF REVISION OF THE TEXT**
07/01/2013