SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nifedi-Denk 20 Retard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: nifedipine

Each prolonged-release tablet contains 20 mg nifedipine.

Excipient with known effect: Each prolonged-release tablet contains 36.2 mg of lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Oblong, greyish-red film-coated tablets with score line on both sides. The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Chronic stable angina pectoris (effort angina)
- Vasospastic angina pectoris (Prinzmetal's angina, variant angina)
- Essential hypertension

4.2 Posology and method of administration

Posology
Treatment should as far as possible be administered individually on the basis of the severity of the condition and the patient's response.

The target dose should be reached gradually, depending on the medical condition concerned.

Patients with severe cerebrovascular disorders should be treated with low doses.
Patients with high blood pressure suffering from severe cerebrovascular disease and patients expecting an excessive response to nifedipine due to low body weight or due to multiple treatment with other antihypertensives should be treated with nifedipine 10 mg prolonged-release tablets. Patients whose side effects to the nifedipine treatment would seem to make a more subtle adjustment of the dosage level desirable should also have the dose of nifedipine 10 mg prolonged-release tablets adapted individually.

If not prescribed otherwise, the recommended dose for adults is:

Chronic stable angina pectoris
1 prolonged-release tablet (nifedipine 20 mg) twice daily.

If necessary the dose may be increased gradually to 2 x 40 mg of nifedipine.

Vasospastic angina pectoris (Prinzmetal's angina, variant angina)
1 prolonged-release tablet (nifedipine 20 mg) twice daily.
If necessary the dose may be increased gradually to 2 x 40 mg of nifedipine.

Essential hypertension
1 prolonged-release tablet (nifedipine 20 mg) twice daily.
If necessary the dose may be increased gradually to 2 x 40 mg of nifedipine.

When co-administering agents that inhibit or induce the cytochrome P450 3A4 system, it may be necessary to adjust the nifedipine dose or, if necessary, to withhold the use of nifedipine completely (see section 4.5).

Additional information on special populations

Paediatric population
The use of nifedipine in children and adolescents below 18 years of age is not recommended. The safety and efficacy of nifedipine in children under the age of 18 years have not been established.
Currently available data for the use of nifedipine in hypertension are described in section 5.1.

Elderly patients (> 65 years)
The pharmacokinetics of nifedipine are altered in elderly people so that lower maintenance doses of nifedipine may be necessary.

Patients with hepatic insufficiency
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 4.4 and section 5.2).

Patients with renal insufficiency
Based on pharmacokinetic data, no dosage adjustment is required in patients with renal impairment (see section 5.1).

Method of administration
Oral use.

As a rule, the tablets are swallowed whole, not chewed, with sufficient liquid (e.g. one glass of water) after meals. Preferably Nifedi-Denk 20 Retard should be taken at the same time in the morning and evening.

Nifedi-Denk 20 Retard must not be taken with grapefruit juice (see section 4.5).

For Nifedi-Denk 20 Retard, it is recommended that the individual doses be taken at intervals of 12 hours, but at not less than intervals of 4 hours.

Discontinuation of treatment with Nifedi-Denk 20 Retard, particularly in case of high dosage, should proceed gradually.

Due to the photosensitivity of the ingredient nifedipine, the prolonged-release tablets should not be divided, as otherwise the light shield provided by the lacquer is no longer guaranteed.

The duration of administration should be determined by the physician.

4.3 Contraindications

Nifedipine is contraindicated in case of:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- cardiac-circulatory shock
- unstable angina pectoris
- high-grade aortic stenosis
- acute myocardial infarct (within the first 4 weeks)
- concomitant treatment with rifampicin, since effective nifedipine plasma levels are not obtained due to enzyme induction (see section 4.5)
- pregnancy (before week 20) and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Special caution and medical supervision is necessary in patients with:

- severe hypotension (less than 90 mmHg systolic)
- decompensated cardiac insufficiency
- dialysis patients with malignant hypertonia and hypovolaemia (a marked drop in blood pressure can arise owing to vasodilation)
- pregnancy (see sections 4.3 and 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 section 5.2). Therefore, nifedipine should be used with caution in patients with severe hepatic impairment.

Nifedipine is metabolised via the cytochrome P450 3A4 system. For this reason, active substances known to affect this enzyme system can alter the first-pass metabolism or excretion of nifedipine (see section 4.5).

Plasma levels of nifedipine can be increased, for example, by the following drugs that are known to be inhibitors of this enzyme system:

- macrolide antibiotics (e.g. erythromycin)
- anti-HIV protease inhibitors (e.g. ritonavir)
- antimycotics of the azole type (e.g. ketoconazole)
- antidepressants: nefazodone and fluoxetine
- quinupristin/dalfopristin
- valproic acid
- cimetidine
- tricyclic antidepressants, vasodilators
- cisapride.

If nifedipine is taken at the same time as these drugs, blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered.

Nifedipine is contraindicated before week 20 of pregnancy. Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine should only be considered for women with severe hypertension in whom standard therapy is ineffective (see section 4.6).

If nifedipine is used together with intravenously administered magnesium sulphate, blood pressure must be carefully monitored since there is the possibility of an exaggerated fall in blood pressure that can harm both mother and foetus.

This medicine contains lactose.
Patients with rare hereditary problems of galactose intolerance, total 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, which is present in both the intestinal mucosa and the liver. For this reason, concomitant administration of drugs that induce or inhibit this enzyme system can affect the first-pass metabolism (after oral administration) or excretion of nifedipine (see section 4.4).

Both the extent and duration of interactions should be considered if nifedipine is to be administered together with the medicines listed below.

Drugs that inhibit the cytochrome P450 3A4 system
When nifedipine is used concomitantly with the drugs listed below, which are known to be weak or moderate inhibitors of this enzyme system, blood pressure should be monitored and where necessary the nifedipine dose adapted (see section 4.2).

Macrolide antibiotics (e.g. erythromycin)
No interaction studies have been conducted with nifedipine and macrolide antibiotics. However, since certain macrolide antibiotics are known to inhibit the CYP3A4 system, increased plasma levels of nifedipine following concomitant administration cannot be excluded (see section 4.4).

Although structurally related to the macrolide antibiotics, azithromycin is not an inhibitor of CYP3A4.

Anti-HIV protease inhibitors (e.g. ritonavir)
No clinical interaction studies have been conducted with nifedipine and protease inhibitors. Protease inhibitors are known inhibitors of the cytochrome P450 3A4 system. Drugs of this class have also been shown to inhibit the cytochrome P450 3A4-mediated metabolism of nifedipine *in vitro*. When these drugs are used together with nifedipine, a marked increase in nifedipine plasma levels cannot be excluded due to a reduced first-pass metabolism and reduced elimination (see section 4.4).

Antimycotics of the azole type (e.g. ketoconazole)
No formal interaction studies with nifedipine and antimycotics of the azole type have been conducted. Drugs of this class are known inhibitors of the cytochrome P450 3A4 system. For this reason, the possibility of increased systemic bioavailability of nifedipine due to a reduced first-pass metabolism following concomitant oral use of the two drugs cannot be excluded (see section 4.4).

Fluoxetine
No clinical interaction studies have been conducted with nifedipine and fluoxetine. Fluoxetine has been shown to inhibit cytochrome P450 3A4-mediated nifedipine metabolism *in vitro*. For this reason, the possibility of increased nifedipine plasma levels following concomitant use of the two drugs cannot be excluded (see section 4.4).

Nefazodone
No clinical interaction studies have been conducted with nifedipine and nefazodone. Nefazodone is a known inhibitor of cytochrome P450 3A4-mediated metabolism. For this reason, the possibility of increased nifedipine plasma levels following concomitant use of the two drugs cannot be excluded (see section 4.4).

Quinupristin/dalfopristin
Concomitant use of quinupristin/dalfopristin and nifedipine can cause increased plasma levels of nifedipine (see section 4.4).

Valproic acid
No interaction studies have been conducted with nifedipine and valproic acid. As valproic acid has been shown to increase plasma levels of the structurally similar calcium antagonist nimodipine by enzyme inhibition, increased plasma levels and hence an increased effect of nifedipine cannot be excluded (see section 4.4).

Cimetidine
Due to the inhibition of cytochrome P450 3A4, cimetidine can result in increased nifedipine plasma levels and as a result an enhanced antihypertensive effect of nifedipine (see section 4.4).

Tricyclic antidepressants, vasodilators
The antihypertensive effect can be increased.

Cisapride
Coadministration of cisapride and nifedipine can result in increased plasma levels of nifedipine.

Drugs that induce the cytochrome P450 3A4 system
Rifampicin
Rifampicin is a strong cytochrome P450 3A4 inducer. Following concomitant administration with rifampicin, the bioavailability of nifedipine is markedly reduced and hence the efficacy is decreased. The use of nifedipine in combination with rifampicin is therefore contraindicated (see section 4.3).

Antiepileptics (e.g. phenytoin, carbamazepine, phenobarbital)
Phenytoin induces the cytochrome P450 3A4 system. When phenytoin and nifedipine are used concomitantly, the bioavailability of nifedipine is reduced and therefore its efficacy attenuated. When the two products are taken at the same time, the clinical reaction to nifedipine should be observed and if necessary an increase in the nifedipine dose considered. If the nifedipine dose is increased during concomitant use of the two drugs, a reduction in the nifedipine dose should be considered after the end of phenytoin therapy.

Formal studies examining the possible interactions between nifedipine and carbamazepine or phenobarbital have not been conducted. According to experience with the structurally similar calcium antagonist nimodipine, however, it cannot be excluded that, due to their enzyme-inducing effect, the concomitant use of carbamazepine or phenobarbital may result in reduced plasma levels and hence an attenuated effect of nifedipine.

Effects of nifedipine on other drugs
Antihypertensive drugs
Nifedipine can potentiate the antihypertensive effect of concomitantly administered drugs such as:
- diuretics
- beta-receptor blockers
- ACE inhibitors
- angiotensin-1 (AT1) receptor antagonists
- other calcium antagonists
- alpha-receptor blockers
- PDE-5 inhibitors
- alpha-methyldopa.

Beta-receptor blockers
During simultaneous treatment with beta-receptor blockers, the occurrence or exacerbation of heart failure has been observed in isolated cases. Patients should therefore be carefully monitored.

Digoxin
Coadministration of nifedipine and digoxin can result in reduced digoxin excretion and hence increased digoxin plasma levels. For this reason, as a precaution the patient should be monitored for symptoms of digoxin overdose and plasma levels tested. Where necessary, the glycoside dose should be reduced.

Theophylline
Nifedipine can cause an increase in theophylline plasma levels.

Vincristine
Nifedipine reduces the excretion of vincristine, as a result of which the adverse effects of vincristine may be increased. A dose reduction of vincristine should therefore be considered.

Cephalosporins
Following concomitant administration of cephalosporins (e.g. cefixime) and nifedipine, increased cephalosporin plasma levels have been observed.

Quinidine
In individual cases, nifedipine causes a decrease in quinidine plasma levels or discontinuation of nifedipine causes a marked increase in quinidine plasma levels such that, in the event of combined therapy or discontinuation of nifedipine, monitoring of quinidine plasma levels and, if necessary, an adjustment of the quinidine dose is recommended. In some cases, there have been reports of an increase in nifedipine plasma levels as a result of quinidine, whereas in other cases no change in the pharmacokinetics of nifedipine has been observed. If therefore the administration of quinidine is initiated during treatment with nifedipine, it is recommended to monitor blood pressure carefully and where necessary to reduce the dose of nifedipine.

Tacrolimus
Tacrolimus is metabolised via the cytochrome P450 3A4 system. Coadministration of tacrolimus and nifedipine can result in increased tacrolimus plasma levels. For this reason, regular monitoring of plasma levels and, if necessary, a reduction of the tacrolimus dose is recommended.

Interactions with food and drink
Grapefruit juice
Grapefruit juice inhibits the cytochrome P450 3A4 system. Due to a reduced first-pass metabolism and retarded excretion, blood levels of nifedipine can be increased and the duration of action prolonged, as a result of which the antihypertensive effect can be potentiated. After regular consumption of grapefruit juice, this effect can persist for at least 3 days after the last intake of grapefruit juice. The consumption of grapefruit or grapefruit juice should therefore be avoided in chronological association with nifedipine treatment (see section 4.2).

Other forms of interaction
The spectrophotometric determination of vanillylmandelic acid in urine can result in falsely increased values under nifedipine; the HPLC determination remains unaffected.

4.6 Fertility, pregnancy and lactation

Pregnancy
Nifedipine is contraindicated before week 20 of pregnancy. Nifedipine should not be used during pregnancy unless the clinical condition of the woman requires treatment with nifedipine. Nifedipine should only be considered for women with severe hypertension in whom standard therapy is ineffective (see section 4.4).

There is no experience from suitable controlled clinical trials in pregnant women.

The available information is insufficient to exclude negative effects on the unborn and new-born child.

Animal studies revealed evidence of an embryotoxic, foetotoxic and teratogenic effect of nifedipine (see section 5.3).

From the clinical experience available, a specific prenatal risk has not been identified, although an increase in perinatal asphyxia, caesarean section and intrauterine growth retardation has been reported. It is unclear whether these observations are due to the underlying hypertension, its treatment or to a specific drug effect.

Acute pulmonary oedemas have 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 must not be used during breast-feeding. Nifedipine is excreted into breast milk. The nifedipine concentration in milk is almost comparable with the mother's serum concentration (see section 4.3).

Fertility
In individual 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 cases in which *in vitro* fertilisation was repeatedly unsuccessful, 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

Treatment with this drug requires regular medical monitoring. Different reactions in individuals may alter reactivity to such an extent that the ability to drive a vehicle, operate machinery or work without a safe support may be impaired. This applies in particular to the initial period of treatment, an increase in the dosage, a change in medication as well as in combination with alcohol.

4.8 Undesirable effects

Adverse drug reactions observed in placebo-controlled studies with nifedipine (sorted by CIOMS III categories of frequency: 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.

The frequencies of adverse drug reactions 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 follows:

Very common: > 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000

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)	Very common	Common	Un-common	Rare	Very rare	Not known
Blood and lymphatic system disorders				Leucopenia, Anaemia, Thrombo-cytopenia, Thrombo-cytopenic purpura	Agranulo-cytosis	
Immune system disorders			Allergic reactions, Allergic oedema/ angio-oedema (including laryngeal oedema[1]), Pruritus, Rash	Urticaria		Anaphy-lactic/-anaphy-lactoid reactions
Metabolism and nutrition disorders				Hypergly-caemia		
Psychiatric disorders			Anxiety reactions, Sleep disorders			
Nervous system disorders	Headache	Vertigo, Dizziness, Asthenia	Migraine, Tremor, Par/-Dysaesthe-sia, Drowsiness /tiredness, Nervous-ness			Hypo-aesthesi a
Eye disorders			Visual distur-bances			Eye pain
Cardiac disorders		Palpita-tions	Tachycardia, Chest pain (angina pectoris[2])		Myocardial infarction[2]	
Vascular disorders	Oedema (including peripheral oedema)	Vasodilata-tion (e.g. flushing)	Hypoten-sion, Syncope			
Respiratory, thoracic, and mediastinal disorders			Nosebleed, Nasal congestion, Dyspnoea			Pulmo-nary oedema[3]

System organ class (MedDRA)	Very common	Common	Un-common	Rare	Very rare	Not known
Gastrointes-tinal disorders		Constipa-tion, Nausea	Gastroin-testinal and abdominal pain, Dyspepsia, Flatulence, Dry mouth	Gingival hyperplasia, Anorexia, Feeling of fullness, Eructation		Emesis, Oesophagi-tis
Hepatobiliary disorders			Transient increase in liver enzymes	Jaundice		
Skin and subcutaneous tissue disorders		Erythrom-elalgia, particularly at the beginning of treatment, Sweating	Erythem a	Allergic photosensi-tivity, Palpable purpura	Exfoliative dermatitis	Toxic epidermal necrolysis
Musculoske-letal and connective tissue disorders			Muscle cramps, Joint swelling, Myalgia			Arthralg ia
Renal and urinary disorders			Polyuria, Dysuria In the presence of renal impairment, temporary exacerbation of renal function			
Reproductive system and breast disorders			Erectile dysfunction	Gynaeco-mastia, which is reversible after discontinu-ing nifedi-pine		
General disorders and administra-tion site conditions		General malaise	Non-specific pain, chills			

[1] may result in a life-threatening outcome

[2] Episodes of angina pectoris or, in patients with existing angina pectoris, an increase in frequency, duration and severity of episodes can occur uncommonly, particularly at the beginning of treatment. There have been isolated reports of the occurrence of myocardial infarction.

[3] Cases have been reported when used as tocolytic during pregnancy (see section 4.6)

In dialysis patients with malignant hypertension and hypovolaemia, a marked fall in blood pressure can occur as a result of vasodilatation.

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 national reporting system.

4.9 Overdose

Symptoms of intoxication
The following symptoms have been observed with severe nifedipine intoxication:
Loss of consciousness up to coma, drop in blood pressure, tachycardial/bradycardial cardiac dysrhythmias, hyperglycaemia, metabolic acidosis, hypoxia, cardiac shock or lung oedema.

Therapeutic measures for intoxication
Elimination of nifedipine and recovery of stable cardiovascular circulation are primary objectives. After oral ingestion extensive gastric lavage, possibly combined with small intestinal lavage is indicated.

Particularly with intoxication through prolonged-release preparations, it is aimed for a complete elimination, also from the small intestine, in order to avoid expected late absorption.

The administration of laxatives with calcium antagonists may however result in inhibition of the intestinal muscle up to atony of the intestine. Nifedipine cannot be dialysed. However, plasmapheresis (high plasma protein binding, relatively low volume of distribution) is recommended.

Bradycardial cardiac dysrhythmias should be treated symptomatically with atropine and or beta-sympathomimetic drugs. In case the bradycardial dysrhythmia is life-threatening temporary pacemaker therapy is required.

Hypotonia, resulting from cardiac shock and arterial vasodilation can be treated with calcium (10 – 20 ml of calcium gluconate solution 10 %, as slow intravenous injection, repeated if necessary). As a result, calcium levels may be higher than normal or slightly elevated. If no adequate increase of blood pressure is achieved with calcium, a vasoconstrictive sympatomimetic like dopamine (up to 25 µg per kg bodyweight per minute), dobutamine (up to 15 µg per kg bodyweight per minute) or noradrenaline, epinephrine or norepinephrine is administered. The doses of these medicines depends on the desired effect.

Additional fluids or volumes should be withheld because of the risk of cardiac overload under haemodynamic control.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: calcium antagonist, 1.4-dihydropyridine derivative.
ATC Code: C08CA05

Mechanism of action
Nifedipine belongs to the group of calcium antagonists of 1.4-dihydropyridine type. Calcium antagonists exert an inhibiting action on the flow of calcium through the cell membranes. Nifedipine acts as a calcium antagonist at the smooth muscle cells, particularly around the coronary vessels and the

peripheral resistance vessels. This results in vasodilation. In therapeutic doses, nifedipine has practically no direct effect on the myocardium.

Nifedipine enlarges especially the big coronary arteries of the heart by reducing muscle tone. This results in an improvement of blood flow. Nifedipine causes a decrease in the total peripheral resistance as a result of the vasodilation.

At the start of treatment with this calcium antagonist, there is a reflex increase in heart rate and cardiac output. However, this increase is not sufficiently pronounced to compensate for the vasodilation.

During long-term treatment with nifedipine, the cardiac output increased initially returns to its original value. Particularly pronounced drop in blood pressure after intake of nifedipine is observed in hypertonic patients.

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
After peroral, fasting intake, nifedipine is absorbed almost completely. Nifedipine undergoes first-pass metabolism in the liver with the result that the systemic availability of orally administered immediate release nifedipine is 50 - 70 %. Peak plasma and serum concentrations are reached approx. 15 minutes after administration of a solution containing nifedipine and after 30 to 85 minutes after use of other non-slow release formulations.

Distribution
Around 95 % to 98 % of nifedipine is bound to plasma protein (albumin). A mean volume of distribution V_{ss} of 0.77 – 1.12 l/kg was found.

Biotransformation
Nifedipine is almost completely metabolized in the liver (high first-pass effect), primarily by oxidative processes. These metabolites show no pharmacodynamic activity.
Neither the unchanged substance nor the metabolite (M-1) is considerably eliminated by the kidneys (< 0.1 % of the dosage).
The polar metabolites M-2 and M-3 are found for about 50% of the dosage in the urine (partially conjugated). The predominant portion is excreted within 24 hours. The rest is excreted with the faeces.

Elimination
The elimination half-life is 1.7 – 3.4 hours (non-slow release formulations).
Accumulation of the substance during long-term therapy has not been reported following normal dosing.

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).

The table below shows the maximum plasma concentration (C_{max}), the related time (t_{max}) and the area under the concentration-time-curve (AUC) for nifedipine prolonged-release tablets

Dosage form	C_{max} [µg/l]	t_{max} [h]	AUC [µg x h/l]
Nifedipine 20 mg prolonged-release tablets	26 - 77	1.5 – 4.2	300 - 537

The terminal elimination half-life for nifedipine 20 mg prolonged-release tablets is 5.9 – 10.8 hours.

5.3 Preclinical safety data

Preclinical data, based on conventional studies of acute toxicity, chronic toxicity and mutagenic and carcinogenic potential, reveal no particular risks for humans.

In-vivo and *in-vitro* studies on mutagenicity proved negative. Thus, a mutagenic effect in humans can be fully ruled out.

A long-term study (2 years) in rats revealed no evidence of tumour generating potential in nifedipine.

Experimental studies in three animal species (rat, rabbit, mouse) revealed evidence of teratogenic effects, including digital anomalies, malformations of the extremities, cleft palates, cleft sternum and malformations 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 survival rates in neonatal rats (not evaluated in other species). All of the doses associated with teratogenic, embryotoxic or foetotoxic effects in experimental studies were maternally toxic and were several times the recommended maximum dose for humans (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Maize starch
Lactose monohydrate
Polysorbate 80
Magnesium stearate [vegetable]
Hypromellose
Macrogol 6000
Talc
Titanium dioxide
Red ferric oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 °C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Nifedi-Denk 20 Retard is available in PVC/PVDC/aluminium blisters.

Pack size: 30 and 100 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstrasse 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

10717.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

02.03.1990

10. DATE OF REVISION OF THE TEXT

11/2019

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription