

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nivadil 16mg Prolonged release capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Nilvadipine 16.0 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard. (Prolonged release capsule)

Hard gelatin capsules with an opaque brown cap (overprinted with "NV16" in white) and an opaque brown/red body containing yellow round pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nivadil is indicated for the treatment of essential hypertension.

4.2 Posology and method of administration

For oral administration.

The prolonged release capsule should be swallowed whole, with a little liquid, in the morning. It may be taken after breakfast.

Adults

The recommended dose is 1 Nivadil 8 mg prolonged release capsule per day in the morning as a starting dose. If after 2 - 4 weeks of therapy an adequate anti-hypertensive effect is not achieved, a daily dose of 16 mg nilvadipine (2 x 8 mg Nivadil prolonged release capsules, or 1 x 16 mg Nivadil prolonged release capsule, in the morning) may improve the blood pressure response.

Renal impairment: No dosage adjustment is required in mild to moderate renal insufficiency. Nivadil should not however be used in patients with severe renal insufficiency.

Hepatic impairment: In patients with cirrhosis of the liver, due to diminished first-pass effect, the bioavailability is increased by a factor of 2 to 3. The currently available data lead to the recommendation that a daily dose of 1 x 8 mg nilvadipine (equivalent to 1 Nivadil 8 mg prolonged release capsule) may only be exceeded under close monitoring in such patients.

The Elderly

Plasma levels in elderly patients may be higher than in younger patients and increasing the dose in elderly patients should therefore be done cautiously.

Children

Not recommended.

The duration of use is at the discretion of the physician.

Nivadipine should not be taken with grapefruit juice (see interactions).

4.3 Contraindications

Nivadil should not be used in cases of cardiovascular shock, in case of pronounced aortic stenosis, during and in the first 4 weeks after acute myocardial infarction, in case of unstable angina pectoris.

Nivadil should not be used in cases of proven hypersensitivity to the active substance or to any of the excipients listed in 6.1.

Nivadil should not be used in patients with severe renal insufficiency (creatinine clearance < 30 ml/min, dialysis patients) since as yet only insufficient therapeutic experience has been gained in this regard.

Nivadil is contraindicated in pregnancy and lactation.

Safety and efficacy of Nivadil have not been established in children

Nivadil, like any calcium antagonist, should not be administered concurrently with dantrolene infusion because of the risk of ventricular fibrillation.

4.4 Special warnings and precautions for use

Cimetidine and, to a lesser extent, other histamine H₂- antagonists may lead to an increase in the Nilvadipine plasma concentration. Therefore, the daily dose of 1 x 8 mg Nilvadipine (equivalent to 1 Nivadil 8 mg prolonged release capsule) should not be exceeded.

Nilvadipine should be administered with care in patients with severe hepatic impairment (liver cirrhosis) the dose should not be increased because Nivadil has a higher bio-availability in such patients. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min, dialysis patients) this product should be administered only under very close supervision and with extreme caution since as yet only insufficient therapeutic experience has been gained in this regard.

Care should also be taken in cases of decompensated cardiac insufficiency. Patients with mild bradycardia, first degree AV block or prolonged PR interval should be observed closely.

4.5 Interaction with other medicinal products and other forms of interaction

The concurrent administration of Nilvadipine and other anti-hypertensive drugs or tricyclic anti-depressive agents may result in an additional anti- hypertensive effect. Clinical studies have not yielded any indication of a negative inotropic effect; nevertheless, patients concomitantly treated with Nivadil and a beta-receptor blocker should be particularly carefully monitored, since drugs from this class of substances may result in heart failure when administered in combination with beta-receptor blockers.

Certain structurally related drugs may amplify the negative inotropic action of anti-arrhythmic agents like amiodarone and quinidine. In isolated cases simultaneous treatment with other drugs of the same pharmacological class has led to the observation of a decrease in the plasma quinidine level; monitoring of the plasma quinidine level is therefore recommended in patients on combination therapy. Similar observations have not been made with Nilvadipine. Since in rare cases Nilvadipine may cause an increase in plasma digoxin level, monitoring of this parameter is recommended

Other dihydropyridine calcium entry blockers have been reported to increase the plasma concentration of concomitantly administered cyclosporin. Until further clinical data concerning the concomitant administration of Nilvadipine and cyclosporin are available, it is recommended that cyclosporin plasma levels are monitored during a co-medication of Nivadil and cyclosporin.

Since Nivadil is metabolised by cytochrome P-450, drugs or food constituents that induce or inhibit this system may affect plasma concentrations of Nivadil.

In vitro studies show that Nilvadipine is metabolised by cytochrome P450 3A4 (CYP3A4). Nilvadipine should be administered with care when coadministered with CYP3A4 inhibitors, like: antiproteases, ketoconazole, itraconazole, erythromycin, and clarithromycin.

Anticonvulsants which induce cytochrome P-450 have been reported to decrease the bio-availability of dihydropyridines. Although there is no experience in this regard with Nivadil, it is recommended not to use Nivadil in patients concomitantly treated with enzyme- inducing anticonvulsants such as phenytoin, carbamazepine or phenobarbital.

Concurrent dosing of Cimetidine, and, to a lesser extent, other structurally related substances, Nilvadipine in a specific interaction study led on average to a doubling of Nilvadipine plasma levels. A daily dose of 1 x 8 mg Nilvadipine should not be exceeded when Nilvadipine and cimetidine are used concomitantly.

Taking Nivadil after a high fat breakfast increase bio- availability by 42%. The patient should be informed that taking Nivadil in the fasted state may decrease its bio-availability.

As with other calcium channel blockers of the dihydropyridine group, a stronger increase in Nilvadipine concentrations in the blood has been reported when Nilvadipine was taken together with grapefruit juice than when it was taken with water.

Nilvadipine should not be taken with grapefruit juice because its metabolism may be inhibited.

In an animal study, concomitant use of verapamil and intravenous dantrolene resulted in hyperkalemia accompanied by ventricular fibrillation and circulatory collapse. The relevance of these results for Nilvadipine is not known, but a risk that these events occur clinically cannot be excluded when Nilvadipine is used concomitantly with dantrolene.

4.6 Fertility, pregnancy and lactation

Pregnancy

No clinical experience with Nilvadipine in pregnancy or lactation is present. Preclinical investigations have not yielded any indication of a damaging potential of the substance on the foetus. The class of dihydropyridines has shown the potential to prolong delivery and parturition, which was not observed with Nilvadipine. As a consequence, Nilvadipine could be used in pregnancy only if the benefit justifies the potential risk to the foetus.

Lactation

The results of animal tests have shown that Nilvadipine (or its metabolites) is excreted in human milk. Therefore, breast feeding is not advised during use of Nilvadipine. Since there has yet been no experience gained regarding the possible effects of the substance on the suckling infant, the child should be weaned from the breast in cases in which treatment of the nursing mother with Nivadil is regarded as necessary.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with Nilvadipine. However, caution should be exercised because dizziness may occur during antihypertensive treatment.

The management of hypertension with this drug requires regular checks by the physician. The occurrence of reactions, which may differ in severity from one person to another, may impair the patient's ability to drive vehicles and to operate machinery. This precaution applies particularly at the beginning of therapy, or when dosage is changed, or with concurrent consumption of alcohol.

4.8 Undesirable effects

The frequency of adverse reactions is defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common >1/100, <1/10	Uncommon >1/1000, 1/100	Rare >1/10,000,<1/1000	Very rare <1/10,000,
Blood and the lymphatic system disorders			Anaemia	Leukopenia, Thrombocytopenia
Metabolism and nutrition disorders			Appetite disorder	
Nervous system disorders	Headache, Dizziness		Tinnitus, Nervousness, Insomnia	
Eye disorders			Increased intraocular pressure, Blurred vision	
Ear and labyrinth disorders			Epistaxis, Dry mouth	
Cardiac disorders		Tachycardia, Palpitations, Angina Pectoris		Myocardial infarction
Vascular disorders	Flushing	Hypotension, Hypertensive crisis		
Respiratory, thoracic and mediastinal disorders			Dyspnoea	
Gastrointestinal disorders		Nausea, Abdominal discomfort, Abdominal distension, Constipation, Diarrhoea	Vomiting, Increased weight, Decreased weight	Gingival hyperplasia
Hepato-biliary disorders		Transaminases increased, Blood alkaline phosphatase increased		
Skin and subcutaneous tissue disorders		Hypersensitivity reactions, Rash, Pruritus, Erythema	Paraesthesia	Peripheral coldness, Alopecia
Musculoskeletal, connective tissue and bone disorders		Tremor, Myalgia, Arthralgia, Sensation of heaviness	Neck pain, Chest discomfort	
Renal and urinary disorders			Pollakiuria	
Reproductive system and breast disorders			Erectile dysfunction	Gynaecomastia
General disorders and administration site conditions	Peripheral oedema	Fatigue	Hyperhidrosis	

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms of intoxication

In general, clinical symptoms following an overdose of calcium antagonists develop within 30 to 60 minutes after administration of a dose five to ten times higher than the therapeutic dose.

There has been no clinical experience with acute overdoses of Nivadil. Flush, headache, hypotension, electrophysiological effects (sinus bradycardia, prolonged AV conduction, second and third degree AV block, reflex tachycardia may also be experienced), effects on the central nervous system (drowsiness, confusion and, rarely, convulsions), gastrointestinal symptoms (nausea and vomiting) and metabolic effects (hyperglycaemia) can theoretically be expected to occur with overdose.

Intoxication treatment

Hospital treatment is necessary in the event of intoxication. Symptomatic treatment and continuous ECG monitoring are indicated.

Since there is no known specific antidote, the therapy of cases of intoxication should be directed by clinical symptoms. The immediate administration of activated charcoal and intensive gastric lavage are recommended measures when the intoxication is recognised early.

An intravenous (dosage 0.2 ml/kg body weight) injection of calcium (preferably 10 ml of a calcium chloride solution of 10%) should be given over a period of 5 minutes, up to a total dose of 10 ml 10%. Contractility of the myocardium, sinus rhythm and atrioventricular conduction will thus be improved. The treatment can be repeated every 15 to 20 minutes (up to a total of 4 doses) based on the patient's response. Calcium levels should be checked.

However, when administering laxatives, attention should be paid to the possible inhibition of the intestinal musculature (atony) that may occur with calcium antagonists. Hemodialysis is not indicated since Nilvadipine is not removed by dialysis. Plasmapheresis (high plasma protein binding, relatively small distribution volume) on the other hand, is recommended.

Bradycardias are treated symptomatically with atropine and/or beta-sympathomimetic agents; in cases of life-threatening bradycardia, the temporary implantation of a pacemaker device is indicated.

Hypotension as a consequence of cardiogenic shock and arterial vasodilatation is treated with calcium (1-2 g calcium gluconate intravenously), dopamine (up to 25 µg/kg/bw per minute) dobutamine (up to 15 µg/kg/bw per minute) or epinephrine/norepinephrine. The dose levels of these drugs are determined by the response of the patient.

The serum calcium concentration should be maintained at normal or slightly raised levels. Due to risk of cardiac overload, fluid or volume should be substituted cautiously with careful monitoring of haemodynamic parameters.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Very low concentrations of the active constituent nilvadipine inhibit the influx of calcium into the cell of the smooth vascular musculature and thereby cause vasodilatation. The myogenic vascular-wall tonus is reduced and the peripheral vascular resistance diminished. This in turn results in an antihypertensive effect. In the therapeutic dose range, nilvadipine has no effects on the cardiac conduction system.

In hypertensive patients, the onset of the acute effect is approximately 2 hours after single oral administration. In long-

term therapy, the maximum antihypertensive effect is reached after 3 - 4 weeks.

Nivadil has been used in clinical testing phase for up to 36 months without any indication of the development of tolerance (tachyphylaxis).

5.2 Pharmacokinetic properties

In solution, nilvadipine - with a half-life of 5 - 10 minutes, is very rapidly absorbed from the gastrointestinal tract. Maximum concentrations (c_{max}) were achieved after 40 minutes (t_{max}).

A dose-dependent pharmacokinetic profile was observed for doses between 6 and 16 mg.

Nilvadipine, like its polar metabolites, is highly bound to plasma proteins (98 - 99%). Nilvadipine is rapidly and well distributed in the body tissues and is subject to a slow back-diffusion. Due to a distinct first-pass effect, the absolute bioavailability ranges between 14 and 19%, resulting in an apparent distribution volume value of 1 l/kg after single administration and 3.9 l/kg after repeated administration. Under long-term therapy, once-daily administration leads to virtually no accumulation as regards c_{max} or AUC. The pre-dose values cumulate by a factor of 1.5 as a result of the filling of the tissue compartment. Steady-state is reached after 4 - 5 days.

Nilvadipine is almost completely transformed into polar, pharmacodynamically inactive metabolites in the liver.

Only 0.1% and less than 0.2% of the oral dose are eliminated as unchanged parent substance in the urine and faeces, respectively. The metabolites are renally eliminated to a degree of 70 - 80%, the remainder being excreted with the faeces. The terminal half-life for the active substance is approximately 15 - 20 hours.

The available data showed no effects of mild to moderate renal insufficiency on the plasma pharmacokinetics and on the elimination pattern. There are as yet no data regarding the use of the substance in cases of severe renal function disorders. The oral bioavailability of nilvadipine was found to be significantly higher by 42% in elderly (66 years and older) vs. younger subjects.

In patients with cirrhosis of the liver, due to diminished first-pass effect, the bioavailability is increased by a factor of 2 to 3. The currently available data lead to the recommendation that a daily dose of 1 x 8 mg nilvadipine (equivalent to 1 Nivadil 8 mg prolonged release capsule) may only be exceeded under close monitoring in such patients.

In animal experiments (rats), it was shown that nilvadipine is able to cross both the blood-brain barrier as well as the placental barrier and is excreted in breast milk.

Bioavailability

Nilvadipine is released from the prolonged release capsule form independent of the pH. The relative bioavailability of Nivadil prolonged release capsules is approximately 60 - 70% as compared with an oral solution.

5.3 Preclinical safety data

(a) Acute toxicity

The oral LD₅₀ of Nilvadipine in dogs is 480 mg/kg. The corresponding value is more than twice as high in mice, and three times higher in rats.

After reddening of the oral mucous membranes, conjunctiva, and hairless parts of the body (ears, abdominal skin), effects pharmacodynamically caused by peripheral vasodilatation, the following intoxication symptoms were observed in dogs:

Hyperpnoea, stretching motions, salivation, vomiting, diarrhoea, and collapse. After high doses (from 320 mg/kg up), also ptosis, dilatation of the nictitating membrane, and pale mucous membranes. Animals lethally intoxicated died between 6 hours and 3 days after administration.

(b) Subacute and chronic toxicity

Several trials performed in rats and dogs over periods of up to 53 weeks revealed isolated indications of exaggerated pharmacodynamic or counterregulatory effects only after extreme overdosing. In dogs receiving nilvadipine, dose-related effects include haemorrhaging, inflammation and fibroses of the right atrium. The 40 mg/dog dose (approximately 9 mg/kg) was tolerated without any detrimental effect. Comparison of the serum concentrations based on the maximum human-therapeutic dose (16 mg/day) yields a 31-fold safety margin. Neither species displayed any special toxic-effect reactions. Cases of gingival hyperplasia that occurred after long-term administration of high doses of nilvadipine, effects that have also been observed in man and animal species after other calcium antagonists and after hydantoin compounds, were reversible after discontinuation of medication.

(c) Mutagenic and carcinogenic potential

Extensive mutagenicity investigations all yielded negative results.

Investigations in mice and rats provided no indication of any carcinogenic potential for nilvadipine. In mice, dose-related inflammatory processes and haemorrhages were observed in the region of the urogenital tract.

(d) Reproduction toxicology

Embryotoxicity investigations in rats and rabbits yielded no indication of any teratogenic potential.

In rats, changes in the gestation period and dystocia were observed at the end of pregnancy after doses of 10 mg/kg body weight/day. As a consequence, an increased mortality was seen among the new-born animals.

Investigations in rats yielded no indication of impaired fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

(a) Contents of capsule

Maize starch

Microcrystalline cellulose

Povidone

Croscarmellose sodium

(b) Capsule shell

Iron oxides (E172)

Titanium dioxide (E171)

Gelatin

(c) Printing ink

Shellac

Titanium dioxide (E171)

Propylene Glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Nature

Blister made of PVC/PVDC Film on aluminium foil (250 mm coated with 40 g/m² PVDC; 20 mm Al).

Package sizes

Original packages containing: 28 prolonged release capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Astellas Pharma Co. Ltd
5 Waterside
Citywest Business Campus
Naas Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1241/13/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd July 1996

Date of last renewal: 22nd July 2006

10 DATE OF REVISION OF THE TEXT

May 2015