Nitrendipine
(10 mg and 20 mg) tablets, (5 mg/mL) oral solution

Core Safety Profile

4.2 Dosage and method of administration

Additional information on special populations
The safety and efficacy of nitrendipine in children under the age 18 years have not been established.

For tablets only:
In patients with severe disturbances of liver function treatment should commence with the lowest available tablet dose (10 mg nitrendipine = 1 tablet of Baypress 10 mg / day) and the patient carefully monitored during the therapy (see *section 5.2*).

4.3 Contraindications

Baypress is contraindicated:

- in patients with known hypersensitivity to nitrendipine or to any of the excipients (see *section 4.4, 6.1*)
- in patients with unstable angina pectoris and after acute myocardial infarction within the first 4 weeks
- during pregnancy and lactation (see *section 4.6*)
- in cases of decompensated heart failure (*for Baypress oral solution only*)

From experience with the structurally similar calcium antagonist nifedipine it has to be expected that rifampicin accelerates the metabolism of nitrendipine due to enzyme induction, and that efficient nitrendipine plasma levels might thus not be obtained. Therefore, concomitant use of rifampicin is contraindicated (see *section 4.5*).

4.4 Special warnings and precautions for use

Decompensated heart failure (for Baypress tablets only)
Patients with decompensated heart failure should be treated with caution.

Hepatic disorders
In patients with severe disturbances of liver function the effects of nitrendipine can be potentiated and prolonged. In these cases the patient should be carefully monitored by frequent control of blood pressure during the therapy (see *section 4.2, 5.1*).

Angina pectoris
As with other vasoactive substances, angina pectoris may very rarely occur (data from spontaneous reports) with immediate release nitrendipine, especially at the start of the treatment. Data from clinical studies confirm that the occurrence of angina pectoris attacks is uncommon (see *section 4.8*).

CYP 3A4 System
Nitrendipine is metabolized via the CYP 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 nitrendipine (see *section 4.5*).

Drugs, which are inhibitors of the CYP 3A4 system and therefore may lead to increased plasma concentrations of nitrendipine are, e.g.:

- 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 and ranitidine.

Upon co-administration with these drugs, the blood pressure should be monitored and, if necessary, a reduction of the nitrendipine dose should be considered (see *section 4.5.*).

Lactose
Since the Baypress 10 mg tablet contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see *section 6.1)*

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Drugs that affect nitrendipine

Nitrendipine is metabolized via the CYP 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 or the clearance of nitrendipine.

The extent as well as the duration of the interaction should be taken into account when administering nitrendipine together with the following drugs:

Rifampicin
From experience with the structurally similar calcium antagonist nifedipine it has to be expected that rifampicin accelerates the metabolism of nitrendipine due to enzyme induction. Thus, efficacy of nitrendipine could be reduced when concomitantly administered with rifampicin. The use of nitrendipine in combination with rifampicin is therefore contraindicated (see *section 4.3*).

Upon co-administration of the following inhibitors of the CYP 3A4 system the blood pressure should be monitored and, if necessary, a reduction in the nitrendipine dose considered (see *section 4.2*).

Macrolide antibiotics (e.g., erythromycin)
No interaction studies have been carried out with nitrendipine and macrolide antibiotics. Drugs of this class are known to inhibit the CYP 3A4 mediated metabolism of other drugs. Therefore, the potential for an increase of nitrendipine plasma concentrations upon co-administration of nitrendipine with these macrolide antibiotics cannot be excluded (see *section 4.4*).
Azithromycin, although structurally related to the class of macrolide antibiotic is void of CYP 3A4 inhibition.

Anti-HIV protease inhibitors (e.g., ritonavir)
No formal studies have been performed to investigate the potential interaction between nitrendipine and certain anti-HIV protease inhibitors. Drugs of this class have been reported to be potent inhibitors of the CYP 3A4 system. Therefore the potential for an increase of nitrendipine plasma concentrations upon co-administration with these protease inhibitors cannot be excluded (see *section 4.4*).

Azole antimycotics (e.g., ketoconazole)
A formal interaction study investigating the potential of drug interaction between nitrendipine and certain azole antimycotics has not been performed. Drugs of this class are known to inhibit the CYP 3A4 system, and various interactions have been reported for other dihydropyridine calcium antagonists. Therefore, when administered orally together with nitrendipine, a substantial increase in systemic bioavailability of nitrendipine due to a decreased first-pass metabolism cannot be excluded (see *section 4.4*).

Nefazodone
No formal studies have been performed to investigate the potential interaction between nitrendipine and nefazodone. This antidepressant drug has been reported to be a potent inhibitor of the CYP 3A4. Therefore, the potential for an increase in nitrendipine plasma concentrations upon co-administration with nefazodone cannot be excluded (see *section 4.4*).

Fluoxetine
Based on experience with the structurally similar dihydropyridine calcium-antagonist nimodipine, co-administration with the antidepressant fluoxetine led to about 50 % higher plasma concentrations of nimodipine.
Fluoxetine exposure was markedly decreased, while its active metabolite norfluoxetine was not affected. Therefore the potential for a clinically relevant increase in nitrendipine plasma concentrations upon co-administration with fluoxetine cannot be excluded (see *section 4.4*).

Quinupristin/Dalfopristin
Based on experience with the structurally similar calcium-antagonist nifedipine, co-administration of quinupristin/dalfopristin may lead to increased plasma concentrations of nitrendipine (see *section 4.4*).

Valproic acid
No formal studies have been performed to investigate the potential interaction between nitrendipine and valproic acid. As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in nitrendipine plasma concentrations and hence an increase in efficacy cannot be excluded (see *section 4.4*).

Cimetidine, Ranitidine
Cimetidine and - to a lesser extent - ranitidine can lead to an increase in the plasma nitrendipine level and thus potentiate the effects of nitrendipine (see *section 4.4*).

4.5.2 Further studies

CYP 3A4 system-inducing anti-epileptic drugs, such as phenytoin, phenobarbitone, carbamazepine
A formal interaction study investigating the potential of drug interaction between nitrendipine and these anticonvulsants has not been performed. However, phenytoin, phenobarbitone and carbamazepine are known as potential inducers of the CYP 3A4 system. Concomitant administration of these anticonvulsants may lead to clinically relevant reduction of the bioavailability of nitrendipine and hence a decrease in efficacy may be anticipated. If the dose of nitrendipine is increased during co-administration with phenytoin, phenobarbitone or carbamazepine, a reduction of the nitrendipine dose should be considered when the treatment with anticonvulsants is discontinued.

4.5.3 Effects of nitrendipine on other drugs

Blood pressure lowering drugs
Nitrendipine may increase the blood pressure lowering effect of concomitantly applied antihypertensives, such as:

- diuretics,
- beta-blockers,
- ACE-inhibitors,
- Angiotensin 1 (AT1) receptor-antagonists,
- other calcium antagonists,
- alpha-adrenergic blocking agents,
- PDE5 inhibitors,
- alpha-methyldopa.

Digoxin
Increased plasma levels of digoxin have to be anticipated when digoxin is taken simultaneously. Patients should thus be monitored for symptoms of digoxin overdosage, if necessary by determination of the digoxin plasma levels, and the glycoside dose may have to be reduced.

Muscle relaxants
The duration and intensity of action of muscle relaxants like pancuronium may be enhanced under therapy with nitrendipine.

4.5.4 Drug-food interactions

Grapefruit juice
Grapefruit juice inhibits the CYP 3A4 system. Administration of dihydropyridine calcium antagonists together with grapefruit juice thus results in elevated plasma concentrations due to a decreased first pass metabolism or reduced clearance.
As a consequence, the blood pressure lowering effect may be increased. Based on experience with the structurally similar calcium-antagonist nisoldipine this effect may last for at least 3 days after the last ingestion of grapefruit juice.

Ingestion of grapefruit / grapefruit juice is therefore to be avoided while taking nitrendipine (see *section 4.2*).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of nitrendipine in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). Animal studies using clearly maternally toxic doses of nitrendipine revealed evidence of malformation (see *section 5.3*).
Nitrendipine is contraindicated during pregnancy (see *section 4.3*").

Lactation
Nitrendipine is excreted in human milk.
The effect of nitrendipine on newborns/infants is unknown.
Nitrendipine is contraindicated during the breastfeeding period (see *section 4.3*).

Fertility
In single cases of in-vitro fertilization calcium antagonists 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 fertilization, and where no other explanation can be found, calcium antagonists should be considered as possible causes.
When pregnancy is planned but fertility might be affected, alternative treatment may be considered.

4.7 Effects on ability to drive or use machines

Reactions to the drug, which can vary in intensity from individual to individual, may impair the ability to drive or to operate machinery. This applies particularly at the beginning of treatment, on changing the medication, and in combination with alcohol.

4.8 Undesirable effects

Summary of the safety profile
Safety information from clinical trials as well as from post-marketing surveillance or any other source is analyzed and reflected in the ADR section of nitrendipine. Frequencies of occurrence are calculated from clinical trial analysis or estimated from post-marketing surveillance.

The most common ADRs (frequency common: ≥1/100 to < 1/10) are headache, palpitations, vasodilation, oedema, flatulence, feeling unwell, and anxiety reactions. None of these ADRs is considered severe from the overall experience. Except from 'feeling unwell' and 'anxiety reactions' the ADRs are attributable to the mode of action of nitrendipine.

The most severe ADRs are hypotension, angina pectoris (chest pain), and allergic reaction including angioedema (all frequency uncommon: ≥ 1/1,000 to < 1/100). These ADRs, dependent on their course, might require immediate medical intervention.
ADRs listed under "common" were observed with a frequency below 3 % with the exception of oedema (6.2 %), headache (4.7 %) and vasodilatation (3.0 %).

The frequency of adverse drug reactions (ADRs) is based on placebo-controlled studies with nitrendipine sorted by CIOMS III categories of frequency (clinical trial data base: nitrendipine n = 824; placebo n = 563.
“Gingival hyperplasia” was reported from spontaneous cases. In consequence, a frequency of < 1/400 was estimated by applying the rule of 3/X.

The frequencies of ADRs reported with Baypress are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:

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)

Table 01:

System Organ Class (MedDRA)	Common	Uncommon
Immune system disorders		Allergic reaction including skin reactions and allergic oedema/angioedema
Psychiatric disorders	Anxiety reactions	Sleep disorders
Nervous system disorders	Headache	Vertigo Migraine Dizziness Somnolence Hypaesthesia
Eye disorders		Visual disturbances
Ear and labyrinth disorders		Tinnitus
Cardiac disorders	Palpitations	Angina pectoris Chest pain Tachycardia
Vascular disorders	Oedema Vasodilatation	Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnea Nosebleed
Gastrointestinal disorders	Flatulence	Gastrointestinal and abdominal pain Diarrhea Nausea Vomiting Dry mouth Dyspepsia Constipation Gastroenteritis Gingival hyperplasia
Hepatobiliary disorders		Transient increase in liver enzymes
Musculoskeletal, connective tissue		Myalgia

System Organ Class (MedDRA)	Common	Uncommon
Renal and urinary disorders		Polyuria
General disorders and administration site conditions	Feeling unwell	Unspecific pain

4.9 Overdose

Symptoms
An increased occurence of flush, headache, blood pressure reduction (with circulatory collapse), and a change in the heart rate (tachycardia or bradycardia) must be anticipated in acute overdosage/intoxication.

Treatment of overdose in man
The initial therapeutic measure to be considered is gastric lavage followed by instillation of activated charcoal. The vital functions must be monitored. If there is an extreme fall in blood pressure, dopamine or noradrenaline is indicated. Attention should be paid to possible catecholamine side effects (particularly heart rhythm disturbances).

If bradycardia occurs, as it is the case with overdosage or intoxication with other calcium antagonists, atropine or orciprenaline is indicated.

On the basis of experience of intoxication with other calcium antagonists, repeated intravenous administration of 10 mL volumes of calcium gluconate or calcium chloride 10 %, followed by administration as a drip infusion (beware of hypercalcaemia), usually leads to a rapid improvement in the symptoms. Catecholamines have occasionally been effective in such cases only at high doses. Subsequent treatment should by governed by the most prominent symptoms.