SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Ibusta 10 mg, harde capsules met gereguleerde afgifte
Ibusta 20 mg, harde capsules met gereguleerde afgifte

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Product Name] 10 mg hard modified-release capsules
Each capsule contains 10 mg of barnidipine hydrochloride, equivalent to 9.3 mg barnidipine.

[Product Name] 20 mg hard modified-release capsules
Each capsule con 20 mg of barnidipine hydrochloride, equivalent to 18.6 mg barnidipine.

Excipients with known effect
Each 10 mg capsule contains approximately 87 mg of sucrose
Each 20 mg capsule contains approximately 174 mg of sucrose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release capsule, hard

[Product Name] 10 mg hard modified-release capsules
Size No.3 hard gelatin capsules filled with yellow to pale yellow pellets. Capsule cap: yellow with black ″1000″ imprinting. Body: yellow with black ″0010″ imprinting.

[Product Name] 20 mg hard modified-release capsules
Size No.1 hard gelatin capsules filled with yellow to pale yellow pellets. Capsule cap: yellow with black ″1000″ imprinting. Body: yellow with black ″0020″ imprinting.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate essential hypertension.

4.2 Posology and method of administration

Posology
The recommended starting dosage is 10 mg once daily, in the morning. It may be increased to 20 mg once daily if necessary. The decision to increase the dosage should only be taken after complete stability is achieved on the initial dosage. This usually takes at least 3-6 weeks.

Paediatric population
As there are no data in children (under 18 years) barnidipine should not be administered to children.

Elderly patients
The dosage need not be adjusted in elderly patients. Extra care at the start of treatment is advisable.

Patients with renal impairment

In patients with mild to moderate renal impairment, care should be taken when increasing the dosage from 10 to 20 mg once daily. See the "Contraindications" and "Special warnings and precautions for use" sections.

Patients with hepatic impairment
See the "Contraindications" section.

Method of administration
Take the capsules preferably with a glass of water. [Product Name] can be taken before, during and after a meal.

4.3 Contraindications

- Hypersensitivity to the active substance (or to any dihydropyridine) or to any of the excipients listed in section 6.1
- Hepatic impairment
- Severe renal impairment (creatinine clearance < 10 ml/min)
- Unstable angina pectoris and acute myocardial infarction (in the first 4 weeks)
- Untreated heart failure
- Blood levels of barnidipine may be increased when used in combination with strong CYP3A4 inhibitors (results in vitro interaction studies). Therefore, antiproteases, ketoconazole, itraconazole, erythromycin and clarithromycin should not be used concomitantly.

4.4 Special warnings and precautions for use

Barnidipine should be used with caution in patients with mild to moderate renal impairment (creatinine clearance between 10 and 80 ml/min) (see section 4.2 "Posology and method of administration").

The combination of a calcium antagonist with a drug that exerts a negative inotropic effect may lead to cardiac decompensation, hypotension or an (additional) myocardial infarction in high-risk patients (e.g. patients with a history of myocardial infarction).

As with all other dihydropyridines, barnidipine should be used with caution in patients with left ventricular dysfunction, in patients suffering from obstruction of the outflow channel of the left ventricle and patients with isolated right-sided cardiac decompensation, e.g. cor pulmonale. Barnidipine has not been studied in NYHA class III or IV patients.

Caution is recommended also when barnidipine is administered to patients with sick sinus (if a pacemaker is not in situ).

In vitro studies indicate that barnidipine is metabolised by cytochrome P450 3A4 (CYP3A4). No in vivo interaction studies on the effect of drugs that inhibit or induce the cytochrome P450 3A4 enzyme on the pharmacokinetics of barnidipine, have been carried out. Based on the results of in vitro interaction studies, care should be taken when barnidipine is prescribed concomitantly with mild CYP3A4 inhibitors or inducers (see the "Interactions with other medicinal products and other forms of interaction" section).

The capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The concurrent administration of barnidipine and other antihypertensive drugs may result in an additional antihypertensive effect.

Barnidipine can be used concurrently with betablockers or ACE inhibitors.

The pharmacokinetic interaction profile of barnidipine has not been studied in full. In vitro studies show that barnidipine is metabolised by cytochrome P450 3A4 (CYP3A4).

No elaborate in vivo interaction studies on the effect of drugs which inhibit or induce the CYP3A4 enzyme on the pharmacokinetics of barnidipine, have been carried out.

In vitro data show that cyclosporin may inhibit the metabolism of barnidipine. Until in vivo information is available, barnidipine should not be prescribed concomitantly with the strong CYP3A4 inhibitors: antiproteases, ketoconazole, itraconazole, erythromycin and clarithromycin (see section 4.3 Contraindications). Care should be taken with concomitant use of mild CYP3A4 inhibitors or inducers. In case of concomitant use of CYP3A4 inhibitors it is discouraged to increase the dosage of barnidipine to 20 mg.

Concurrent dosing of cimetidine in a specific interaction study led on average to a doubling of barnidipine plasma levels. Care should therefore be exercised when using barnidipine concomitantly with cimetidine.
A higher dose of barnidipine may be necessary when barnidipine is administered concomitantly with enzyme inducing drugs, such as phenytoin, carbamazepine and rifampicin. Should a patient stop using an enzyme inducing drug, lowering the dosage of barnidipine should be considered.

Based on the results of in vitro interaction studies with, among other things, simvastatin, metoprolol, diazepam and terfenadine, it is considered unlikely that barnidipine has any effect on the pharmacokinetics of other drugs which are metabolised by cytochrome P450 isoenzymes.

An in vivo interaction study showed that barnidipine does not influence the pharmacokinetics of digoxin. In a specific interaction study alcohol led to an increase of barnidipine plasma levels (40%), which increase may be considered clinically not relevant. As with all vasodilating and antihypertensive agents, caution should be exercised when alcohol is taken concomitantly as it may potentiate their effect.
Although barnidipine kinetics was not significantly altered by administration with grapefruit juice, a modest effect was observed.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical experience with barnidipine in pregnancy or lactation is present. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal or postnatal development. Only indirect effects are observed (see 5.3). The class of dihydropyridines has shown the potential to prolong delivery and parturition, which was not observed with barnidipine. As a consequence, barnidipine could be used in pregnancy only if the benefit justifies the potential risk to the foetus.

Breast-feeding
The results of animal tests have shown that barnidipine (or its metabolites) is excreted in human milk. Therefore, breast feeding is not advised during use of barnidipine.

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 for barnidipine. However, caution should be exercised because dizziness/vertigo may occur during antihypertensive treatment.

4.8 Undesirable effects

System organ class	**10 mg dosage**	**20 mg dosage**
Immune system disorders		

• Anaphylactoid reaction	Not known (frequency cannot be estimated from the available data)	Not known (frequency cannot be estimated from the available data)
Nervous system disorders		
• Headache	Common (≥1/100 to <1/10)	Very common (≥1/10)
• Dizziness/vertigo	Common (≥1/100 to <1/10)	Common (≥1/100 to <1/10)
Cardiac disorders		
• Palpitations	Common (≥1/100 to <1/10)	Common (≥1/100 to <1/10)
• Tachycardia, sinus tachycardia, heart rate increased	Not known (frequency cannot be estimated from the available data)	Not known (frequency cannot be estimated from the available data)
Vascular disorders		
• Flushing	Common (≥1/100 to <1/10)	Very common (≥1/10)
Hepato-biliary disorders		
• Liver function test abnormal	Not known (frequency cannot be estimated from the available data)	Not known (frequency cannot be estimated from the available data)
Skin and subcutaneous tissue disorders		
• Rash	Not known (frequency cannot be estimated from the available data)	Not known (frequency cannot be estimated from the available data)
General and administration site conditions		
• Peripheral oedema	Common (≥1/100 to <1/10)	Very common (≥1/10)

The symptoms tend to diminish or disappear during treatment (within one month for peripheral oedema and two weeks for flushing, headache and palpitations).

Although never observed, the following adverse event may be of interest, as it is in the use of other dihydropyridines: gingival hyperplasia.

Some dihydropyridines may rarely lead to precordial pain or angina pectoris. Very rarely patients with pre-existing angina pectoris may experience increased frequency, duration or severity of these attacks. Isolated cases of myocardial infarction may be observed.

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 listed in Appendix V.

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.

Hypotension, electrophysiological effects (sinus bradycardia, prolonged AV conduction, second and third degree AV block, tachycardia), effects on the central nervous system (drowsiness, confusion and, rarely, convulsions), gastrointestinal symptoms (nausea and vomiting) and metabolic effects (hyperglycaemia) can theoretically be expected.

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

In the event of an overdose, a gastric lavage should be performed as soon as possible.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives, ATC code: C08CA12

Mechanism of action
Barnidipine (pure S,S isomer) is a lipophilic 1,4-dihydropyridine calcium antagonist showing high affinity for the calcium channels of the smooth muscle cells in the vascular wall. Receptor kinetics of barnidipine are characterised by a slow onset of action and a strong and long-lasting binding. The reduction in peripheral resistance brought about by barnidipine results in blood pressure lowering. When using barnidipine, the antihypertensive effect remains during the entire 24-hour dose interval.

Use of barnidipine in chronic treatment does not lead to an increase in basic heart frequency.
The impact of barnidipine on cardiovascular morbidity or mortality has not been studied. However, recently completed, controlled studies of other long acting dihydropyridines indicate similar beneficial effects on morbidity and mortality compared to other antihypertensives in hypertension of the elderly.

Metabolic effects
Barnidipine does not exert any negative effect on serum lipids profile, glucose level or blood electrolytes.

5.2 Pharmacokinetic properties

Absorption
After repeated administration of barnidipine 20 mg to healthy individuals, the concomitant intake of food did not have a statistically significant effect on AUC, C_{max}, T_{max} or $t_{½}$.
Maximum plasma levels are obtained 5 to 6 hours after oral administration of barnidipine 20 mg.
Barnidipine shows an absolute bioavailability of 1.1%.
Barnidipine plasma concentrations may show considerable interpersonal variation.

Distribution
In vitro studies show that barnidipine binds at the rate of 26-32% to human erythrocytes and to a high extent (89-95%) to plasma proteins. In vitro analysis of protein components indicates that barnidipine mainly binds to serum albumin, followed by α1 acid glycoprotein and high density lipoproteins. To a much lesser extent binding to γ globulin takes place.
No drug interactions based on elimination of plasma protein binding have been observed in in-vitro studies.

Biotransformation
Barnidipine is to a great extent metabolised into inactive metabolites. No in vivo chiral inversion of the pure S,S isomer takes place. Main reactions are N-debenzylisation of the side chain, hydrolysis of the N-benzylpyrrolidine ester, oxidation of the 1,4-dihydropyridine ring, hydrolysis of the methyl ester and reduction of the nitro group. The metabolism of barnidipine seems mainly mediated by the CYP3A isoenzyme family.

Elimination
The median terminal elimination plasma half-life of barnidipine was 20 hours after repeated administration, according to a two-compartment analytical model.

Elimination mainly takes place through metabolism. Barnidipine and/or its metabolites are excreted in faeces (60%), urine (40%) and breath (less than 1%). No un-metabolised barnidipine is excreted in urine.

Special patient groups
After a single dose, barnidipine plasma levels are 3 to 4 times higher in patients with mild to moderate hepatic impairment than in healthy volunteers. The variability in plasma levels is also increased. Barnidipine plasma levels are on average twice as high in patients with renal impairment not needing haemodialysis than in healthy volunteers. The average plasma level in patients needing haemodialysis is more than 3 times as high as in healthy volunteers, accompanied by increased variability.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Sugar spheres (containing sugar syrup, corn starch and sucrose)
Carboxymethylethylcellulose
Polysorbate 80
Ethylcellulose
Talc

Capsule shell:
Titanium dioxide (E171)
Yellow iron oxide (E172)
Gelatin

Printing ink:
Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°.

6.5 Nature and contents of container

OPA/Alu/PVC – Aluminum perforated blisters containing 28 capsules.

6.6 Special precautions for disposal and other handling

Do not remove granules from the capsules.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sigillata Limited
Inniscarra,
Main Street,
Rathcoole,
Co. Dublin D24 E029
Ierland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Ibusta 10 mg, harde capsules met gereguleerde afgifte – RVG 127089
Ibusta 20 mg, harde capsules met gereguleerde afgifte – RVG 127090

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 26 april 2022

10. DATUM VAN HERZIENING VAN DE TEKST

Laatst gedeeltelijke wijziging betreft rubriek 7: 10 oktober 2023