PROFESSIONAL INFORMATION FOR BRADHET 5 & 7,5

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

BRADHET 5 film coated tablet

BRADHET 7,5 film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BRADHET 5: Each film coated tablet contains 5 mg ivabradine equivalent to 5,39 mg ivabradine as hydrochloride.

BRADHET 7,5: Each film coated tablet contains 7,5 mg ivabradine equivalent to 8,085 mg ivabradine as hydrochloride.

Contains sugar (lactose monohydrate).

BRADHET 5: Contains 72,610 mg lactose monohydrate.

BRADHET 7,5: Contains 69,915 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

BRADHET 5: White to off white-colored, oval shaped, film-coated tablet, scored on both edges, debossed with “V” on the one side and “9” bisected “1” on other side.

BRADHET 7,5: Tan colored oval shaped, film-coated tablet, debossed with “V” on the one side and “92” on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of chronic stable angina pectoris:

BRADHET is indicated for the symptomatic treatment of chronic stable angina pectoris, in patients with normal sinus rhythm and heart rate ≥ 70 bpm, as monotherapy or in combination with beta-blockers.

Treatment of chronic heart failure:

BRADHET is indicated in adults in sinus rhythm with mild to moderate (NYHA II & III class) symptomatic heart failure whose heart rate is ≥ 77 bpm to reduce cardiovascular events (cardiovascular mortality or hospitalisation for worsening heart failure), in combination with standard therapy including beta-blockers or when beta-blockers are contraindicated or not tolerated.

4.2 Posology and method of administration

Posology

Symptomatic treatment of chronic stable angina pectoris:

It is recommended that the decision to initiate or titrate treatment takes place using serial heart rate measurements, ECG or ambulatory 24-hour monitoring.

The starting dose of **BRADHET** in patients below 75 years of age should not exceed 5 mg twice daily. After two to four weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains above 60 bpm, the dose may be increased to a maximum of 7,5 mg twice daily depending on the therapeutic response.

If there is no improvement in symptoms of angina within 3 months after start of treatment, treatment of **BRADHET** should be discontinued (see **section 4.4**).

In addition, discontinuation of treatment should be considered if there is only limited symptomatic response and when there is no clinically relevant reduction in resting heart rate within three months.

If, during treatment, heart rate decreases below 50 bpm at rest or the patient experiences symptoms related to bradycardia, such as dizziness, fatigue or hypotension, the dosage must be titrated downward including the lowest dose of 2,5 mg twice daily (one half 5 mg tablet twice daily). After dose reduction, heart rate should be monitored (see **section 4.4**). Treatment must be discontinued if the heart rate remains below 50 bpm or symptoms of bradycardia persist, despite dose reduction.

Treatment of chronic heart failure:

The recommended starting dose of ivabradine is 5 mg twice daily in patients below 75 years of age. After two weeks of treatment, the dose can be increased to a maximum of 7,5 mg twice daily, if resting heart rate is persistently above 60 bpm or decreased to 2,5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm, or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension.

If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If during treatment, the heart rate decreases persistently to below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7,5 mg twice daily or 5 mg twice daily.

If the heart rate increases persistently to above 60 beats per minute at rest, the dose can be up titrated to the next higher dose in patients receiving 2,5 mg twice daily or 5 mg twice daily.

Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist (see **section 4.4**).

Special populations

Elderly patients:

In patients aged 75 years or more, a lower starting dose should be considered.

(2,5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.

Patients with renal impairment:

No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min (see **section 5**).

No data are available in patients with creatinine clearance below 15 ml/min. **BRADHET** should therefore be used with precaution in this population.

Patients with hepatic impairment:

No dose adjustment is required in patients with mild hepatic impairment.

BRADHET is not recommended in patients with moderate hepatic insufficiency, since there is limited data and is contraindicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population (see **section 4.3**).

Paediatric population

The safety and efficacy of **BRADHET** in children aged below 18 years have not yet been established.

Method of administration

BRADHET tablets must be taken orally twice daily, i.e. once in the morning and once in the evening. **BRADHET** tablets should be taken with food.

4.3 Contraindications

Pregnancy and lactation, as BRADHET has shown to be teratogenic in animal reproductive studies (see section 4.6).

- Known hypersensitivity to ivabradine or to any of the excipients of **BRADHET** (see **section 6.1**).
- 3rd degree atrioventricular (AV) Block.
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker).
- Resting heart rate below 70 bpm prior to treatment.
- Severe hypotension (< 90/50 mmHg).
- Cardiogenic shock.
- Unstable or acute heart failure.
- Acute coronary syndrome.
- Unstable angina pectoris.
- Use in patients with congenital long QT syndrome or in patients treated with QT-prolonging medicines should be avoided (see **section 4.4**).
- In combination with strong cytochrome P450 inhibitors such as azole antifungals, macrolide antibiotics, HIV protease inhibitors (see **section 4.5**).
- Concomitant use of St John's Wort.

- **BRADHET** is not recommended in patients with moderate liver dysfunction (limited data in these populations) and is contraindicated in severe liver dysfunction (no data).
- Combination with verapamil or diltiazem, which are moderate CYP3A4 inhibitors with heart-rate reducing properties (see **section 4.5**).
- Women of childbearing potential not using appropriate contraceptive measures (see **section 4.6**).
- Concomitant use of grapefruit juice is not recommended (see **section 4.5**).
- **Concomitant use with QT-prolonging medicines:**

  The concomitant use of cardiovascular (quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone) or non-cardiovascular (tricyclic antidepressant, antipsychotics, erythromycin IV, pentamidine, pimozide, mefloquine) QT-prolonging medicines with **BRADHET** should be avoided since QT-prolongation may be exacerbated by heart rate reduction.

  - **BRADHET** has not been studied in patients with rapid conduction disorders i.e. WPW.
  - Cardiac dysrhythmias:
    - sick sinus syndrome.
    - sino-atrial block.
- **Stroke:**

  The use of **BRADHET** is not recommended immediately after a stroke since no data are available in these situations.
- **Use in patients with AV-block of 2nd degree:**

  BRADHET is not recommended in patients with AV-block of 2nd degree.
- Acute myocardial infarction.

4.4 Special warnings and precautions for use

BRADHET treatment should be discontinued if the symptoms of angina pectoris do not improve with 3 months of **BRADHET** treatment.

Lack of benefit on clinical outcomes in patients with symptomatic chronic stable angina pectoris:

BRADHET is indicated only for symptomatic treatment of chronic stable angina pectoris, because **BRADHET** has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death).

Measurement of heart rate:

Given that the heart rate may fluctuate considerably over time, serial heart rate measurements, ECG or ambulatory 24-hour monitoring is recommended when determining resting heart rate before initiation of **BRADHET** treatment and in patients on treatment with **BRADHET** when titration is considered. This also applies to patients who develop a low heart rate on treatment with **BRADHET**, in particular when heart rate decreases below 50 bpm, or after dose reduction (see **section 4.2**).

Chronic heart failure:

Heart failure must be stable before considering ivabradine treatment.

Use in patients with a low heart rate:

BRADHET must not be initiated in patients with a pre-treatment resting heart rate below 70 beats per minute (see **section 4.3**).

If, during **BRADHET** treatment, heart rate decreases below 50 bpm at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward or discontinued. Treatment must be discontinued if heart rate below 50 bpm persists (see **section 4.2**).

Combination with other anti-angina medications:

Concomitant use of **BRADHET** with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated (see **sections 4.3** and **4.5**). Additional efficacy of **BRADHET** in combination with dihydropyridine calcium channel blockers has not been established.

Use in patients with congenital QT syndrome or in patients treated with QT- prolongation medicines:

Since **BRADHET** reduces heart rate it should be avoided in patients with congenital QT syndrome or treated with QT-prolongations medicines. If the combination appears necessary, close cardiac monitoring is needed.

Heart rate reduction, as caused by **BRADHET**, may exacerbate QT-prolongation, which may give rise to severe dysrhythmias, in particular *Torsade de pointes*.

Cardiac dysrhythmias:

BRADHET is not effective in the treatment or prevention of cardiac dysrhythmias and likely loses its efficacy when a tachy-dysrhythmia occurs (i.e. ventricular or supra-ventricular tachycardia).

BRADHET is not recommended in patients with atrial fibrillation or with other cardiac dysrhythmias that interfere with sinus node function.

In patients treated with **BRADHET** the risk of developing atrial fibrillation is increased (see **section 4.8**). Atrial fibrillation has been more common in patients concomitantly using amiodarone or potent class I anti-dysrhythmics.

It is recommended to regularly clinically monitor **BRADHET** treated patients for the occurrence of atrial fibrillation (sustained of paroxysmal), which should also include ECG monitoring if clinically indicated (i.e. in case of exacerbated angina, palpitations or irregular pulse).

Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their medical practitioner if these occur.

If atrial fibrillation develops during treatment, the balance of benefits and risks of continued **BRADHET** treatment should be carefully reconsidered.

Chronic heart failure patients with intraventricular conductions defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be closely monitored.

Visual function:

Ivabradine influences on retinal function. To date, there is no evidence of a toxic effect of ivabradine on the retina, but the effects of long-term ivabradine treatment beyond one year on retinal function are currently not known. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Wolf-Parkinson-White-syndrome:

BRADHET has not been studied in patients with Wolf-Parkinson-White-syndrome (see **section 4.3**).

Moderate to severe liver dysfunction:

BRADHET is not recommended in patients with moderate liver dysfunction since there is limited data in these populations and is contraindicated in severe liver dysfunction (see **section 4.3**).

Aortic and/or Mitral valvular disease*:*

Due to the lack of data, **BRADHET** is not recommended in patients with severe aortic and/or mitral valvular disease.

Stroke:

The use of ivabradine is not recommended immediately after a stroke since no data is available in these situations.

Concomitant use with cytochrome P450 3A4 (CYP3A4) inhibitors or inducers:

Strong CYP3A4 inhibitors:

As these medicines significantly increase **BRADHET** plasma concentrations, their concomitant use with **BRADHET** is contraindicated (see **section 4.3**).

Moderate CYP3A4 inhibitors:

As these medicines increase ivabradine plasma concentrations, their concomitant use with **BRADHET** may require a downward titration of the dose of **BRADHET** depending on heartrate (see **section 4.5**).

CYP3A4 inducers:

As these medicines decrease ivabradine plasma concentrations, their prolonged concomitant use with **BRADHET** may require an upward titration of the dose of **BRADHET** depending on the therapeutic

response. In this case, heart rate monitoring is recommended when discontinuing CYP3A4 inducers (see **section 4.5**).

Hypertension requiring blood pressure treatment modifications:

As patients treated with **BRADHET** may experience episodes of increased blood pressure, blood pressure should be monitored at appropriate intervals (see **section 4.8**).

Patients with hypotension:

Limited data are available in patients with mild to moderate hypotension, and **BRADHET** should therefore be used with caution in these patients. **BRADHET** is contraindicated in patients with severe hypotension (blood pressure < 90/50 mmHg) (see **section 4.3**).

Lactose warning

BRADHET contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicine and other forms of interaction

Pharmacokinetic interactions:

Cytochrome P450 3A4 (CYP3A4):

Ivabradine is metabolised by cytochrome P450 3A4 (CYP3A4) and is a weak inhibitor of this cytochrome. Therefore, ivabradine is unlikely to influence the metabolism and plasma concentrations of other CYP3A4 substrates. CYP3A4 inhibitors and inducers are liable to interact with ivabradine and to influence its metabolism and pharmacokinetics. Drug-drug interaction studies have established that CYP3A4 inhibitors increase ivabradine plasma concentrations, while inducers decrease them. Increased plasma concentrations of ivabradine may be associated with excessive bradycardia (see **section 4.3**).

Concomitant use contraindicated:

The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin taken orally, josmycin, telithromycin), HIV protease

inhibitors (including nelfinavir, ritonavrir) is contraindicated (see **section 4.3**). The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased the mean plasma exposure of ivabradine by 7 to 8 fold.

Moderate CYP3A4 inhibitors:

Specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with diltiazem and verapamil resulted in an increased ivabradine exposure (2 to 3 fold increase in AUC) with an additional heart rate reduction of 5 bpm.

The concomitant use of ivabradine with these medicines is contraindicated (see **section 4.3**).

Concomitant use not recommended:

Grapefruit juice: Ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be avoided.

Concomitant use with caution:

The concomitant use of **BRADHET** with **other moderate CYP3A4 inhibitors** (i.e. fluconazole) may be considered at the starting dose of 2,5 mg twice daily and if resting heart rate is above 70 bpm, while monitoring heart rate.

CYP3A4 metabolism inducers such as rifampicin, barbiturates, phenytoin and Hypericum perforatum (St John's Wort):

Prolonged concomitant use of these medicines with ivabradine may decrease ivabradine exposure and activity and therefore require an upward titration of the dose of **BRADHET**. The combination of **BRADHET** 10 mg twice daily with St John's Wort was shown to reduce the area under the curve (AUC) of ivabradine by 50 %. The intake of St John's Wort is not recommended (see **section 4.3**).

Other concomitant use:

Specific interaction studies have shown no clinically significant pharmacokinetic or pharmacodynamic interactions between **BRADHET** and any of the following: digoxin, HMG CoA reductase inhibitors (statins),

proton pump inhibitors (e.g. omeprazole, lansoprazole), dihydropyridine calcium channel blockers (nifedipine, amlodipine, lacidipine), aspirin and warfarin.

In pivotal phase III clinical trials the following medicines were frequently combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone, calcium channel blockers (e.g. nifidipine), short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics (including: biguanides, sulphonylureas, alpha-glucosidases inhibitors, DPP-4 inhibitors, glitazones (thiazolidinediones), aspirin and other anti-platelet medicines.

Pharmacodynamic interactions:

Concomitant use not recommended:

QT-prolonging medicines:

- *Cardiovascular* QT-prolonging medicines (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).
- Non cardiovascular QT-prolonging medicines (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).

The concomitant use of cardiovascular and non-cardiovascular QT-prolonging medicines with **BRADHET** should be avoided since QT-prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is required.

Concomitant use with precaution:

Potassium-depleting diuretics (thiazide diuretics and loop diuretics):

Hypokalaemia can increase the risk of dysrhythmia. As **BRADHET** may cause bradycardia, the resulting combination of hypokalaemia and bradycardia is a predisposing factor to the onset of severe dysrhythmias, especially in patients with long QT syndrome, whether congenital or substance induced (see **section 4.3**).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of child childbearing potential

Women of childbearing potential should use appropriate contraceptive measures during treatment (see **section 4.3**).

Pregnancy

Animal reproduction studies have shown embryotoxic and teratogenic effects at doses similar to those used in humans.

Lactation

Animal studies indicate that ivabradine is excreted in milk. Therefore, BRADHET is contraindicated during pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

BRADHET may cause transient visual symptoms consisting mainly of phosphenes. The possible occurrence of such visual symptoms should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur.

BRADHET may also cause headache, generally during the first month of treatment, and dizziness, possibly related to bradycardia (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

Ivabradine has been studied in clinical trials involving nearly 45 000 patients. The frequent adverse events with **BRADHET**, luminous phenomena (phosphenes) and bradycardia, are dose dependant and are related to the pharmacological effect of the medicine.

b) Tabulated summary of adverse reactions

Blood and lymphatic system disorders

Less frequent: Eosinophilia

Metabolism and nutrition disorders

Less frequent: Hyperuricaemia

Nervous system disorders

Frequent: Headache, generally during the first month of treatment, dizziness, possibly related to bradycardia

Less frequent: Syncope, possibly related to bradycardia

Eye disorders

Frequent: Luminous phenomena (phosphenes), blurred vision

Less Frequent: Visual impairment, diplopia

Ear and labyrinth disorders

Less frequent: Vertigo

Cardiac disorders

Frequent: Bradycardia, AV 1st degree block (ECG prolonged PQ interval), atrial fibrillation, ventricular extrasystoles

Less frequent: Palpitations, supraventricular extrasystoles, AV 2nd degree block, AV 3rd degree block, sick sinus syndrome

Vascular disorders

Frequent: Increased blood pressure

Frequency unknown: Hypotension, possibly related to bradycardia

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea

Gastrointestinal disorders

Less frequent: Nausea, constipation, diarrhoea

Frequency unknown: Abdominal pain

Skin and subcutaneous tissue disorders

Less Frequent: Angioedema, rash, erythema, pruritus, urticaria

Musculoskeletal and connective tissue disorders

Less frequent: Muscle cramps

General disorders and administration site conditions

Less Frequent: Asthenia, possibly related to bradycardia, fatigue, possibly related to bradycardia, malaise, possibly related to bradycardia

Investigations

Less frequent: Elevated creatinine in blood, ECG prolonged QT interval

c. Description of selected adverse reactions

Luminous phenomena (phosphenes) were reported by 14,5 % of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. Phosphenes may also be described as a halo, image decomposition (stroboscopic and kaleidoscopic), coloured bright lights, or multiple images (retinal persistency). The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority resolved during treatment. Less than 1 % of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by patients particularly within the first 2 to 3 months of treatment initiation and patients experienced a severe bradycardia below or equal to 40 bpm.

In patients with angina pectoris, artrial fibrillation developed in about 5 % of patients treated with ivabradine. In a pooled analysis of all the Phase II/III double blind controlled clinical trials with a duration of at least 3 months including more than 40 000 patients, the atrial fibrillation developed in 4,86 % of ivabradine treated patients compared to 4,08 % in controls.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za and to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com

4.9 Overdose

Symptoms:

In overdose, side effects will be exacerbated and exaggerated (see **section 4.8**).

Overdose may lead to severe and prolonged bradycardia, which should be treated symptomatically in a specialised environment.

Management:

In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicines such as dobutamine may be considered. Temporary cardiac electrical pacing may be instituted if required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 7.1.4 Vasodilators – coronary and other medicines used in angina pectoris

Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations **ATC code:** C01EB17.

Ivabradine is a heart-rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate.

The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, myocardial contractility or ventricular repolarisation.

In experimental models the adaptability of myocardial contractility, cardiac output, mean coronary blood flow velocity and vascular resistance observed during exercise is preserved. In animal models used to mimic exercise-induced ischaemia that causes angina pectoris in humans, ivabradine reduces myocardial ischaemia and myocardial contractility dysfunction induced by stunning.

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. At recommended doses, heart rate reduction is approximately 10 beats per minute (bpm) at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. Analysis of heart rate reduction indicates a trend towards a plateau effect at higher doses.

Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:

- in clinical electro-physiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals.

5.2 Pharmacokinetic properties

Under physiological conditions, ivabradine is released from tablets and is highly soluble (> 10 mg/ml). Ivabradine is the S-enantiomer with no bioconversion demonstrated *in vivo*. The N-desmethylated derivative of ivabradine has been identified as the main active metabolite in humans.

Absorption:

About 90 % of ivabradine is absorbed after oral administration, with a peak plasma level reached in about 0,75 – 1,5 hours. The absolute bioavailability of ivabradine tablets is around 40 %, due to first-pass effect. Food delays absorption by about 1 hour, and increases plasma exposure by 20 – 30 %.

Distribution:

Ivabradine is approximately 70 % plasma protein bound and the volume of distribution at steady-state is close to 100 litres in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml. The average plasma concentration is 10 ng/ml at steady-state.

Biotransformation:

Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative (S18982), and its exposure is about 40 % of that of the parent compound, with similar pharmacokinetic and pharmacodynamic properties. The metabolism of this active metabolite also involves CYP3A4.

Ivabradine has low affinity for CYP3A4, shows no sign of enzyme induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Inversely, strong inhibitors and inducers of CYP3A4 may substantially affect ivabradine plasma concentrations (see **section 4.5**).

Elimination:

Ivabradine is eliminated with a plasma half-life of 2 hours. The total clearance is about 400 ml/min and the renal clearance is about 70 ml/min. Excretion of metabolites and little amounts of unchanged compounds occurs to a similar extent via faeces and urine.

Linearity/non-linearity:

The kinetics of ivabradine are linear.

Special populations:

Elderly:

No pharmacokinetic differences (AUC and C_{max}) have been observed between elderly (≥ 65 years) or very elderly patients (≥ 75 years) and the overall population.

Renal impairment:

In patients with renal insufficiency (15 – 60 ml/min), no specific dosage adjustment is required since this condition has no significant impact on ivabradine clearance.

Hepatic impairment:

No specific dosage adjustment is required in patients with mild liver dysfunction (Child Pugh score less than 7). The use of ivabradine is not recommended in patients with moderate liver dysfunction (limited data, see Warnings) and is contraindicated in severe liver dysfunction (no data available see **section 4.3**).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Corn starch
- Colloidal silicon dioxide
- Lactose monohydrate
- Magnesium stearate
- Maltodextrin
- Purified water
- Opadry tan 03G580014 (consists of HPMC 2910/hypromellose, titanium dioxide, macrogol/PEG, glycerin, magnesium stearate)
- Opadry tan 03G570019 (consists of HPMC 2910/hypromellose, titanium dioxide, macrogol/PEG, glycerin, magnesium stearate, iron oxide yellow, ferrosoferric oxide NF/black iron oxide, iron oxide red)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

- Store at 25 °C, excursions permitted to 15 °C to 30 °C (59 °F – 89 °F).
- Keep the tablets in the original container until required for use.
- This medicine does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottle:

Tablets are pack in a white opaque high density polyethylene container (HDPE) container with white opaque polypropylene child resistant closure with pulp liner containing 2,0 g silica gel canister as a desiccant.

Pack size: 60's and 180's

Blister strips:

Blister strips of cold form pack film with desiccant as a forming film and plain aluminium form pack film with desiccant as a lidding foil, containing 10 tablets per blister.

Pack sizes: 10 tablets per blister. 10's x 10 blisters packed in a box.

HDPE bottle and blister strips are enclosed in an outer carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate Campus

Building No. 2, First floor,

74 Waterfall Drive,

Midrand,

2066,

Telephone: 012 644 1220,

Email address: Nokuthula.n@hetero.com.

8 REGISTRATION NUMBER(S)

BRADHET 5: 57/7.1.4/0277.

BRADHET 7,5: 57/7.1.4/0278.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10 JUNE 2025

10 DATE OF REVISION OF THE TEXT

N/A