PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

IVABRADINE 5 UNICORN film coated tablet

IVABRADINE 7,5 UNICORN film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IVABRADINE 5 UNICORN contains 5,39 mg ivabradine hydrochloride corresponding to 5 mg of ivabradine base.

IVABRADINE 7,5 UNICORN contains 8,085 mg ivabradine hydrochloride corresponding to 7,5 mg of ivabradine base.

Excipients with known effect:

Contains sugar:

IVABRADINE 5 UNICORN contains 50 mg lactose monohydrate per film-coated tablet.

IVABRADINE 7,5 UNICORN contains 75 mg lactose monohydrate per film-coated tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets.

IVABRADINE 5 UNICORN: White coloured, oval shape, biconvex,

film-coated tablet, scored and engraved with ´5´ on one side, plain on the other side.

IVABRADINE 7,5 UNICORN: White coloured, oval shape, biconvex, film coated tablet, scored and engraved with ´7.5´ on one side, plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of chronic stable angina pectoris:

IVABRADINE UNICORN 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:

IVABRADINE UNICORN 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 well 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 IVABRADINE UNICORN 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 with IVABRADINE UNICORN 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 UNICORN 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 5.1).

No data are available in patients with creatinine clearance below 15 ml/min.

IVABRADINE UNICORN should therefore be used with precaution in this population.

Patients with hepatic impairment:

No dose adjustment is required in patients with mild hepatic impairment. IVABRADINE UNICORN 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, as it has not been studied in this population (see section 4.3).

Paediatric population

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

Method of administration

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

Missed dose:

Doctors should advise patients who forget to take IVABRADINE UNICORN to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

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

- Hypersensitivity to ivabradine or to any of the ingredients of IVABRADINE UNICORN.
- 3rd degree AV block.

- Pacemaker dependent (heart rate imposed exclusively by the pacemaker).
- Resting heart below 70 bpm prior to treatment.
- Severe hypotension (< 90/50 mm Hg).
- 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.
- IVABRADINE UNICORN 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 IVABRADINE UNICORN should be avoided since QT-prolongation may be exacerbated by heart rate reduction.

- IVABRADINE UNICORN 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 IVABRADINE UNICORN is not recommended immediately after a stroke since no data is available in these situations.

Use in patients with AV-block of 2nd degree:

IVABRADINE UNICORN is not recommended in patients with AV-block of 2nd degree.

4.4 Special warnings and precautions for use

If the symptoms of angina pectoris do not improve within 3 months, treatment with IVABRADINE UNICORN should be discontinued.

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

IVABRADINE UNICORN is indicated only for symptomatic treatment of chronic stable angina pectoris, as it 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 IVABRADINE UNICORN treatment, as well as those patients already on treatment with IVABRADINE UNICORN and titration is considered. This also applies to patients who develop a low heart rate whilst on treatment with IVABRADINE UNICORN, 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 UNICORN treatment.

Use in patients with a low heart rate:

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

If, during IVABRADINE UNICORN 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 medicines:

Concomitant use of IVABRADINE UNICORN with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated (see sections 4.3 and 4.5).

Additional efficacy of IVABRADINE UNICORN 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:

As IVABRADINE UNICORN 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.

Since IVABRADINE UNICORN reduces heart rate it may exacerbate QT-prolongation, which may in turn give rise to severe dysrhythmias, in particular *Torsade de pointes*.

Cardiac dysrhythmias:

IVABRADINE UNICORN 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).

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

In patients treated with IVABRADINE UNICORN 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.

IVABRADINE UNICORN treated patients should be regularly clinically monitored 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 doctor if these occur.
If atrial fibrillation develops during treatment, the balance of benefits and risks of continued IVABRADINE UNICORN 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, as contained in IVABRADINE UNICORN, 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:

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

Moderate to severe liver dysfunction:

IVABRADINE UNICORN 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, IVABRADINE UNICORN is not recommended in patients with severe aortic and/or mitral valvular disease.

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

- ***Strong CYP3A4 inhibitors:***

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

- ***Moderate CYP3A4 inhibitors:***

As these medicines increase IVABRADINE UNICORN plasma concentrations, their concomitant use with IVABRADINE UNICORN may require a downward titration of the dose of IVABRADINE UNICORN depending on heart rate (see section 4.5).

- ***CYP3A4 inducers:***

As these medicines decrease IVABRADINE UNICORN plasma concentrations, their prolonged concomitant use with IVABRADINE UNICORN may require an upward titration of the dose of IVABRADINE UNICORN depending on the therapeutic response. In this case, heart rate monitoring is recommended when discontinuing CYP3A4 inducers (also see section 4.5).

Hypertension requiring blood pressure treatment modifications:

Patients treated with IVABRADINE UNICORN may experience episodes of increased blood pressure, blood pressure should therefore be monitored at appropriate intervals

(see section 4.8).

Patients with hypotension:

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

Stroke:

The use of IVABRADINE UNICORN is not recommended immediately after a stroke since no data is available in these situations (see section 4.3)

Renal impairment:

IVABRADINE UNICORN must be used with caution in severe renal impairment (creatinine clearance of less than 15 ml/minute).

Lactose monohydrate

IVABRADINE UNICORN contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency, or glucose-galactose malabsorption should not take IVABRADINE UNICORN.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions:

Cytochrome P450 3A4 (CYP3A4):

IVABRADINE UNICORN is metabolised by cytochrome P450 3A4 (CYP3A4) and is a

weak inhibitor of this cytochrome. Therefore, IVABRADINE UNICORN is unlikely to influence the metabolism and plasma concentrations of other CYP3A4 substrates.
CYP3A4 inhibitors and inducers are liable to interact with IVABRADINE UNICORN and to influence its metabolism and pharmacokinetics.
Medicine-medicine interaction studies have established that CYP3A4 inhibitors increase IVABRADINE UNICORN plasma concentrations, while inducers decrease them.
Increased plasma concentrations of IVABRADINE UNICORN may be associated with excessive bradycardia (see section 4.3).

Concomitant use contraindicated:

Potent CYP3A4 inhibitors

The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconozole), macrolide antibiotics (clarithromycin, erythromycin taken orally, josmycin, telithromycin), HIV protease inhibitors (including nelfinavir, ritonavir) 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 UNICORN by 7 to 8- fold.

Moderate CYP3A4 inhibitors

Specific interaction studies in healthy volunteers and patients have shown that the combination of IVABRADINE UNICORN 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, as in IVABRADINE UNICORN, 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:

Moderate CYP3A4 inhibitors

Concomitant 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, whilst 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 UNICORN may decrease ivabradine exposure and activity and therefore require an upward titration of the dose of IVABRADINE UNICORN.

The combination of IVABRADINE UNICORN 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 ivabradine, as in IVABRADINE UNICORN, and any of the following: digoxin, HMG CoA reductase inhibitors (simvastatin), proton pump

inhibitors (omeprazole, lansoprazole), dihydropyridine calcium channel blockers (amlodipine, lacidipine), aspirin and warfarin.

In pivotal phase III clinical trials, the following medicines were routinely combined with ivabradine with no evidence or safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, 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 IVABRADINE UNICORN 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 IVABRADINE UNICORN 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).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females Women of child-bearing potential should use appropriate contraceptive measures during treatment with IVABRADINE UNICORN.

Pregnancy

Animal reproduction studies have shown embryo toxic and teratogenic effects at doses similar to those in humans. IVABRADINE UNICORN is therefore contraindicated during pregnancy (see section 4.3)

Breastfeeding

Animal studies indicate that ivabradine as contained in IVABRADINE UNICORN is excreted in milk.

IVABRADINE UNICORN is therefore contraindicated during lactation (see section 4.3).

Fertility

Studies in rats have shown no effect on fertility in males and females

4.7 Effects on ability to drive and use machines:

IVABRADINE UNICORN may cause transient luminous phenomena consisting mainly of phosphenes. The possible occurrence of such luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ	Frequency	Side effects Class
Blood and lymphatic system disorders	Less frequent	Eosinophilia
Metabolism and nutrition disorders	Less frequent	Hyperuricaemia
Nervous system disorders	Frequent Less frequent	Headache, generally during the first month of treatment, dizziness Syncope
Eye disorders	Frequent Frequency unknown	Luminous phenomena (phosphenes), blurred vision Diplopia*, visual impairment*
Ear and labyrinth Disorders	Less frequent	Vertigo
Cardiac disorders	Frequent	Bradycardia, AV 1st degree block (ECG prolonged QT

System Organ	Frequency	Side effects Class
	Less frequent	interval), ventricular extrasystoles, atrial fibrillation Palpitations, supraventricular extrasystoles, AV 2nd degree block, AV 3rd degree block, sick sinus syndrome
Vascular disorders	Frequent Frequency unknown	Increased blood pressure Hypotension*, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea
Gastrointestinal disorders	Less frequent Frequency unknown	Nausea, constipation, diarrhoea Abdominal pain*
Skin and subcutaneous tissue disorders	Frequency unknown	Angioedema*, rash*, erythema*, pruritus*, urticaria*
Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle cramps
General disorders and administrative site conditions	Frequency unknown	Asthenia*, malaise*, fatigue*
Investigations	Less frequent	Elevated creatinine in blood,

System Organ	Frequency	Side effects Class
		ECG prolonged QT interval

*Post marketing adverse effects

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 inlight intensity. Phosphenes may also be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), coloured bright lights, or multiple image (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 (77,5 %) resolved during treatment. Less than 1 % of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by 3,3 % of patients particularly within the first 2 to 3 months of treatment initiation. 0,5 % of patients experienced a severe bradycardia below or equal to 40 bpm.

In patients with angina pectoris, atrial fibrillation developed in about 5 % of patients treated with ivabradine, as in IVABRADINE UNICORN.

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.

d). Paediatric population

Not applicable.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found on SAHPRA's website: www.sahpra.org.za under "online services"

4.9 OVERDOSE

Signs and 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 of overdose:

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

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

Pharmacological classification: A 7.1.4 Vasodilators – coronary and other medicines used in angina pectoris.

Pharmacodynamic properties

Mechanism of action

Ivabradine is a heart lowering medicine, 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-arterial, atrioventricular or intraventricular conduction times, nor on 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.

Ivabradine can interact also with the retinal current I_h which closely resembles cardiac I_f.

It participates in the temporal resolution of the visual system, by curtailing the retinal

response to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of I_h by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field (see section 4.8).

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 and bioavailability:

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 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 N-desmethylated derivative of ivabradine has been identified as the main active metabolite in humans. 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.

Conversely, 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 over an oral dose range of 0,5 – 24 mg.

Pharmacokinetics in special patient groups

Elderly

No pharmacokinetic differences have been observed between the elderly (> 65 years) or

very elderly patients (> 75 ears 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 hepatic dysfunction due to limited data (see section 4.4), and is contraindicated in severe liver dysfunction (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate (E470b)

Microcrystalline cellulose (E460(i))

Opadry White (consisting of glycerol (E422), hypromellose (E464), magnesium stearate (E470b), macrogol 6000 (E1521), titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Aluminium/aluminium blister strips packed in an outer carton containing 14, 28 or 56 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Cnr. Searle & Pontac Streets

Cape Town

South Africa

8001

8. REGISTRATION NUMBER(S)

IVABRADINE 5 UNICORN: A52/7.1.4/0894

IVABRADINE 7,5 UNICORN: A52/7.1.4/0895

9. DATE OF FIRST AUTHORISATION

24 August 2021

10. DATE OF REVISION OF THE TEXT