PROFFESIONAL INFORMATION

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

Verahexal® 240 SR (film-coated slow release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VERAHEXAL 240 SR film-coated slow release tablet contains 240 mg verapamil hydrochloride.

VERAHEXAL 240 SR contains sugar (8,84 mg lactose monohydrate per tablet).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Oblong, light-green film-coated tablet with scores on both sides and smooth, intact surface.

Length: 19,1 to 19,3 mm

Width: 8,1 to 8,3 mm

Height: 6,2 to 6,5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- 1. Mild to moderate hypertension.
- 2. Prophylaxis of angina pectoris.
- 3. Supraventricular tachydysrhythmia.
- 4. Prophylaxis of supraventricular relapses after electro-cardioversion.

4.2 Posology and method of administration

Hypertension*:*

One tablet daily preferably in the morning. Should the desired response not be achieved within 7 days, the dose may be increased to 1 tablet in the morning and half a tablet in the evening. Maximum dose 1 (one) tablet every 12 hours.

Angina pectoris and supraventricular dysrhythmia:

Half to one tablet every 12 hours.

4.3 Contraindications

- Hypersensitivity to verapamil or to any of the excipients listed in section 6.1.
- Hypotension associated with cardiogenic shock.
- Heart failure.
- Second- or third-degree AV block.
- Myocardial infarction (acute stage).
- Sick sinus syndrome.
- Left ventricular failure.
- Sino-atrial block.
- Bradycardia of less than 50 beats/minute.
- Hypotension of less than 90 mm Hg systolic.
- Patients with atrial flutter/fibrillation in the presence of an accessory pathway (e.g. Wolff-Parkinson-White syndrome) may develop increased conduction across the anomalous pathway and ventricular tachycardia may be precipitated.
- Combination with ivabradine (see section 4.5).
- Pregnancy: Verapamil does cross the placenta and should not be administered during pregnancy.

- Breastfeeding: Verapamil is excreted in the breast milk – discontinue breast feeding while taking VERAHEXAL 240 SR.

4.4 Special warnings and precautions for use

Impaired liver and kidney function:

Since verapamil is extensively metabolised in the liver and is almost exclusively excreted via the urine, careful dose-titration is required in patients with liver disease. Although the pharmacokinetics of verapamil in patients with renal impairment are not affected, caution should be exercised and careful patient monitoring is recommended. Verapamil is not removed during dialysis. These patients should be monitored for abnormal prolongation of the PR interval or other signs of over dosage.

Elevated liver enzymes: elevation of transaminases with and without concomitant elevations in alkaline phosphatases and bilirubin have been reported. Such elevations are usually transient.

AV block:

Verapamil may affect impulse conduction and should therefore be used with caution in patients with bradycardia or first-degree AV block. PR interval prolongation is related to verapamil plasma concentrations. Significant first-degree block and progressive development to second- or third-degree block may require reduction of dose or less frequently discontinuation of therapy.

Heart failure:

Because verapamil is a negative inotrope, congestive cardiac failure or pulmonary oedema may occur in susceptible patients. VERAHEXAL 240 SR should not be administered to patients with severe left ventricular dysfunction or to patients with any degree of left ventricular dysfunction, should they be receiving a beta adrenergic blocking agent.

Ideally patients with mild ventricular dysfunction should be treated with digitalis and/or diuretics, before treatment with VERAHEXAL 240 SR.

Hypotension:

Less frequently verapamil may induce symptomatic hypotension in normotensive patients. In hypertensive patients, decreases in blood pressure below normal values are unusual. When treating hypertension with VERAHEXAL 240 SR, monitoring of the patient's blood pressure at regular intervals is required.

Accessory bypass tract (Wolff – Parkinson – White or Lown – Ganong – Levine):

After receiving intravenous verapamil certain patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter with a co-existing accessory AV pathway have developed an increased antegrade conduction across the accessory pathway leading to ventricular fibrillation. Such patients receiving oral verapamil may be at risk.

Hypertrophic cardiac myopathies:

Pulmonary oedema and/or severe hypotension, sinus bradycardia, AV block and sinus arrest may occur in these patients. Reducing the dose often reduces these side effects.

HMG CoA reductase inhibitors:

Caution should be exercised in treatment with HMG CoA reductase inhibitors (e.g., simvastatin, atorvastatin or lovastatin) for patients taking VERAHEXAL 240 SR. These patients should be started at the lowest possible dose of VERAHEXAL 240 SR and titrated upwards. If VERAHEXAL 240 SR treatment is to be added to patients already taking an HMG CoA reductase inhibitor (e.g. simvastatin, atorvastatin or lovastatin), refer to advice in the respective statin professional information.

Attenuated neuromuscular transmission:

Verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy. The recovery from the neuromuscular blocking agent, vecuronium, is prolonged by verapamil. Use with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

Lactose:

VERAHEXAL 240 SR contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take VERAHEXAL 240 SR.

4.5 Interactions with other medicines and other forms of interaction

In vitro metabolic studies indicate that verapamil hydrochloride is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4 causing elevation of plasma levels of verapamil hydrochloride while inducers of CYP3A4 have caused a lowering of plasma levels of verapamil hydrochloride, therefore, patients should be monitored for medicine interactions.

The following are potential medicine interactions associated with VERAHEXAL 240 SR:

Acetylsalicylic acid:

Concomitant use of VERAHEXAL 240 SR with aspirin may increase the risk of bleeding.

Alcohol:

Increase in blood alcohol has been reported.

Alpha blockers:

VERAHEXAL 240 SR may increase the plasma concentrations of prazosin and terazosin which may have an additive hypotensive effect.

Anti-dysrhythmics:

Disopyramide: this agent should not be administered 48 hours before or 24 hours after VERAHEXAL 240 SR administration.

Flecainide: additive effects on AV node conductivity, myocardial contractility and repolarisation, as well as on the negative inotropic effect.

Quinidine: this combination may lead to significant hypotension and pulmonary oedema may occur in patients suffering from hypertrophic cardiac myopathy. VERAHEXAL 240 SR may increase the plasma concentrations of quinidine. This combination should probably be avoided in the above-mentioned patients.

The combination of VERAHEXAL 240 SR and antidysrhythmic agents may lead to additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Anticonvulsants:

VERAHEXAL 240 SR may increase the plasma concentrations of carbamazepine. This may produce side effects such as diplopia, headache, ataxia or dizziness. VERAHEXAL 240 SR may also increase the plasma concentrations of phenytoin.

Antidepressants:

VERAHEXAL 240 SR may increase the plasma concentrations of imipramine.

Antidiabetics:

VERAHEXAL 240 SR may increase the plasma concentrations of glibenclamide (glyburide).

Antihypertensives, diuretics, vasodilators:

Potentiation of the hypotensive effect. The dose of other hypotensives may have to be lowered.

Anti-infectives:

Rifampicin may reduce the plasma concentrations of VERAHEXAL 240 SR which may produce a reduced blood pressure lowering effect. Erythromycin, clarithromycin and telithromycin may increase the plasma concentrations of VERAHEXAL 240 SR.

Antineoplastics:

VERAHEXAL 240 SR may increase the plasma concentrations of doxorubicin.

Barbiturates:

Phenobarbital may reduce the plasma concentrations of VERAHEXAL 240 SR.

Benzodiazepines and other anxiolytics:

VERAHEXAL 240 SR may increase the plasma concentrations of buspirone and midazolam.

Beta-blockers:

VERAHEXAL 240 SR may increase the plasma concentrations of metoprolol and propranolol, which may lead to additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Intravenous beta-blockers should not be given to patients under treatment with VERAHEXAL 240 SR.

Cardiac glycosides:

VERAHEXAL 240 SR may increase the plasma concentrations of digitoxin and digoxin. Verapamil has been shown to increase the serum concentration of digoxin and caution should be exercised with regard to digitalis toxicity. The digitalis level should be determined and the glycoside dose reduced if required.

Colchicine:

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Verapamil is known to inhibit CYP3A and P-gp. When VERAHEXAL 240 SR and colchicine are administered together, inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine. Combined use is not recommended.

H_2 Receptor antagonists:

Cimetidine may increase the plasma concentrations of VERAHEXAL 240 SR.

HIV antiviral medicines:

Due to the metabolic inhibitory potential of some of the HIV antiviral agents, such as ritonavir, plasma concentrations of verapamil may increase. Caution should be used or dose of VERAHEXAL 240 SR may be decreased.

Immunosuppressants:

VERAHEXAL 240 SR may increase the plasma concentrations of ciclosporin, everolimus, sirolimus and tacrolimus.

Inhalation anaesthetics:

When used concomitantly, inhalation anaesthetics and calcium antagonists, such as VERAHEXAL 240 SR, should each be titrated carefully to avoid additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure)

Lipid lowering medicines:

VERAHEXAL 240 SR may increase the plasma concentrations of atorvastatin, lovastatin and simvastatin.

Treatment with HMG CoA reductase inhibitors (e.g., simvastatin, atorvastatin or lovastatin) in a patient taking VERAHEXAL 240 SR should be started at the lowest possible dose and titrated upwards. If VERAHEXAL 240 SR treatment is to be added to patients already taking an HMG CoA reductase inhibitor (e.g., simvastatin, atorvastatin or lovastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations.

Atorvastatin may increase verapamil levels. Although there is no direct *in vivo* clinical evidence, there is strong potential for VERAHEXAL 240 SR to significantly affect atorvastatin pharmacokinetics in a similar manner to simvastatin or lovastatin. Consider using caution when atorvastatin and VERAHEXAL 240 SR are concomitantly administered.

Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with VERAHEXAL 240 SR.

Lithium:

Serum levels of lithium may be reduced. However, there may be increased sensitivity to lithium.

Neuromuscular blocking agents employed in anaesthesia:

The effects may be potentiated.

Serotonin receptor agonists:

VERAHEXAL 240 SR may increase the plasma concentrations of almotriptan.

Theophylline:

VERAHEXAL 240 SR may increase the plasma concentrations of theophylline.

Uricosurics:

Sulfinpyrazone may reduce the plasma concentrations of VERAHEXAL 240 SR resulting in a reduced blood pressure lowering effect.

Anticoagulants:

When oral verapamil was co-administered with dabigatran etexilate (150 mg), a P-gp substrate, the C_{max} and AUC of dabigatran were increased, but magnitude of this change differed depending on time between administration and the formulation of verapamil. Co-administration of verapamil and dabigatran etexilate resulted in increased dabigatran exposure (increase of C_{max} by about 90 % and AUC by about 70 %).

Close clinical surveillance is recommended when VERAHEXAL 240 SR is combined with dabigatran etexilate and particularly for the occurrence of bleeding, notably in patients with a mild to moderate renal impairment. The risk of bleeding may increase. The dose of dabigatran etexilate with VERAHEXAL 240 SR may need to be reduced. (See “dabigatran etexilate label for dosing instructions”).

Other Cardiac therapy:

Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of verapamil to ivabradine (see section 4.3).

Other:

St. John's Wort may reduce the plasma concentrations of VERAHEXAL 240 SR, whereas grapefruit juice may increase the plasma concentrations of VERAHEXAL 240 SR.

Metformin:

Co-administration of verapamil with metformin may reduce the efficacy of metformin

VERAHEXAL 240 SR and alcohol:

Like many other common medicines, verapamil has been shown to increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated when used with VERAHEXAL 240 SR.

4.6 Fertility, pregnancy and lactation

Pregnancy

Verapamil does cross the placenta. Although animal studies have not shown any teratogenic effects, VERAHEXAL 240 SR should not be administered during pregnancy (see section 4.3).

Breastfeeding

Verapamil is excreted in the breast milk – discontinue breastfeeding while taking VERAHEXAL 240 SR (see section 4.3).

4.7 Effects on ability to drive and use machines

Depending on individual susceptibility, the patients' ability to drive a vehicle, operate machinery or work under hazardous conditions may be impaired. This is particularly true in the initial stages of treatment, when changing over from another medicine or when the dose is raised.

4.8 Undesirable effects

Immune system disorders:

Less frequent: Allergic reactions (e.g. erythema, pruritus, urticaria).

Nervous system disorders:

Frequency unknown: Headache, dizziness, paresthesia, tremor and extrapyramidal syndrome.

Ear and labyrinth disorders:

Frequency unknown: Vertigo and tinnitus.

Cardiac disorders:

Frequency unknown: Bradycardic dysrhythmias such as sinus bradycardia, sinus arrest with asystole, first, second and third degree AV block, bradydysrhythmia in atrial fibrillation, peripheral oedema, palpitations, tachycardia, development or aggravation of heart failure, SA block.

Vascular disorders:

Less frequent: Flushing.

Frequency unknown: Hypotension.

Gastrointestinal disorders:

Less frequent: Gingival hyperplasia.

Frequency unknown: Nausea, vomiting, constipation, ileus and abdominal pain/discomfort.

Skin and subcutaneous tissue disorders:

Frequency unknown: Ankle oedema, Quincke's oedema, Stevens-Johnson syndrome, erythema multiforme, erythromelalgia, alopecia and purpura.

Musculoskeletal and connective tissue disorders:

Frequency unknown: Muscular weakness, myalgia and arthralgia.

Reproductive system and breast disorders:

Less frequent: Impotence (erectile dysfunction), galactorrhoea, gynaecomastia.

General disorders and administration site conditions:

Frequency unknown: Fatigue.

Investigations:

Less frequent: A reversible impairment of liver function characterized by an increase of transaminase and/or alkaline phosphatase.

Frequency unknown: Rises in blood prolactin levels, hepatotoxicity.

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 to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected side effects can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

The course of symptoms in VERAHEXAL 240 SR intoxication depends on the amount taken, the point in time at which detoxification measures are taken and myocardial contractility (age related). The main symptoms are as follows: Bradycardia, hypotension or tachycardia, blood pressure fall (at times to values not detectable), acute respiratory distress, shock symptoms, loss of consciousness, 1st and 2nd degree AV block (frequently as Wenckebach's Phenomenon with or without escape rhythms), total AV block with total AV dissociation, escape rhythm, asystole, bradycardia up to high degree AV block and sinus arrest,

hyperglycaemia, stupor and metabolic acidosis. Fatalities have occurred as a result of overdose.

The therapeutic measures to be taken depend on the point in time at which VERAHEXAL 240 SR was taken and the type and severity of intoxication symptoms. In intoxications with large amounts of slow-release preparations, it should be noted that the release of the active substance and the absorption in the intestine may take more than 48 hours. Verapamil hydrochloride cannot be removed by haemodialysis. Depending on the time of ingestion, it should be taken into account that there may be some lumps of incompletely dissolved tablets along the entire length of the gastro-intestinal tract, which function as active medicine depots.

Specific measures to be taken: elimination of cardio-depressive effects, hypotension or bradycardia. The specific antidote is calcium, e.g. 10 – 20 ml of a 10 % calcium gluconate solution administered intravenously (2,25 – 4,5 mmol) repeated if necessary or given as a continuous drip infusion (e.g. 5 mmol/hour).

The following measures may also be necessary: in case of 2nd or 3rd degree AV block, sinus bradycardia, asystole: atropine, isoprenaline, orciprenaline or pacemaker therapy. *In case of hypotension:* dopamine, dobutamine, noradrenaline. *If there are signs of continuing myocardial failure:* dopamine, dobutamide, if necessary repeated calcium injections.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A.7.1 Vasodilators. Hypotensive medicines

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine derivatives. ATC-Code: C08DA01

Verapamil, a phenylalkylamine calcium antagonist, has a balanced profile of cardiac and peripheral effects. It decreases the flow of calcium ions across the cell membranes of cardiac

and of arterial smooth muscle cells. It lowers heart rate, increases myocardial perfusion and reduces coronary spasm. In a clinical study in patients after myocardial infarction, verapamil reduced total mortality, sudden cardiac death and reinfarction rate.

Verapamil reduces the oxygen demand of the heart by intervening in the energy utilizing metabolic processes of the myocardial cells and also decreasing the total peripheral resistance. It lowers high blood pressure by vasodilation, without reflex tachycardia. Because of its user-dependent action on the voltage-operated calcium channel, the effects of verapamil are more pronounced on high than on normal blood pressure. Verapamil also prolongs impulse conduction in the AV node.

As early as day one of treatment, blood pressure falls; the effect is found to persist also in long term therapy. Verapamil is suitable for the treatment of all types of hypertension: for monotherapy in mild to moderate hypertension; combined with other antihypertensives (in particular with diuretics and, according to more recent findings, with ACE inhibitors) in more severe types of hypertension. In hypertensive diabetic patients with nephropathy, verapamil in combination with ACE inhibitors led to a marked reduction of albuminuria and to an improvement of creatinine clearance.

5.2 Pharmacokinetic properties

Absorption:

More than 90 % of an orally-administered dose of verapamil is absorbed. Due to an intensive hepatic first pass metabolism, the absolute bioavailability is about 22 % with a variability of about 10 – 35 %. Under multiple dosing, bioavailability increases by about 30 %. Bioavailability is not affected by food consumption.

Distribution, biotransformation and elimination:

Plasma concentrations reach their peak 4 – 8 hours after medicine intake. Plasma protein binding of verapamil is about 90 %. The elimination half-life is about 5 – 8 hours. The mean residence time of modified-release verapamil is 18 hours. After repeated single daily doses, steady-state conditions are reached between 3 – 4 days.

Within 5 days, approximately 70 % of an orally-administered dose is excreted in the urine and about 16 % with the faeces. Only 3 – 4 % is eliminated renally as unchanged medicine. The medicine is extensively metabolised. A number of metabolites are generated in humans (twelve have been identified). Of these metabolites only norverapamil has any appreciable pharmacological effect (approximately 20 % that of the parent compound, which was observed in a study with dogs). Norverapamil represents about 6 % of the dose eliminated in urine. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. Renal insufficiency does not affect the kinetics of verapamil.

Special Populations:

Geriatric:

Aging may affect the pharmacokinetics of verapamil given to hypertensive patients. Elimination half-life may be prolonged in the elderly. The antihypertensive effect of verapamil was found not to be age-related.

Renal insufficiency:

Impaired renal function has no effect on verapamil pharmacokinetics, as shown by comparative studies in patients with end-stage renal failure and subjects with healthy kidneys. Verapamil and norverapamil are not significantly removed by haemodialysis.

Hepatic insufficiency:

The half-life of verapamil is prolonged in patients with impaired liver function owing to lower oral clearance and a higher volume of distribution.

5.3 Preclinical safety data

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 0,6 and 1,2 times respectively the maximum recommended human oral daily dose based on a body surface area comparison (mg/m^2) and have revealed no evidence of teratogenicity. In the rat, however, a dose similar to the clinical dose was embryocidal and retarded foetal growth and development. These effects occurred in the presence of maternal toxicity (reflected by reduced food consumption and reduced weight gain of dams). This oral dose has also been shown to cause hypotension in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Colloidal silica anhydrous

Magnesium stearate

Microcrystalline cellulose

Polyvidone

Sodium alginate.

Film-coating:

Green varnish consists of quinolone yellow (E104) and indogitine (E132)

Hypromellose

Lactose monohydrate

Macrogol 4000

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Do not use after the expiry date stated on the label/carton.

6.5 Nature and contents of container

The tablets are packed into white opaque polypropylene securitainers containing 30 or 100 tablets each.

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER

31/7.1/0637

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 April 2002

10. DATE OF REVISION OF THE TEXT

14 April 2021

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	Verahexal 240 SR	S2	BOT1302329
Namibia	Verahexal 240 SR	NS2	04/7.1/1359
Zimbabwe	Verahexal 240 SR	PP10	2014/12.6/4867

ATC Code: C08DA01 - Phenylalkylamine derivatives

Name and address of manufacturer:

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[1]Company Reg. No.: 1990/001979/07