Pharmacode position may change as per Supplier's m/c requirement & additional small pharma code may appear on the front / back panel

TIDALVOR P1532667

TIDALVOR P1532667

APPROVED
By Berenice Campbell at 12:05 pm, Dec 22, 2022

PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TIDALVOR 5 mg (tablet)
TIDALVOR 20 mg (tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **TIDALVOR 5 mg** film coated tablet contains 5 mg tadalafil. Contains sugar: 52,5 mg lactose monohydrate.
Each **TIDALVOR 20 mg** film coated tablet contains 20 mg tadalafil. Contains sugar: 210,0 mg lactose monohydrate.

Contains sodium.
TIDALVOR contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

TIDALVOR 5 mg:
Light yellow coloured, oval shaped, film-coated tablet debossed with '5' on one side and 'TL' on the other side.

TIDALVOR 20 mg:
Yellow coloured, oval shaped, film-coated tablet debossed with '20' on one side and 'TL' on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TIDALVOR is indicated for the treatment of erectile dysfunction. In order for **TIDALVOR** to be effective, sexual stimulation is required.

4.2. Posology and method of administration

Posology

In adult men:
The recommended dose is 5 mg taken once a day at approximately the same time of day.

The recommended maximum dose of **TIDALVOR** is 20 mg taken prior to anticipated sexual activity and without regard to food.

TIDALVOR 20 mg can be taken up to 36 hours and as early as 16 minutes prior to sexual activity. Patients may initiate sexual activity at varying time points relative to dosing in order to determine their own optimal window of responsiveness.

The maximum recommended dosing frequency of **TIDALVOR** is once per day.

Special populations
Renal impairment
Dosage adjustments are not required in patients with mild or moderate renal impairment. Once-a-day dosing of **TIDALVOR** is not recommended in patients with severe renal impairment.

Paediatric population
TIDALVOR is not indicated for children under the age of 18 years.

Method of administration
For oral use.

4.3. Contraindications

- Hypersensitivity to the active substance, tadalafil, or to any of the excipients of **TIDALVOR** listed in section 6.1.
- Administration of **TIDALVOR** to patients who are using any form of organic nitrate.
- Patients with severe hepatic insufficiency (Child-Pugh Class C).
- Loss of vision in one or both eyes because of non-arteritic anterior ischaemic optic neuropathy (NAION) regardless whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4)
- Previous experience of unilateral or bilateral decrease or loss of hearing with or without associated vestibular symptoms.

4.4. Special warnings and precautions for use

Before treatment with **TIDALVOR**
A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Sexual activity carries a potential cardiac risk for patients with pre-existing cardiovascular disease. Prior to initiating any treatment for erectile dysfunction, medical practitioners should consider the cardiovascular status of their patients. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1) and as such potentiates the hypotensive effect of nitrates (see section 4.3). **TIDALVOR** should not be used in men with cardiac disease for whom sexual activity is inadvisable.

It is not known if tadalafil is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular
Tadalafil has systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing **TIDALVOR**, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects.

In patients who are taking α-1 blockers, concomitant administration of **TIDALVOR** may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

In a clinical pharmacology study of 18 healthy volunteers who received a single dose of tadalafil, no symptomatic hypotension was observed with simultaneous administration of tamsulosin, an α- [1A] blocker (see section 4.5).

The use of **TIDALVOR** is not recommended in the following patients:
- with myocardial infarction within the last 90 days.
- with unstable angina or angina occurring during sexual intercourse.
- with New York Heart Association Class 2 or greater heart failure in the last 6 months.
- with uncontrolled dysrhythmia, hypotension (< 90/50 mm Hg), or uncontrolled hypertension.
- with a stroke within the last 6 months.

Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and should report the episode to their medical practitioner.

Vision
Non-arteritic anterior ischemic optic neuropathy (NAION) is a cause of decreased vision including permanent loss of vision. Visual defects and cases of NAION have been reported in connection with the intake of **TIDALVOR** and other PDE5 inhibitors. Analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to tadalafil, the patient should be advised that in case of sudden visual defect, he should stop taking **TIDALVOR** and consult a medical practitioner immediately (see section 4.3). Medical practitioners should also discuss with patients that individuals who have already experienced NAION are at increased risk of NAION.

Decreased or sudden hearing loss
Cases of sudden hearing loss have been reported after the use of tadalafil. Patients should be advised to stop taking **TIDALVOR** and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events may be accompanied by tinnitus and dizziness.

Renal and hepatic impairment
Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to influence clearance by dialysis, once-a-day dosing of tadalafil is not recommended in patients with severe renal impairment.

Once-a-day administration has not been evaluated in patients with hepatic insufficiency.

Priapism and anatomical deformation of the penis
Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

TIDALVOR should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease) or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Use with CYP3A4 inhibitors
Caution should be exercised when prescribing **TIDALVOR** to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin), as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

TIDALVOR and other treatments for erectile dysfunction
The safety and efficacy of combinations of **TIDALVOR** and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take **TIDALVOR** in such combinations.

Lactose
Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency, glucose-galactose malabsorption should not take **TIDALVOR.**

Sodium
TIDALVOR contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on tadalafil

Cytochrome P450 inhibitors
TIDALVOR is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily), increased tadalafil 20 mg single-dose exposure (AUC) 4-fold and C_{max} by 22 %.

Transporters
The role of transporters (for example, p-glycoprotein) in the disposition of tadalafil is not known. Therefore, there is the potential of medicine interactions mediated by inhibition of transporters.

Cytochrome P450 inducers
A selective CYP3A4 inducer, rifampicin (rifampicin, 600 mg daily), reduced tadalafil single-dose exposure (AUC) by 88 % and C_{max} by 46 %, relative to the AUC and C_{max} values for tadalafil alone. This reduced exposure can be anticipated to decrease the efficacy of tadalafil; the magnitude of decreased efficacy is unknown. It can be expected that concomitant administration of other CYP3A4 inducers, such as phenobarbitone, phenytoin and carbamazepine may also decrease plasma concentrations of tadalafil.

Ritonavir (200 mg twice daily) an inhibitor of CYP3A4, 2C9, 2C19 and 2D6, increased tadalafil single-dose exposure (AUC) by 124 % with no change in C_{max}. Although specific interactions have not been studied, other HIV protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors such as erythromycin and itraconazole, would likely increase tadalafil exposure.

Antacids
Simultaneous administration of an antacid (magnesium hydroxide/aluminium hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil.

H2-antagonists
An increase in gastric pH resulting from administration of nizatidine, an H2 antagonist, had no significant effect on tadalafil pharmacokinetics.

Effects of tadalafil on other medicines
Nitrates
In clinical studies, tadalafil was shown to augment the hypotensive effects of nitrates. Therefore, administration of tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.3).

Anti-hypertensives
Tadalafil has systemic vasodilatory properties and may augment the blood pressure lowering effects of antihypertensive medicines. Additionally, in patients taking multiple antihypertensive medicines whose hypertension was not well controlled, greater reductions in blood pressure were observed. These reductions were not associated with hypotensive symptoms in the vast majority of patients. Appropriate clinical advice should be given to patients when they are treated with antihypertensive medications and tadalafil.

Tadalafil had no clinically significant effect on blood pressure changes due to tamsulosin, an α-adrenergic receptor blocking agent.

The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Some patients experienced dizziness. Therefore, this combination is not recommended (see section 4.4).

CYP1A2 substrates
Tadalafil had no clinically significant effect on the pharmacokinetics or pharmacodynamics of theophylline, a CYP1A2 substrate.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

Alcohol
Tadalafil did not affect alcohol concentrations and alcohol did not affect tadalafil concentrations. At high doses of alcohol (0,7 g/kg), the addition of tadalafil did not induce statistically significant mean blood pressure decreases. In some subjects, postural dizziness and orthostatic hypotension were observed. When tadalafil was administered with lower doses of alcohol (0,6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone.

Cytochrome P450 metabolised medicines
Tadalafil does not inhibit or induce CYP450 isoforms, including CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

CYP2C9 substrates (e.g. R-warfarin)
Tadalafil had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did tadalafil affect changes in prothrombin time induced by warfarin.

Aspirin
Tadalafil did not potentiate the increase in bleeding time caused by aspirin.

Antidiabetic medicinal products
Specific interaction studies with antidiabetic medicinal products were not conducted.

Riociguat
Studies have shown an additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. Riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination. Riociguat should not be used concomitantly with PDE5 inhibitors such as tadalafil.

5-alpha reductase inhibitors
No new adverse reactions were identified when tadalafil was co-administered with finasteride. However, as a formal interaction study evaluating the effects of tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

4.6 Fertility, pregnancy and lactation

TIDALVOR is not indicated for use by women.
Safety and efficacy of **TIDALVOR** in pregnancy and lactation have not been established.

Pregnancy
TIDALVOR should not be used during pregnancy.

Breastfeeding
TIDALVOR should not be used during breastfeeding.

Fertility
Although animal studies indicate impairment of fertility, subsequent clinical studies suggest this is unlikely in humans. A decrease in sperm concentration has however, been seen in some men (see section 5.3).

4.7 Effects on ability to drive and use machines

TIDALVOR has a negligible influence on the ability to drive or use machines. However, there have been reports of dizziness, therefore patients should be aware of how they react to **TIDALVOR** before driving or using machines.

4.8 Undesirable effects

a. Summary of the safety profile
The most commonly reported adverse reactions in patients taking tadalafil for the treatment of erectile dysfunction were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of tadalafil. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with tadalafil once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

b. Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Immune system disorders	Less frequent	Hypersensitivity reactions, Angioedema[2]
Nervous system disorders	Frequent	Headache
	Less frequent	Dizziness, Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures, Transient amnesia
Eye disorders	Less frequent	Blurred vision, Sensations described as eye pain. Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]
Ear and labyrinth disorders	Less frequent	Tinnitus, Sudden hearing loss
Cardiac disorders[1]	Less frequent	Tachycardia, Palpitations, Myocardial infarction, Unstable angina pectoris[2], Ventricular dysrythmia[2]
Vascular disorders	Frequent	Flushing
	Less frequent	Hypotension[3], Hypertension

DETACH BEFORE DISPENSING

You may experience headache, discomfort in your stomach, back or muscle pain and an erection that lasts longer than 4 hours.

If you forget to take TIDALVOR
If you forget to take **TIDALVOR**, take it as soon as you remember. Do not take a double dose to make up for a forgotten dose

4. POSSIBLE SIDE EFFECTS

TIDALVOR can have side effects.
Not all side effects reported for **TIDALVOR** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **TIDALVOR** please consult your doctor, pharmacist or other healthcare provider for advice.
If any of the following happen, stop taking **TIDALVOR** and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Difficulty breathing
- Severe skin rash or itching
- Swollen tongue or lips

These all are very serious side effects. If you have them, you may have had a serious reaction to **TIDALVOR**. You may need urgent medical attention or hospitalisation.
Tell your doctor immediately or got to the casualty department at your nearest hospital if you notice any of the following:
- Chest pain
- An erection that lasts longer than 4 hours
- Sudden loss of vision

These all are serious side effects. You may need urgent medical attention.
Tell your doctor if you notice any of the following:
Frequent side effects:
- Headache
- Reddening of the face (flushing)
- Stuffy nose
- Discomfort in your stomach
- Back pain, pain in your muscles or any part of your body

Less frequent side effects:
- Dizziness
- Loss of consciousness or numbness on one side of the body
- Fainting, severe headache (migraine), sudden memory loss
- Blurred vision or loss of vision, eye pain, swelling of eyelids, redness or itching of the eye
- Ringing in ears, loss of hearing
- Changes in heart rhythm, chest pain or feeling of pressure in chest
- Low or high blood pressure
- Difficulty breathing, nose bleeds
- Stomach pain, nausea, vomiting, heartburn or burning sensation in your throat
- Rash, sweating
- Blood in urine
- Prolonged erections, blood in the sperm or bleeding from the penis
- Chest pain, tiredness, swelling of the legs or face

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", **found** online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of **TIDALVOR.**

5. How to store TIDALVOR

Store at or below 25 °C.
Keep HDPE containers tightly closed.
Keep the blisters in the carton until required for use.
STORE ALL MEDICINES OUT OF REACH OF CHILDREN.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What TIDALVOR contains
The active ingredient is tadalafil.
TIDALVOR 5 mg: Each film-coated tablet contains 5 mg tadalafil and 52,5 mg lactose monohydrate.
TIDALVOR 20 mg: Each film-coated tablet contains 20 mg tadalafil and 210,0 mg lactose monohydrate.
The other ingredients of **TIDALVOR** are cellulose microcrystalline, copovidone, croscarmellose sodium, lactose monohydrate, macrogol, glycerol hydroxystearate, magnesium stearate, opadry yellow 03K82778, opadry yellow 03K82780 and silica colloidal anhydrous.
In addition, opadry yellow 03K82778 and opadry yellow 03K82780 contains hypromellose, iron oxide yellow (C.I. No. 77492), talc, titanium dioxide (C.I. No. 77891) and triacetin.

What TIDALVOR looks like and contents of the pack
TIDALVOR 5 mg:
Light yellow coloured, oval shaped, film-coated tablet debossed with '5' on one side and 'TL' on the other side.

TIDALVOR 20 mg:
Yellow coloured, oval shaped, film-coated tablet debossed with '20' on one side and 'TL' on the other side.

TIDALVOR 5 mg:
Blister Pack:
Tablets are packed in 25 micron PVC film coated with 60 g/m² PVdC as the forming material and 25 micron aluminum foil as the lidding material.
Pack size: 30's – Each carton contains 3 blisters of 10 tablets each.

HDPE Pack:
Tablets are packed in white opaque round 40 ml HDPE container with 33 mm neck finish closed with 33 mm white opaque polypropylene child resistant closure with wad having induction sealing liner.
Pack size: 30's – One HDPE container contains 30 tablets.

TIDALVOR 20 mg:
Blister Pack:
Tablets are packed in 25 micron PVC film coated with 60 g/m² PVdC as the forming material and 25 micron aluminum foil as the lidding material.
Pack size: 2's – Each carton contains 1 blisters of 2 tablets each.
4's – Each carton contains 1 blisters of 4 tablets each.

Holder of Certificate of Registration
AUROGEN SOUTH AFRICA (PTY) LTD
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Registration number
TIDALVOR 5 mg: 49/7.1.5/0992
TIDALVOR 20 mg: 49/7.1.5/0993

This leaflet was last revised in
30 August 2022

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

TIDALVOR 5 mg (tablet)
TIDALVOR 20 mg (tablet)
Tadalafil
(Contains sugar: 52,5 mg and 210,0 mg lactose monohydrate respectively)

Read all of this leaflet carefully before you start taking TIDALVOR.
- Keep this leaflet. You may need to read it again.
- **TIDALVOR** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.

What is in this leaflet

1. What **TIDALVOR** is and what it is used for.
2. What you need to know before you take **TIDALVOR**.
3. How to take **TIDALVOR**.
4. Possible side effects.
5. How to store **TIDALVOR**.
6. Contents of the pack and other information.

1. What TIDALVOR is and what it is used for

TIDALVOR contains the active substance tadalafil.
This belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors.
TIDALVOR is a treatment for men with erectile disfunction. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.
Following sexual stimulation tadalafil works by helping the blood vessels in your penis to relax, allowing the flow of blood into your penis. The result of this is an improved erection. Tadalafil will not help you if you do not have erectile dysfunction. It is important to note that tadalafil for the treatment of erectile dysfunction does not work if there is no sexual stimulation. You and your partner will need to engage in foreplay, just as you would if you were not taking any medicines for erectile dysfunction.

2. What you need to know before you take TIDALVOR

Do not take TIDALVOR:
- If you are hypersensitive (allergic) to tadalafil or any of the other ingredients of **TIDALVOR** (listed in section 6).
- If you are taking any form of a group of medicines called nitrates. These are used in the treatment of angina.
- If you have a serious heart disease or recently had a heart attack within the last 90 days
- If you recently had a stroke within the last 6 months.
- If you have low blood pressure or uncontrolled high blood pressure.
- If you have a severe hepatic (liver) insufficiency (Child-Pugh Class C).
- If you have ever had loss of vision because of a condition called non-arteritic anterior ischemic optic neuropathy (NAION), also described as "stroke of the eye". This may or may not have been connected to taking a medicine like tadalafil.
- If you have previously experienced loss of hearing in one or both ears, with or without symptoms like vertigo and dizziness.

Warnings and precautions
Tell your doctor if you have a history of heart disease. Be aware that sexual activity carries a possible risk to patients with heart disease because it puts an extra strain on your heart.

Take special care with [PRODUCT NAME]:
- If you are taking medicines to control your blood pressure as the dosage of these medicines might have to be adjusted to prevent your blood pressure from dropping too low.
- If you notice any symptoms or feel any discomfort when you begin sexual activity, stop immediately and report the incident to your doctor.
- Let your doctor know immediately if you experience sudden loss of vision or any change in vision
- Let your doctor know immediately if you experience a sudden loss of hearing or decrease in ability to hear. You may experience dizziness and ringing in your ears with this loss of hearing.
- If you have kidney or liver disease
- If you experience prolonged erections (4 hours or more) while taking tadalafil. If this is not treated immediately it can lead to permanent damage and loss of potency.
- If you have any malformations of the penis
- If you suffer from a type of anaemia called sickle cell anaemia or any type of cancer.
- If you are taking other medication for erectile dysfunction as **TIDALVOR** should not be taken with certain other medicines (see section "Other medicines and **TIDALVOR**" below).
- It is not known if **TIDALVOR** is effective in patients who have had:
  - pelvic surgery,
  - removal of all or part of the prostate gland in which nerves of the prostate are cut (radical non-nerve-sparing prostatectomy).

Children and adolescents:
TIDALVOR is not intended for use by children and adolescents under the age of 18.
Other medicines and TIDALVOR:
- Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)
- Please talk to your doctor or pharmacist if you are taking any of the following medicines:
  - Medicines to control your blood pressure
- Ketoconazole, itraconazole (used to treat fungal infections)
- Rifampicin (used to treat tuberculosis)
- Medicines used for the treatment and control of seizures (fits)
- Ritonavir, saquinavir (used in the treatment of HIV/AIDS)
- Antacids (used to neutralise acid in the stomach)

TIDALVOR with food and drink
TIDALVOR may be taken with or without food.
Grapefruit juice may affect how well **TIDALVOR** will work and should be taken with caution.
Drinking alcohol may affect your ability to get an erection and may temporarily lower your blood pressure. If you have taken or are planning to take **TIDALVOR**, avoid excessive drinking (blood alcohol level of 0.08 % or greater), since this may increase the risk of dizziness when standing up.
Pregnancy and breastfeeding:
TIDALVOR is not indicated for use in women.
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking this medicine.
- You should not use this medicine during pregnancy.
- You should not breastfeed while using **TIDALVOR**.

Driving and using machines:
You may experience dizziness while using **TIDALVOR.**
It is not always possible to predict to what extent **TIDALVOR** may interfere with your daily activities of a patient. Dizziness may occur, therefore you should ensure that you do not engage in the above activities until you are aware of the extent to which **TIDALVOR** affects you.
TIDALVOR contains lactose:
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
TIDALVOR contains sodium
TIDALVOR contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take TIDALVOR

- Do not share medicines prescribed for you with any other person.
- Always take **TIDALVOR** exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are not sure.
- The recommended dose is one 5 mg tablet taken once a day at approximately the same time of the day.
- The maximum dose is 20 mg a day.
- You should not use **TIDALVOR** more than once a day.
- **TIDALVOR** 20 mg may be taken up to 36 hours or as early as 16 minutes prior to when you want to engage in sexual activity.
- Swallow the tablet whole with a glass of water.
- If you have the impression that the effect of **TIDALVOR** is too strong or too weak, tell your doctor or pharmacist.

If you take more TIDALVOR than you should
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal congestion
	Less frequent	Dyspnoea, Epistaxis
Gastrointestinal disorders	Frequent	Dyspepsia
	Less frequent	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux
Skin and subcutaneous tissue disorders	Less frequent	Rash, Urticaria,Stevens-Johnson syndrome[2], Exfoliative dermatitis[2], Hyperhydrosis (sweating)
Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain, Myalgia, Pain in extremity
Renal and urinary disorders	Less frequent	Haematuria
Reproductive system and breast disorders	Less frequent	Prolonged erections
		Priapism, Penile haemorrhage, Haematospermia
General disorders and administration site conditions	Less frequent	Chest pain[1], Peripheral oedema, Fatigue, Facial oedema[2], Sudden cardiac death[1,2]

(1) Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).
(2) Post marketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.
(3) More commonly reported when tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse events
A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations
Although there is limited data in patients over 65 years of age, in clinical trials with tadalafil taken on demand for the treatment of erectile dysfunction, diarrhoea was reported more frequently in patients over 65 years of age.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of **TIDALVOR** is important. It allows continued monitoring of the benefit/risk balance of **TIDALVOR.** Healthcare professionals 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

4.9 Overdose
Single doses of up to 500 mg have been given to healthy subjects and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.

In cases of overdose, standard supportive measures should be adopted as required. Haemodialysis contributes negligibly to tadalafil elimination.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacological classification: A 7.1.5 Vasodilators – peripheral

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction ATC code: G04BE08

Mechanism of action
Tadalafil improves impaired erectile function by increasing blood flow to the penis, in response to sexual stimulation.

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Tadalafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects
Studies *in vitro* have shown that tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum.

Additionally, tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. Tadalafil is also > 10 000-fold more potent for PDE5 than for PDE7 through PDE10.

5.2 Pharmacokinetic properties
Absorption
Tadalafil is well absorbed after oral administration and the mean observed plasma concentration (C_{max}) is achieved at a median time of 2 hours after dosing.

The rate and extent of absorption of tadalafil are not influenced by food. Thus, tadalafil may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution
The mean volume of distribution is approximately 63 L. At therapeutic concentrations, 94 % of tadalafil in plasma is bound to proteins. Less than 0,0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation
Tadalafil is predominantly metabolised by the cytochrome P450 CYP3A4 isoform.

The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13 000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination
The mean half-life is 17,5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

Linearity / non-linearity
Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2,5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

Special populations
Elderly
Healthy elderly subjects (65 years or over), had a lower oral clearance of tadalafil, resulting in 25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal impairment
In subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment, tadalafil exposure (AUC) was higher than in healthy subjects. In subjects with renal insufficiency, including those on haemodialysis, tadalafil exposure AUC was higher than in healthy subjects.

Hepatic impairment
Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects. No dose adjustment is required in these patients. No data are available in patients with severe hepatic impairment (Child-Pugh Class C).

Patients with diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
TIDALVOR contains the following inactive ingredients:
Cellulose microcrystalline, copovidone, croscarmellose sodium, lactose monohydrate, macrogol, glycerol hydroxystearate, magnesium stearate, opadry yellow 03K82778, opadry yellow 03K82780 and silica colloidal anhydrous.

Composition of opadry yellow 03K82778 and opadry yellow 03K82780:
Hypromellose, iron oxide yellow (C.I. No. 77492), talc, titanium dioxide (C.I. No. 77891) and triacetin

6.2 Incompatibilities
Not applicable

6.3 Shelf life
4 years

6.4 Special precautions for storage
Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.
Keep HDPE containers tightly closed.
Keep the blisters in the carton until required for use.

6.5 Nature and contents of container
TIDALVOR 5 mg:
1) Blister Pack:
Tablets are packed in 25-micron PVC film coated with 60 g/m^2 PVdC as the forming material and 25-micron aluminum foil as the lidding material.

Pack size: 30's – Each carton contains 3 blisters of 10 tablets each.

2) HDPE Pack:
Tablets are packed in white opaque round 40 ml HDPE container with 33 mm neck finish closed with 33 mm white opaque polypropylene child resistant closure with wad having induction sealing liner.

Pack size: 30's – One HDPE container contains 30 tablets.

TIDALVOR 20 mg:
1) Blister Pack:
Tablets are packed in 25-micron PVC film coated with 60 g/m^2 PVdC as the forming material and 25-micron aluminum foil as the lidding material.

Pack size: 2's – Each carton contains 1 blister of 2 tablets each.
4's – Each carton contains 1 blister of 4 tablets each.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
AUROGEN SOUTH AFRICA (PTY) LTD
Woodhill Office Park, Building 1, First floor
53 Phillip Engelbrecht Avenue
Meyersdal Ext 12, 1448
Johannesburg, South Africa

8 REGISTRATION NUMBER
TIDALVOR 5 mg: 49/7.1.5/0992
TIDALVOR 20 mg: 49/7.1.5/0993

9 DATE OF FIRST AUTHORISATION
30 August 2022

P1532667

DETACH BEFORE DISPENSING

PASIËNTINLIGTINGSBLAD

SKEDULERINGSTATUS
S4

TIDALVOR 5 mg (tablet)
TIDALVOR 20 mg (tablet)
Tadalafiel
(Bevat suiker: 52,5 mg en 210,0 mg laktosemonohidraat onderskeidelik)

Lees hierdie inligtingsblad noukeurig deur voordat jy begin om TIDALVOR te neem.
- Hou hierdie inligtingsblad. Dit mag nodig wees om dit later weer te lees.
- **TIDALVOR** is vir jou persoonlik voorgeskryf en jy moenie jou medisyne met ander persone deel nie. Dit kan skadelik wees vir hulle, al is hulle simptome dieselfde as joune.
- Indien jy enige verdere vrae het, vra asseblief jou dokter, apteker, verpleegkundige of ander gesondheidsorgverskaffer.

Wat is in hierdie inligtingsblad
1. Wat is **TIDALVOR** en waarvoor word dit gebruik.
2. Wat jy moet weet voordat jy **TIDALVOR** neem.
3. Hoe om **TIDALVOR** te neem.
4. Moontlike newe-effekte.
5. Hoe om **TIDALVOR** te berg.
6. Inhoud van die verpakking en ander inligting.

1. Wat is TIDALVOR en waarvoor word dit gebruik
TIDALVOR bevat die aktiewe bestanddeel tadalafiel.
Dit behoort aan die groep medisynes genaamd fosfodiësterase tipe 5-remmers (PDE 5-inhibitors).
TIDALVOR is 'n behandeling vir mans met erektiele disfunksie. Dit is wanneer 'n man se penis nie styf genoeg word of bly om geskik te wees vir seksuele aktiwiteit nie.
Tadalafiel werk deur die bloedvate in jou penis te verslap wanneer jy seksueel geprikkel word, wat toelaat dat bloed in die penis invloei. Dit lei tot 'n verbeterde ereksie. Tadalafiel sal nie jou help indien jy nie erektiele disfunksie het nie. Dit is belangrik om kennis te neem dat tadalafiel vir die behandeling van erektiele disfunksie nie werk indien daar geen seksuele stimulasie is nie. Dit is nodig dat jy en jou maat deelneem aan voorspel, net soos julle sou doen indien jy nie enige medisyne vir erektiele disfunksie geneem het nie.

2. Wat jy moet weet voordat jy TIDALVOR neem
Moenie TIDALVOR neem nie:
- Indien jy hipersensitief (allergies) vir tadalafiel of vir enige van die ander bestanddele van **TIDALVOR** is (gelys by afdeling 6).
- Indien jy medisyne in enige vorm neem wat uit die groep kom wat nitrate genoem word. Dit word gebruik vir die behandeling van angina.
- Indien jy 'n ernstige hartsiekte het of in die afgelope 90 dae 'n hartaanval gehad het.
- Indien jy in die afgelope 6 maande 'n beroerte gehad het.
- Indien jy lae bloeddruk of ongekontroleerde hoë bloeddruk het.
- Indien jy erge hepatiese (lewer) ontoereikendheid het (Child-Pugh Klas C).
- Indien jy al ooit sigverlies ondervind het weens 'n oogtoestand bekend as nie-arteriitiese anterior iskemiese optiese neuropatie (NAION), wat ook beskryf word as 'n beroerte in die oog. Dit mag of mag nie verband hou met die neem van 'n medisyne soos tadalafiel nie.
- Indien jy in die verlede gehoorverlies in een of albei ore ondervind het, met of sonder simptome soos draaiduiseling en duiseligheid.

Waarskuwings en voorsorgmaatreëls
Sê vir jou dokter indien jy 'n geskiedenis van hartsiekte het. Wees bewus daarvan dat seksuele aktiwiteit 'n moontlike risiko inhou vir pasiënte met hartsiekte omdat dit bykomende spanning op die hart plaas.

Neem spesiale sorg met TIDALVOR:
- Indien jy medisynes neem om jou bloeddruk te beheer, aangesien die dosis van hierdie medisynes dalk aangepas moet word om te keer dat jou bloeddruk te laag val.
- Indien jy enige simptome opmerk of enige ongemak ervaar wanneer jy betrokke raak by seksuele aktiwiteit, stop onmiddellik en meld die insident by jou dokter aan.
- Laat dadelik jou dokter weet indien jy skielik sigverlies ervaar of daar enige verandering in jou visie plaasvind.
- Laat dadelik jou dokter weet indien jy skielik gehoorverlies of belemmerde gehoor ondervind. Saam met die gehoorverlies kan jy duiseligheid en of 'n gesuis in jou ore ervaar.
- Indien jy nier- of lewersiekte het.
- Indien jy langdurige ereksies (4 uur of meer) ondervind wanneer jy tadalafiel geneem het. Indien dit nie onmiddellik behandel word nie, kan dit permanente skade of 'n verlies aan potensie veroorsaak.
- Indien jou penis misvorm is.
- Indien jy aan 'n tipe bloedarmoede genaamd sekelselanemie, of enige soort kanker het.
- Indien jy ander medikasie vir erektiele disfunksie neem, aangesien **TIDALVOR** nie saam met sekere ander medisynes geneem mag word nie (sien afdeling "Ander medisynes en **TIDALVOR**" hier onder).
- Dit is onbekend of **TIDALVOR** doeltreffend is by pasiënte wat die volgende gehad het:
  - bekkenchirurgie.
  - verwydering van die hele of dele van die prostaatklier waar senuwees van die prostaat gesny word (radikale niesenuweesparende prostatektomie).

Kinders en adolessente:
TIDALVOR is nie bedoel vir gebruik deur kinders en adolessente jonger as 18 jaar nie.

Ander medisynes en TIDALVOR:
Sê altyd vir jou gesondheidsorgdeskundige indien jy enige ander medisyne neem. (Dit sluit komplementêre of tradisionele medisynes in.)
Bespreek dit asseblief met jou dokter of apteker indien jy enige van die volgende medisynes neem:
- Medisynes om jou bloeddruk te beheer
- Ketokonasool, itrakonasool (gebruik om swaminfeksies te behandel)
- Rifampisien (gebruik om tuberkulose te behandel)
- Medisynes wat gebruik word vir die behandeling en beheer van toevalle (stuipe)
- Ritonavir, sakinavir (gebruik vir die behandeling van MIV/vigs)
- Teensuurmiddels (gebruik om suur in die maag te neutraliseer).

TIDALVOR met kos en drinkgoed
TIDALVOR kan met of sonder kos geneem word.
Pomelosap kan die doeltreffendheid van **TIDALVOR** affekteer en moet versigtig geneem word.
Wanneer jy alkohol drink, kan dit jou vermoë om 'n ereksie te kry belemmer en kan jou bloeddruk tydelik verlaag. Indien jy **TIDALVOR** geneem het of van plan is om dit te neem, vermy die oormatige inname van alkohol (bloedalkoholvlak van 0,08 % of meer), want dit kan die risiko vergroot dat jy duiseling raak wanneer jy opstaan.

Swangerskap en borsvoeding:
TIDALVOR word nie vir gebruik by vrouens aangedui nie.
Indien jy swanger is of jou baba borsvoed, vermoed dat jy swanger mag wees of beplan om swanger te raak, raadpleeg asseblief jou dokter, apteker of gesondheidsorgverskaffer voordat jy hierdie medisyne neem.
- Jy moenie hierdie medisyne neem terwyl jy swanger is nie.
- Jy moenie borsvoed terwyl jy **TIDALVOR** gebruik nie.

Bestuur en gebruik van masjiene:
Jy kan duiseligheid ervaar terwyl jy **TIDALVOR** gebruik.
Dit is nie altyd moontlik om te voorspel tot watter mate **TIDALVOR** met jou daaglikse aktiwiteite mag inmeng nie. Duiseligheid kan voorkom, daarom moet jy seker maak dat jy nie bogenoemde aktiwiteite uitvoer nie, totdat jy weet tot watter mate **TIDALVOR** jou affekteer.

TIDALVOR bevat laktose:
Indien jou dokter jou ingelig het dat jy onverdraagsaam vir sekere suikers is, praat met jou dokter voordat jy hierdie medisyne neem.

TIDALVOR bevat natrium:
TIDALVOR bevat minder as 1 mmol (23 mg) natrium per dosis, dit is wesenlik natriumvry.

3. Hoe om TIDALVOR te neem
- Moenie medisynes wat vir jou voorgeskryf is, met enigiemand anders deel nie.
- Neem **TIDALVOR** altyd presies soos wat jou dokter vir jou gesê het. Vra genus jou dokter of apteker indien jy onseker is.
- Die aanbevole dosis is een 5 mg tablet een keer per dag op nagenoeg dieselfde tyd elke dag geneem.
- Die maksimum dosis is 20 mg per dag.
- Jy behoort nie **TIDALVOR** meer as een keer per dag te gebruik nie.
- **TIDALVOR** 20 mg kan tot soveel as 36 uur voor of so min as 16 minute voordat jy seksuele aktief wil wees, geneem word.
- Sluk die tablet heel in met 'n glas water.
- Indien jy die indruk kry dat die uitwerking van **TIDALVOR** te sterk of te swak is, bespreek dit met jou dokter of apteker.

AUROBINDO Packaging Development	Product Name: TIDALVOR 5 mg & 20 mg (tablet)	Component: Leaflet	Item Code: P1532667	Date & Time: 21.12.2022 & 12:57 PM
	Customer / Country: South Africa	Version No.: 02	Reason of Issue: New	No. of Colours : 1 — Black
Team Leader: Bhogeswara Rao	Dimensions: 360 x 480 mm	Font Type: Helvetica	Font Size: 6 pt	
Initiator: Krishna P				
Design Agency: vakils PREMEDIA	Pharmacode: 32667			

Date - Designer - Run:
1. 14-DEC-2022 (Vikas) - FR
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4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20.

Additional Information: NA

Reviewed / Approved by

Sign / Date