Approved Package Insert

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ZELDINA 25 mg Chewable Tablets

ZELDINA 50 mg Chewable Tablets

ZELDINA 100 mg Chewable Tablets

COMPOSITION

ZELDINA 25 mg: Each chewable tablet contains sildenafil citrate present as 25 mg sildenafil.

ZELDINA 50 mg: Each chewable tablet contains sildenafil citrate present as 50 mg sildenafil.

ZELDINA 100 mg: Each chewable tablet contains sildenafil citrate present as 100 mg sildenafil.

ZELDINA chewable tablets contain the following inactive ingredients:

Polacrilin potassium, silica colloidal anhydrous, lactose monohydrate, povidone K-30, aspartame (E951), croscarmellose sodium, peppermint flavor and magnesium stearate.

Contains sugar (lactose monohydrate)

Contains sweetener (aspartame)

PHARMACOLOGICAL CLASSIFICATION

A 7.1.5 Vasodilators – peripheral

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

ZELDINA restores impaired erectile function by increasing blood flow to the penis in response to sexual stimulation.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Pharmacokinetic properties

Absorption:

Sildenafil is well absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41 % (range 25-63 %). The oral pharmacokinetics of sildenafil is proportional over the recommended dose range (25-100 mg).

When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in Tmax of 60 minutes and a mean reduction in Cmax of 29 %.

Distribution:

The mean steady state volume of distribution (Voss) for sildenafil is 105 litres, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/ml (CV 40 %). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96 % bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil tablets (100 mg single dose), less than 0,0002 % (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Metabolism:

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil.

This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50 % that of the parent substance. Plasma

concentrations of this metabolite are approximately 40 % of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half-life of approximately 4 hours.

Elimination:

The total body clearance of sildenafil is 41 ℓ/hour with a resultant terminal phase half-life of 3-5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80 % of administered oral dose) and to a lesser extent in the urine (approximately 13 % of administered oral dose).

Pharmacokinetics in special patient groups

Elderly:

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90 % higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40 %.

Renal insufficiency:

In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 mℓ/min), the pharmacokinetics of sildenafil were not altered after receiving a 50 mg single oral dose. The mean AUC and Cmax of the N-desmethyl metabolite increased 126 % and 73 % respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance

<30 mℓ/min), sildenafil clearance was reduced, resulting in mean increases in AUC and Cmax of 100 % and 88 % respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased 79 % and 200 % respectively.

Hepatic insufficiency:

In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84 %) and Cmax (47 %) compared to age-matched volunteers with no hepatic impairment.

INDICATIONS

ZELDINA is indicated only for the treatment of erectile dysfunction.

ZELDINA IS NOT AN APHRODISIAC

CONTRA-INDICATIONS

- **Hypersensitivity to sildenafil or to any of the excipients.**
- **Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see Pharmacological action), ZELDINA was shown to potentiate the hypotensive effects of acute or chronic nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form either regularly or intermittently is therefore contraindicated.**
- **Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with**

severe cardiovascular disorders such as unstable angina or severe cardiac failure).

- **ZELDINA is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see Warnings and Special Precautions).**
- **Severe hepatic impairment (e.g. cirrhosis).**
- **Severe renal impairment (e.g. creatinine clearance below 30 mℓ/min).**
- **Concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. erythromycin, ritonavir, saquinavir, ketoconazole, itraconazole).**

WARNINGS AND SPECIAL PRECAUTIONS

There is a potential for cardiac risk of sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including ZELDINA, should not be generally used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure) because of their underlying cardiovascular status.

- A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.
- Prior to initiating any treatment for erectile dysfunction, medical practitioners should consider the cardiovascular status of their patients, since there is a degree of

cardiac risk associated with sexual activity. Medical practitioners should discuss with their patients the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular risk factors. Patients who experience symptoms (e.g. angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their medical practitioner.

- Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (such as aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.
- Concomitant administration of **ZELDINA** to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals (see Interactions). In order to minimize the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating **ZELDINA** treatment. Doctors should advise patients what to do in the event of postural hypotensive symptoms.
- Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure. Prior to prescribing **ZELDINA**, medical practitioners should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilator effects, especially in combination with sexual activity.
- The safety and efficacy of combinations of **ZELDINA** with other treatments for erectile dysfunction has not been studied. Therefore the use of such combinations is not recommended

- Medicines for the treatment of erectile dysfunction, including **ZELDINA**, 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).
- Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy have been reported in connection with the intake of **ZELDINA** and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking **ZELDINA** and consult a medical practitioner immediately.
- Studies with human platelets indicate that **ZELDINA** potentiates the antiaggregatory effect of sodium nitroprusside in vitro. There is no safety information on the administration of **ZELDINA** to patients with bleeding disorders or active peptic ulceration. Therefore **ZELDINA** should be administered to these patients with caution.
- Medical practitioners should discuss with their patients that use of **ZELDINA** offers no protection against sexually transmitted diseases. Counselling of patients about protective measures necessary to guard against sexually transmitted diseases, including the human immunodeficiency virus (HIV/AIDS) should be considered. Precautions against unwanted pregnancy should be taken.
- Medical practitioners should discuss with patients the contraindication of **ZELDINA** with regular and/or intermittent use of organic nitrates.
- Medical practitioners should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been

reported infrequently with **ZELDINA.** In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may occur.

- Non arteritic anterior ischaemic optic neuropathy (NAION) with some loss of vision or irreversible blindness has been reported with the use of the selective phosphodiesterase type-5 inhibitors including sildenafil (contained in **ZELDINA**). NAION appears to be a class effect of these medicines. Most of these patients had risk factors such as low cup to disk ratio ("crowded disk"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidaemia and smoking. **ZELDINA** should not be given to these patients.
- The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contra-indicated: severe hepatic impairment, hypotension (blood pressure below 90 /50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular dysrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of **ZELDINA**.

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered. In addition, medical practitioners should advise patients what to do in the event of postural hypotensive symptoms.

Reports of a sudden unilateral or bilateral decrease or loss of hearing (sensorineural deafness) with or without associated vestibular symptoms with the use of PDE5 inhibitors, including **ZELDINA**. There is insufficient information regarding the reversibility of the hearing loss and the role of underlying risk factors for hearing loss in individual subjects.

ZELDINA chewable tablets contain lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

ZELDINA chewable tablets also contain aspartame which is a source of phenylalanine and should be used with caution in patients with phenylketonuria.

Effects on ability to drive and use machines

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to **ZELDINA**, before driving or operating machinery.

INTERACTIONS

In vivo studies

- A 100 mg single dose of sildenafil co-administered with erythromycin 500 mg twice daily, resulted in a 182 % increase in sildenafil systemic exposure (AUC) at steady state. However with co-administration of sildenafil with azithromycin (500 mg daily for three days), no evidence was found of an effect on the AUC or other kinetic parameters of sildenafil.
- Co-administration of a 100 mg single dose of sildenafil with saquinavir (1200 mg three times daily) or ritonavir (500 mg twice daily) resulted respectively in a 210 % and 1000 % increase in the AUC of sildenafil. (Sildenafil had no effect on either the saquinavir or ritonavir pharmacokinetics). Co-administration of a 100 mg single dose of sildenafil with saquinavir (1200 mg three times daily) or ritonavir (500 mg twice daily) resulted respectively in a 210 % and 1000 % increase in the AUC of sildenafil. (Sildenafil had no effect on either the saquinavir or ritonavir pharmacokinetics).

Effects of other medicinal products on ZELDINA

- Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.
- Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56 % increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers.
- Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bio-availability of **ZELDINA.**

- Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300 % (4-fold) increase in sildenafil Cmax and a 1000 % (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/ml, compared to approximately 5 ng/ml when sildenafil was administered alone. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised and in any event the maximum dose of sildenafil should under no circumstances exceed 25 mg within 48 hours.
- A 100 mg single dose of sildenafil co-administered with erythromycin 500 mg twice daily, resulted in a 182 % increase in sildenafil systemic exposure (AUC) at steady state. However with co-administration of sildenafil with azithromycin (500 mg daily for three days), no evidence was found of an effect on the AUC or other kinetic parameters of sildenafil.
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- Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.

- Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

  Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil.

Effects of ZELDINA on other medicinal products

- Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 > 150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that **ZELDINA** will alter the clearance of substrates of these is enzymes.
- No significant interactions were shown when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.
- There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.
- Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated.

- Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).
- Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dℓ.
- In a specific interaction study, where sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg.
- Symptomatic hypotension may occur when **ZELDINA** is administered concomitantly with alpha blockers (see Warnings and special precautions).

PREGNANCY AND LACTATION

ZELDINA is not indicated for use by women.

No teratogenic effects, impairment of fertility or relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil**.**

There was no effect on sperm motility or morphology after single 100 mg oral doses of **ZELDINA** in healthy volunteers.

DOSAGE AND DIRECTIONS FOR USE

ZELDINA chewable tablets are for oral administration. The tablets should be chewed before swallowed.

Use in adults:

The recommended dose is 50 mg, taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If **ZELDINA** is taken with food, the onset of activity may be delayed compared to the fasted state.

Use in patients with mild to moderately impaired renal function

A starting dose of 25 mg should not be exceeded.

Use in patients with mild to moderately impaired hepatic function

Since **ZELDINA** clearance is reduced in patients with hepatic impairment, a starting dose of 25 mg should not be exceeded.

Use in children and adolescents:

ZELDINA is not indicated for individuals below 18 years of age.

SIDE EFFECTS

Infections and Infestations

Frequent: Flu syndrome

Less frequent: Respiratory tract infection, herpes simplex, pharyngitis, bronchitis, sinusitis, urinary tract infection, laryngitis

Blood and Lymphatic system disorders

Less frequent: Anaemia, leucopenia

Immune system disorders

Less frequent: Allergic reaction

Metabolic and nutrition disorders

Less frequent: Unstable diabetes, hyperglycaemia, hypernatraemia, gout, hyperuricaemia, hypoglycaemic reaction

Psychiatric disorders:

Less frequent: Insomnia, depression, abnormal dreams, anorgasmia

Nervous system disorders

Frequent: Headache, dizziness

Less frequent: Somnolence, hypoaesthesia, cerebro-vascular accident, syncope, hypertonia, paraesthesia, ataxia, neuropathy, vertigo, migraine, tremor, reflexes decreased, neuralgia

Frequency unknown: Transient ischaemic attack, seizure, seizure recurrence

Eye disorders

Frequent: Visual disorders, visual colour distortion, abnormal vision (increased perception of light, blurred vision) chromatopsia (mild and transient, predominantly colour tinge to vision)

Less frequent: Conjunctival disorders, eye disorders, lacrimation disorders, other eye disorders, conjunctivitis, photophobia, dry eyes, eye haemorrhage, eye pain, cataract

Frequency unknown: Non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion, visual field defect

Ear and labyrinth disorders

Less frequent: Vertigo, tinnitus, deafness, ear pain

Cardiac disorders

Frequent: Palpitations

Less frequent: Tachycardia, myocardial infarction, atrial fibrillation, angina pectoris, AV block, cardiac arrest, heart failure, cardiomyopathy

Frequency unknown: Ventricular dysrhythmia, unstable angina, sudden cardiac death

Vascular disorders

Frequent: Flushing (vasodilation)

Less frequent: hypertension, hypotension, epistaxis, shock, postural hypotension

Respiratory, thoracic and mediastinal disorders

Frequent: Nasal congestion (rhinitis)

Less frequent: Epistaxis, respiratory disorder, dyspnoea, asthma, increased cough, increased sputum

Gastro-intestinal disorders

Frequent: Dyspepsia

Less frequent: Nausea, vomiting, diarrhoea, dry mouth, abdominal pain, gastritis, gastroenteritis, gingivitis, rectal haemorrhage, glossitis, oesphagitis, colitis, dysphagia, stomatitis

Skin and subcutaneous tissue disorders

Less frequent: Skin rash, sweating, skin ulcer, pruritus, face oedema, exfoliative dermatitis, photosensitivity reaction, urticaria, contact dermatitis

Frequency unknown: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders

Less frequent: Myalgia, sweating, skin ulcer, pruritus, face oedema, exfoliative dermatitis, photosensitivity reaction, urticaria, contact dermatitis

Reproductive system and breast disorders

Less frequent: Abnormal ejaculation, prostatic disorder, breast enlargement, genital oedema

Frequency unknown: Priapism, prolonged erection

General disorders and administration site conditions

Less frequent: Chest pain, fatigue, asthenia, pain, thirst, chills, oedema, peripheral oedema

Investigations

Less frequent: Increased heart rate, abnormal electrocardiogram, abnormal liver function tests

Injury poisoning and poisoning

Less frequent: Accidental injury/fall

The following side effects have been reported post marketing:

Immune system disorders: Hypersensitivity reactions (including skin rashes)

Nervous system disorders: Seizure, seizure recurrence

Eye disorders: Red eyes/ bloodshot eyes, Non arteritic anterior ischaemic optic neuropathy with some loss of vision or irreversible blindness, diplopia, temporary vision loss/decreased vision, ocular burning, ocular swelling/ pressure, increased intra-ocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular oedema

Cardiac disorders: Myocardial infarction, sudden cardiac death, ventricular dysrhythmia

Vascular disorders: Hypotensive events after the use of sildenafil in combination with alpha blockers, syncope, cerebrovascular haemorrhage, transient ischaemic attack, hypertension

Reproductive system and breast disorders: Prolonged erection, priapism

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In studies with healthy volunteers of single doses up to 800 mg, with sildenafil tablets, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.

In cases of overdose, standard supportive measures and symptomatic treatment should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

IDENTIFICATION

ZELDINA 25 mg:

White, triangular, biconvex tablet, embossed with “25” on one side.

ZELDINA 50 mg:

White, triangular, biconvex tablet, embossed with “50” on one side

ZELDINA 100 mg:

White, triangular, biconvex tablet, embossed with “100” on one side.

PRESENTATION

ZELDINA chewable tablets are packed in transparent PVC/PCTFE aluminium foil blisters containing 1, 2, 4, 8 or 12 chewable tablets, packed in a cardboard carton. Not all pack sizes may be marketed at any one time.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Store in the original packaging to protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ZELDINA 25 mg: 46/7.1.5/0801

ZELDINA 50 mg: 46/7.1.5/0802

ZELDINA 100 mg: 46/7.1.5/0803

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

Date on the registration certificate of the medicine: 20 April 2017

Date of revision: 11 May 2022