SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

EDRONAX® 4 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains reboxetine methanesulphonate equivalent to 4 mg reboxetine free base.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

A white, round, convex, 8 mm diameter tablet with a breakline on one side. A “P” is marked on the left side of the breakline. A “U” is marked on the right side of the breakline. The side opposite the breakline is marked “7671”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EDRONAX is indicated for the acute treatment of depressive illness/major depression.

4.2 Posology and method of administration

Posology

Use in adults

The recommended therapeutic dose of EDRONAX is 4 mg twice daily (8 mg/day) administered orally.

The full therapeutic dose can be given upon starting treatment. After 3 - 4 weeks, this dose can be

increased to 10 mg/day in case of incomplete clinical response.

Special populations

Use in the elderly (> 65 years)

In elderly depressed patients, particularly in the presence of concomitant systemic illnesses and medicines, the recommended therapeutic dose of EDRONAX is 2 mg twice daily (4 mg/day) administered orally. This dose can be increased to 6 mg/day in case of incomplete clinical response after 3 weeks from starting EDRONAX.

Use in patients with renal or hepatic insufficiency

The dose of EDRONAX in patients with renal insufficiency or moderate to severe hepatic insufficiency should be 2 mg twice daily (4 mg/day).

Paediatric population

The use of EDRONAX in patients less than 18 years of age is not recommended, since safety and efficacy have not been established (see section 4.3 and section 4.4).

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to reboxetine or to any of the excipients of EDRONAX (listed in section 6.1)
- Seizure disorders
- Pregnancy and lactation (see section 4.6)
- Use in children and adolescents under 18 years of age (see sections 4.2 and 4.4)
- Concomitant administration with CYP3A4 inhibitors, e.g. ketoconazole, erythromycin, troleandomycin, fluconazole, itraconazole and grapefruit juice

4.4 Special warnings and precautions for use

Plasma levels and half-lives of EDRONAX increase in subjects with renal impairment, especially in severe renal impairment (CL_{CR} < 20 mL/min) where a dose adjustment is required. Similar findings were apparent in elderly subjects and patients with hepatic insufficiency.

Combined usage of monoamine oxidase (MAO) inhibitors (including linezolid [an antibiotic which is a reversible non-selective MOA inhibitor] and methylene blue) and EDRONAX should be avoided until further data are available (see section 4.5).

Switches to mania/hypomania have occurred during the clinical studies. Close supervision of bipolar patients is therefore recommended.

Clinical experience with EDRONAX in patients affected by serious concomitant systemic illnesses is limited. Close supervision should be applied in patients with current evidence of benign prostatic hyperplasia, urinary retention and glaucoma.

Orthostatic hypotension has been observed. Particular attention should be paid when administering EDRONAX with other medicines known to lower blood pressure.

Mydriasis has been reported in association with EDRONAX. Therefore, caution should be used when prescribing EDRONAX to patients with increased intraocular pressure or those at risk of acute narrow-angle glaucoma.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs.

Close supervision of patients and in particular those at high risk should accompany medicine therapy

especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Clinical experience with EDRONAX in the long-term treatment of elderly patients is limited. Lowering of mean potassium levels was found starting from week 14; the magnitude of this reduction did not exceed 0,8 mmol/L and potassium levels never dropped below normal limits.

Use in children and adolescents under 18 years of age

EDRONAX should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking.

Use in young adults (18 – 25 years of age)

In additional analysis of pooled data currently available, antidepressants showed an increased risk of suicidal thinking and behaviour when compared to placebo in young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders.

4.5 Interaction with other medicines and other forms of interaction

EDRONAX is extensively bound to plasma proteins; the available data indicate that the medicine is almost exclusively bound to α_1 acid glycoprotein. Therefore, the concurrent administration of medicines with a high affinity for this fraction of plasma proteins (such as dipyridamole, propranolol, alprenolol, methadone, lidocaine and other local anaesthetics, but also imipramine and chlorpromazine) may cause a shift in plasma concentration of either medicine, potentially resulting in an adverse reaction.

Plasma pharmacokinetics of EDRONAX are not significantly modified when cytochrome P450 2D6 activity is blocked. Therefore, no modification of EDRONAX metabolism is expected in poor metabolisers with deficiency of this isoenzyme.

In vitro studies have shown that EDRONAX does not inhibit the activity of the following cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19 and CYP2E1. At high concentrations, EDRONAX inhibits CYP2D6, but the clinical significance of this observation is unknown. *In vitro* studies show that EDRONAX is a very weak inhibitor of CYP3A4.

In vitro metabolism studies indicate that EDRONAX is primarily metabolised by the CYP3A4 isoenzyme. Therefore, medicines that decrease the activity of CYP3A4 would be expected to increase plasma concentrations of EDRONAX.

In a study in healthy volunteers, ketoconazole, a potent inhibitor of CYP3A4, was found to increase plasma concentrations of EDRONAX enantiomers by approximately 50 %.

Low EDRONAX serum levels have been reported with the concurrent administration of CYP3A4 inducers such as phenobarbital and carbamazepine.

No significant reciprocal pharmacokinetic interaction has been found between EDRONAX and lorazepam. During their co-administration in healthy volunteers, mild to moderate drowsiness and short-lasting orthostatic acceleration of heart rate have been observed.

EDRONAX does not appear to potentiate the effect of alcohol on cognitive functions in healthy volunteers.

Concomitant use of EDRONAX with other antidepressants (tricyclics, MAO inhibitors, SSRIs and lithium) has not been evaluated during clinical studies, however, in an *in vivo* multiple dose study performed in healthy volunteers, no clinically significant interaction between fluoxetine and

EDRONAX was observed.

The extent of absorption of EDRONAX is not significantly influenced by concomitant food intake.

The possibility of hypokalaemia with concomitant use of potassium losing diuretics should be considered. Hyponatraemia, possibly due to syndrome of inappropriate ADH secretion may occur.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of EDRONAX during pregnancy and lactation is contraindicated (see section 4.3).

No clinical trial data on exposure to EDRONAX during pregnancy are available.

Breastfeeding

EDRONAX is excreted in breast milk. The use of EDRONAX during breastfeeding is contraindicated (see section 4.3).

Fertility

There is no clinical trial data on fertility.

4.7 Effects on ability to drive and use machines

Patients should be cautioned about operating machinery and driving during treatment. EDRONAX may cause dizziness. Patients experiencing dizziness should avoid driving and use of machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions that occurred in clinical trials were insomnia, dizziness, hyperhidrosis, constipation and dry mouth, occurring in >10 % of patients. The most serious adverse reactions are akathisia, hyponatraemia and suicide ideation/behaviour.

Tabulated summary of adverse reactions

Side effects reported from clinical trials and post-marketing experience are included in the tables below and categorised as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

MedDRA System organ class	**Frequency**	**Undesirable effects**
Infections and infestations	Common	Urinary tract infection
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Very common	Insomnia
Nervous system disorders	Very common	Dizziness
	Common	Paraesthesia, akathisia, dysgeusia
Eye disorders	Common	Accommodation disorder
	Uncommon	Mydriasis
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Tachycardia, palpitations
Vascular disorders	Common	Hypotension, vasodilatation
Gastrointestinal disorders	Very common	Constipation, dry mouth
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis

Renal and urinary disorders	Common	Urinary hesitancy/retention, dysuria
Reproductive system and breast disorders	Common	Ejaculation disorder, erectile dysfunction
General disorders and administration site conditions	Common	Chills

Post-marketing surveillance

The following post-marketing events have been reported with EDRONAX:

System organ class	**Undesirable effects**
Metabolism and nutrition disorders	Hyponatraemia
Psychiatric disorders	Agitation, anxiety, hallucinations, Suicide ideation/behaviour
Eye disorders	Increased intraocular pressure
Nervous system disorders	Paraesthesia
Vascular disorders	Hypertension, peripheral coldness, Raynaud's phenomenon
Gastrointestinal disorders	Nausea, vomiting
Skin and subcutaneous tissue disorders	Allergic dermatitis
Reproductive system and breast disorders	Testicular pain
General disorders and administration site conditions	Irritability

Adverse events following discontinuation occurred in approximately 5 % of the EDRONAX-treated patients.

Vital signs, including blood pressure and heart rate, body weight and temperature, were evaluated in the majority of EDRONAX-treated patients, and the only modification observed was related to heart rate, particularly on standing, significantly increased vs baseline (> 20 %, to values ≥ 100 beats/min) mainly in adult patients (20 % of the patients on short-term treatment and 23 % of the patients on long-term treatment).

Apart from tachycardia in a minority of cases, no consistent changes of ECG tracings were observed during EDRONAX treatment in adult patients. Similarly, no consistent changes were observed at the ophthalmological examination, carried out upon long-term treatment. In the elderly population, newly observed rhythm disorders (mainly tachycardia) and conduction disorders were apparent at ECG in a minority of cases.

Abnormal laboratory test values have been uncommon during EDRONAX therapy.

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

4.9 Overdose

Signs of overdose include postural hypotension, anxiety and hypertension. In case of overdose, monitoring of cardiac function and vital signs is recommended. General symptomatic supportive and/or emetic measures might be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Central nervous system stimulants: Psychoanaleptics (antidepressants).

Reboxetine is a selective norepinephrine re-uptake inhibitor (NRI). *In vitro* studies have shown that reboxetine is a weak inhibitor of serotonin, lacks dopamine activity, and has no significant affinity for adrenergic, histaminergic or cholinergic receptors. By inhibiting norepinephrine re-uptake, reboxetine causes an acute increase of synaptic concentrations of norepinephrine, followed by a down-regulation and desensitisation of β- and α_2- receptors, coupled with an increase in responsiveness of postsynaptic α_1- receptors.

5.2 Pharmacokinetic properties

The pharmacokinetics of reboxetine after single or multiple oral doses have been studied in healthy young or elderly volunteers, in depressed patients and in subjects with renal or liver insufficiency. After oral administration of a single 4 mg reboxetine dose to healthy volunteers, peak levels of about 130 ng/mL are achieved within 2 hours post-dosing. Data indicate that absolute bioavailability is at least 60 %. Reboxetine plasma levels decay monoexponentially with a half-life of about 13 hours. Steady-state conditions are observed within 5 days. Linearity of the pharmacokinetics was shown in the range of single oral doses in the clinically recommended dose-ranges.

The medicine appears to be distributed into total body water. Reboxetine is 97 % bound to human plasma proteins (with affinity markedly higher for α_1 acid glycoprotein than albumin), with no significant dependence of the concentration of the medicine.

The amount of radioactivity excreted in the urine accounts for 78 % of the dose. Even though unchanged medicine is predominant in the systemic circulation (70 % of total radioactivity, in terms of AUC), only 10 % of the dose is excreted as unchanged medicine in urine. These findings suggest that biotransformation rules the overall elimination of reboxetine and that the metabolites' excretion is limited by their formation. *In vitro* studies indicate that reboxetine is metabolised by the cytochrome P450 isoenzyme CYP3A4. The main metabolic pathways identified are 2-O-dealkylation, hydroxylation of the ethoxyphenoxy ring and oxidation of the morpholine ring, followed by partial or complete glucuro- or sulphoconjugation.

The medicine is available as a racaemic compound (with both enantiomers being active in the experimental models); no chiral inversion, nor reciprocal pharmacokinetic interferences between enantiomers have been observed. Plasma levels of the more potent SS enantiomers are about two times lower, and urinary excretion two times higher, than those of the enantiomeric counterpart. No significant differences were observed in the terminal half-lives of the two enantiomers.

Special populations

Some increase in systemic exposure and half-life up to two-fold is observed in patients with renal insufficiency; similar findings, though less relevant and not consistently observed, were apparent in elderly subjects and patients with hepatic insufficiency.

5.3 Preclinical safety data

Reboxetine did not induce gene mutations in bacterial or mammalian cells *in vitro* but induced chromosomal aberrations in human lymphocytes *in vitro*. Reboxetine did not cause DNA damage in yeast cells or rat hepatocytes *in vitro*. Reboxetine did not cause chromosomal damage in an *in vivo* mouse micronucleus test and did not increase tumour incidence in carcinogenicity studies in mice and rats.

Haemosiderosis was reported in toxicity studies in rats only.

Studies in animals have not demonstrated any teratogenic effect or any effect of the medicine on global reproductive performance. In fertility studies in rats, reboxetine did not alter mating behaviour, fertility or general reproductive performance at oral doses up to 90 mg/kg/day.

Dosages that produced plasma concentrations within the therapeutic range for humans induced an impairment of growth and development and long-term behavioural changes in offspring of rats.

In rats, reboxetine is excreted in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Dibasic calcium phosphate

Magnesium stearate

Microcrystalline cellulose

Silicone dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

The tablets are contained in aluminium-PVDC/PVC-PVDC opaque blisters. Each pack contains 20 or 60 tablets in blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

33/1.2/0246

9. DATE OF FIRST AUTHORISATION

25 February 2000

10. DATE OF REVISION OF THE TEXT

09 December 2021

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