SCHEDULING STATUS:

Schedule 5

PROPRIETARY NAME (and dosage form)

EDRONAX 4 mg TABLETS

COMPOSITION:

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

EDRONAX tablets contain the following inactive ingredients: crospovidone, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and silicone dioxide.

PHARMACOLOGICAL CLASSIFICATION:

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

PHARMACOLOGICAL ACTION:

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 desensitization of β- and α_2- receptors, coupled with an increase in responsiveness of postsynaptic α_1- receptors.

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 drug 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 drug.

The amount of radioactivity excreted in the urine accounts for 78 % of the dose. Even though unchanged drug is predominant in the systemic circulation (70 % of total radioactivity, in terms of AUC), only 10 % of the dose is excreted as unchanged drug 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 metabolized 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 drug 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.

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.

INDICATIONS:

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

CONTRA-INDICATIONS:

Hypersensitivity to the compound.

Seizure disorders.

Pregnancy and lactation

Use in children, as safety and efficacy have not been demonstrated.

Concomitant administration with CYP3A4 inhibitors, e.g. ketoconazole, erythromycin, troleandomycin, fluconazole, itraconazole and grapefruit juice.

WARNINGS:

Plasma levels and half-lives 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 MAO inhibitors and EDRONAX should be avoided until further data are available. *See INTERACTIONS.*

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 drugs known to lower blood pressure.

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/litre 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, antidrepressants 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.

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 drug therapy especially in early treatment and following dose changes. Patient (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 advise immediately if these symptoms present.

Effects on ability to drive and use machines: Patients should be cautioned about operating machinery and driving during treatment.

INTERACTIONS:

EDRONAX is extensively bound to plasma proteins; the available data indicate that the drug is almost exclusively bound to α_1 acid glycoprotein. Therefore, the concurrent administration of drugs 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 drug, 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; EDRONAX is not metabolised by CYP2D6. Therefore, compounds that decrease the activity of CYP3A4 would be expected to increase plasma concentrations of EDRONAX.

Repeated doses of EDRONAX do not affect Cytochrome P450 3A activity as documented by the unmodified urinary excretion of 6-β-hydroxycortisol. As a consequence, no modification is expected in the metabolism of oral contraceptives or other steroids, triazolam, alprazolam, terfenadine, nifedipine, erythromycin, lidocaine and cyclosporine A, when they are co-administered with 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%.

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.

PREGNANCY AND LACTATION:

Pregnancy

The use of EDRONAX during pregnancy and lactation is contra-indicated. See CONTRA-INDICATIONS.

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

Lactation

EDRONAX is excreted in breast milk. The use of EDRONAX during breastfeeding is contra-indicated.

DOSAGE AND DIRECTIONS FOR USE:

Use in adults

The recommended therapeutic dose 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.

Use in the elderly (> 65 years)

In elderly depressed patients, particularly in the presence of concomitant systemic illnesses and medications, the recommended therapeutic dose 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 children

The use of EDRONAX in patients less than 18 years of age is not recommended, since safety and efficacy have not been established. *See CONTRA-INDICATIONS and WARNINGS.*

Use in patients with renal or hepatic insufficiency

The dose in patients with renal insufficiency or moderate to severe hepatic insufficiency should be 2 mg twice daily.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Very Common ≥ 1/10(≥ 10 %); Common ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %) ; Uncommon ≥ 1/1000 and < 1/100 (≥ 0.1 % and < 1 %); Rare ≥ 1/10,000 and < 1/1000 (≥ 0.01 % and < 0.1 %);

Very Rare < 1/10,000 (< 0.01 %)

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Infections and infestations	*Common*	Urinary tract infection
Psychiatric disorders	*Very common*	Insomnia
Nervous system disorders	*Common*	Dizziness, paraesthesia
Ear and labyrinth disorders	*Common*	Vertigo
Cardiac disorders	*Common*	Tachycardia
Vascular disorders	*Common*	Hypotension
Gastrointestinal disorders	*Very common*	Constipation, dry mouth
Skin and subcutaneous tissue disorders	*Very common*	Increased sweating
Renal and urinary disorders	*Common*	Urinary hesitancy/retention
	Uncommon	Dysuria
Reproductive system and breast disorders	*Common*	Male sexual dysfunction

Post-marketing Surveillance

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

Metabolism and nutrition disorders: Hyponatraemia

Psychiatric disorders: Agitation, anxiety, hallucinations

Nervous system disorders: Paraesthesia

Vascular disorders: Hypertension, peripheral coldness, Raynaud's phenomenon

Gastrointestinal disorders: Nausea, vomiting

Reproductive system and breast disorders: Testicular pain

General disorders and administration site conditions: Irritability

No indication of withdrawal syndrome upon EDRONAX discontinuation emerged from the results of the clinical trials: signs and symptoms newly reported on abrupt discontinuation were infrequent, and less frequent in patients treated with EDRONAX (4 %) than in those treated with placebo (6 %).

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 compared with 6 % on placebo, and 23 % of the patients on long-term treatment compared with 17 % on placebo).

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The acute toxicity studies carried out in animals indicate a very low toxicity, with a wide safety margin with respect to the pharmacologically active doses. Clinical signs and cause of death were related to CNS stimulation (mainly convulsive symptoms).

In a few cases doses higher than those recommended were administered to patients (12 mg to 20 mg/day) for a period ranging from a few days to some weeks during clinical studies: newly reported complaints include postural hypotension, anxiety and hypertension.

Two cases of self-overdosing with EDRONAX were reported by the patients during the clinical studies. No major adverse events were observed.

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

IDENTIFICATION:

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”.

PRESENTATION:

The tablets are contained in aluminium-PVDC/PVC-PVDC opaque blisters.

Each pack contains 20 or 60 tablets in blisters.

STORAGE INSTRUCTIONS:

Store below 25 °C.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER:

33/1.2/0246

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

Pfizer Laboratories (Pty) Ltd

85 Bute Lane Sandton

2196

South Africa

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