SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Edronax® 4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 4 mg of reboxetine
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, round, convex 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'. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reboxetine is indicated for the acute treatment of depressive illness/major depression and for maintaining the clinical improvement in patients initially responding to treatment.

4.2 Posology and method of administration

Posology

Adults
The recommended therapeutic dose is 4 mg twice a day (b.i.d.) i.e., 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. The maximum daily dose should not exceed 12 mg/day. The minimum effective dose has not yet been established.

Elderly
Elderly patients have been studied in clinical trials at doses of 2 mg b.i.d. However, safety and efficacy have not been evaluated in placebo-controlled conditions. Therefore, as for other antidepressants that have not been studied in placebo-controlled conditions, reboxetine cannot be recommended.

Paediatric population
Reboxetine should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

Renal or hepatic impairment
The starting dose in patients with renal or hepatic impairment should be 2 mg b.i.d which can be increased based on patient tolerance.

Method of administration
Reboxetine is for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Paediatric population
Reboxetine 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. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

As reboxetine has not been tested in patients with convulsive disorders in clinical studies and since rare cases of seizures have been reported in clinical studies, it should be given under close supervision to subjects with a history of convulsive disorders and it must be discontinued if the patient develops seizures.

Serotonin syndrome
The development of potentially life-threatening serotonin syndrome has been reported with serotonin-norepinephrine reuptake inhibitors [SNRIs], including reboxetine alone, and with concomitant use of other serotonergic drugs (e.g., selective serotonin reuptake inhibitors [SSRIs], other SNRIs, triptans, tricyclic and tetracyclic antidepressants, lithium, opioids [e.g., buprenorphine], tryptophan, buspirone, monoamine oxidase inhibitors [MAOIs], and St. John's Wort) (see section 4.5).

Serotonin syndrome may include mental status changes (e.g., confusion, agitation, hallucinations, delirium, and coma); autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia, diaphoresis, and flushing); neuromuscular abnormalities (e.g., tremor, rigidity, clonus, and hyperreflexia); gastrointestinal signs and symptoms (e.g., nausea, vomiting, diarrhoea). Patients should be monitored for the emergence of serotonin syndrome.

Concomitant use of MAO-inhibitors (including linezolid (an antibiotic which is a reversible non-selective MAOI) and methylene blue) and reboxetine should be avoided in view of the potential risk (tyramine-like effect) based on their mechanisms of action.

Concomitant use of reboxetine with other antidepressants (tricyclics, MAO inhibitors, SSRIs and lithium) has not been evaluated during clinical trials.

If concomitant use of reboxetine with other serotonergic drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see section 4.5). Patients should be made aware of the potential risk of serotonin syndrome. Treatment with reboxetine and any concomitant serotonergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

As with all antidepressants, switches to mania/hypomania have occurred during the clinical studies. Close supervision of bipolar patients is, therefore, recommended.

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. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with

psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug 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 reboxetine in patients affected by serious concomitant systemic illnesses is limited. Close supervision should be applied in patients with current evidence of urinary retention, prostatic hypertrophy, glaucoma and history of cardiac disease.

At doses higher than the maximum recommended, orthostatic hypotension has been observed with greater frequency than that observed at recommended doses. Particular attention should be paid when administering reboxetine with other drugs known to lower blood pressure.

Clinical experience with reboxetine in the long-term treatment of elderly patients is, at present, limited. In this population, 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

In vitro metabolism studies indicate that reboxetine is primarily metabolised by the CYP3A4 isozyme of cytochrome P450; reboxetine is not metabolised by CYP2D6. Therefore potent inhibitors of CYP3A4 (ketoconazole, nefazodone, erythromycin and fluvoxamine), would be expected to increase plasma concentrations of reboxetine. In a study in healthy volunteers, ketoconazole, a potent inhibitor of CYP3A4, was found to increase plasma concentrations of the reboxetine enantiomers by approximately 50%. Because of reboxetine's narrow therapeutic margin, inhibition of elimination is a major concern. Reboxetine, therefore should not be given together with drugs known to inhibit CYP3A4 such as azole antifungal agents, macrolide antibiotics such as erythromycin, or fluvoxamine.

Low reboxetine serum levels have been reported with the concurrent administration of CYP3A4 inducers such as phenobarbital and carbamazepine. Examples of other CYP3A4 inducers that may reduce the serum levels of reboxetine include but are not limited to phenytoin, rifampicin and St John´s Wort.

In vitro studies have shown that reboxetine does not inhibit the activity of the following P450 isoenzymes: CYP1A2, CYP2C9, CYP2C19 and CYP2E1. Pharmacokinetic interactions would not be expected with compounds metabolised by these enzymes. At concentrations which exceed those in clinical use, reboxetine inhibits CYP2D6 and CYP3A4, however, the results of *in vivo* studies suggest that interactions with other drugs metabolised by these enzymes are unlikely.

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

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

Serotonergic medications

Serotonin is formed from dietary tryptophan and stored in the presynaptic terminal. It is released into the synapse where it acts on the presynaptic and postsynaptic terminals and is taken back up into the presynaptic terminal to be degraded by monoamine oxidase. Concomitant administration

with any other medication which increases the amount of free serotonin in the synapse carries the risk of inducing serotonin syndrome. Medications to consider are those which inhibit reuptake of serotonin (SSRIs, SNRIs, tricyclics, and opioids); those which inhibit catabolism of serotonin (MAOIs, triptans, St John's Wort); those which increase production of serotonin (L-tryptophan); those which release serotonin (opioids such as buprenorphine); those directly acting on serotonin receptors (triptans, lithium, opioids); and those working by other mechanisms (lithium, tricyclics, tetracyclics, and opioids) (see section 4.4).

The most serious side effects and even death have been reported following the concomitant use of certain serotonergic medications with monoamine oxidase (MAO) inhibitors. Therefore, MAO inhibitors should be discontinued at least 2 weeks prior to the cautious initiation of therapy with reboxetine. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved (see section 4.4).

Before commencing therapy with reboxetine, the prior medication history should be carefully assessed, and patients should be asked about over-the-counter drug, herbal and illicit drug use. Concomitant use of reboxetine with other medications having serotonergic effect should be avoided wherever possible. Where concomitant administration is unavoidable, the lowest effective dose of reboxetine should be used, and patients should be monitored.

Concomitant use of MAO-inhibitors (including linezolid (an antibiotic which is a reversible non-selective MAOI) and methylene blue) and reboxetine should be avoided in view of the potential risk (tyramine-like effect) based on their mechanisms of action.
Concomitant use of reboxetine with other antidepressants (tricyclics, MAO inhibitors, SSRIs and lithium) has not been evaluated during clinical trials.

Concomitant use of ergot derivatives and reboxetine might result in increased blood pressure.

Food intake delayed the absorption of reboxetine, but did not significantly influence the extent of absorption.

Although data are not available from clinical studies, the possibility of hypokalaemia with concomitant use of potassium losing diuretics should be considered.

In an *in vivo* multiple-dose study performed in healthy volunteers, no clinically significant interaction between fluoxetine and reboxetine was observed. In patients, a different effect and safety profile upon combination of reboxetine and fluoxetine cannot be excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical trial data on exposure to reboxetine during pregnancy are available. However, postmarketing safety data on a very limited number of exposed pregnancies indicate no adverse effects of reboxetine on pregnancy or on the health of the foetus/newborn child.
Animal studies in general do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition. Some impairment of growth and development has been noted in rat neonates (see section 5.3).
Reboxetine should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

Breast-feeding
Reboxetine is known to be excreted in breast milk. The level of active substance transferred in breast milk is anticipated to be very low, however there is insufficient information to exclude a risk to the nursing infant. The use of reboxetine during breast-feeding can be considered if the potential benefits outweigh the risk for the child.

Fertility

There is no clinical trial data on fertility. However, in animal studies no effect on fertility parameters was observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Although reboxetine has been shown to have negligible effect on psychomotor performance in healthy volunteers, any psychoactive drug can impair judgement or skills. Patients should be cautioned about driving or operating hazardous machinery until reasonably certain that their performance has not been affected.

4.8 Undesirable effects

Over 2100 patients received reboxetine in clinical studies, approximately 250 of which received reboxetine for at least 1 year.

The information provided in *Table 1* below is a summary of adverse reactions observed in patients treated with reboxetine in placebo-controlled clinical studies of 8 weeks duration or less. In addition, the table also includes adverse reactions observed from postmarketing experience (frequency not known).

Table 1: Adverse reactions

Very Common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10000 to <1/1000)**	**Not known (Frequency cannot be estimated from the available data)**
Metabolism and nutrition disorders				
	Decreased appetite			Hyponatraemia
Psychiatric disorders				
Insomnia	Agitation*, Anxiety*			Aggressive behaviour, Hallucination, Suicidal Ideation/behaviour**
Nervous system disorders				
Dizziness	Headache, Paraesthesia*, Akathisia, Dysguesia			Serotonin syndrome*
Eye disorders				
	Accommodation disorder	Mydriasis*	Glaucoma*	Intraocular pressure increased
Ear and labyrinth disorders				
		Vertigo		
Cardiac disorders				
	Tachycardia, Palpitations			
Vascular disorders				
	Vasodilatation, Hypotension, Hypertension*			Peripheral coldness, Raynaud`s phenomenon
Gastrointestinal disorders				
Dry mouth, Constipation, Nausea*	Vomiting*			
Skin and subcutaneous tissue disorders				

Hyperhidrosis	Rash*			Allergic dermatitis
Renal and urinary disorders				
	Sensation of incomplete bladder emptying, Urinary tract infection, Dysuria, Urinary retention			
Reproductive system and breast disorders				
	Erectile dysfunction, Ejaculatory pain, Ejaculatory delay			Testicular pain
General disorders and administration site conditions				
	Chills			Irritability

** these adverse reactions also occurred in postmarketing experience*

** Cases of suicidal ideation and suicidal behaviours have been reported during reboxetine therapy or early after treatment discontinuation (see section 4.4).

In placebo-controlled studies of 8 weeks duration or less, adverse events were reported in approximately 80% of reboxetine-treated patients and in approximately 70% of placebo-treated patients. Discontinuation rates for adverse events were approximately 9% and 5% for reboxetine- and placebo-treated patients, respectively.

As for long-term tolerability, 143 reboxetine-treated and 140 placebo-treated adult patients participated in a long term placebo controlled study. Adverse events newly emerged on long term treatment in 28% of the reboxetine treated patients and 23% of the placebo-treated patients and caused discontinuation in 4% and 1% of the cases respectively. There was a similar risk of the development of individual events with reboxetine and placebo. In the long term studies, no individual events were seen which have not been seen on short term treatment.

In short-term controlled studies of patients with depression, no clinically significant between-gender differences were noted in the frequency of treatment emergent symptoms, with the exception of urologic events (such as the sensation of incomplete bladder emptying, dysuria and urinary frequency), which were reported in a higher percentage of reboxetine-treated male patients (31.4% [143/456]) than reboxetine-treated female patients (7.0% [59/847]). In contrast, the frequency of urologic-related events was similar among male (5.0% [15/302]) and female (8.4% [37/440]) placebo-treated patients.

In the elderly population, frequency of total adverse events, as well as of individual events, was no higher than that reported above.

In pre-marketing clinical studies, signs and symptoms newly reported following discontinuation occurred in approximately (5%) of the reboxetine treated patients and approximately (4%) of placebo-treated patients. In post-marketing experience, there have been a few spontaneous reports of withdrawal symptoms including headache, dizziness, nervousness and nausea; however, no consistent pattern of events on cessation of treatment with reboxetine was evident in these reports.

In those short-term studies in depression where heart rate was assessed with ECG, reboxetine was associated with mean increases in heart rate, compared to placebo, of 6 to 12 beats per minute.

In all short-term controlled studies in depression, the mean change in pulse (in beats per minute) for reboxetine-treated patients was 3.0, 6.4 and 2.9 in the standing, sitting and supine positions respectively, compared with 0, 0, and –0.5 for placebo-treated patients in the corresponding positions. In these same studies, 0.8% of reboxetine-treated patients discontinued the drug because of tachycardia compared with 0.1% of placebo-treated patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

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. Elderly might be particularly vulnerable to overdose.

In premarketing clinical studies, there were 5 reports of reboxetine overdose alone or in combination with other pharmacologic agents. The amount of reboxetine ingested was 52 mg as the sole agent by 1 patient and 20 mg in combination with other agents by another patient. The remaining 3 patients ingested unknown quantities of reboxetine. All 5 patients recovered fully. There were no reports of ECG abnormalities, coma, or convulsions following overdose with reboxetine alone.

In postmarketing experience, there have been few reports of overdose in patients taking reboxetine alone; none of these have proved fatal. Non-fatal overdoses in patients have been reported for patients taking up to 240 mg of reboxetine. One fatal overdose was reported in a patient who ingested reboxetine in combination with amitriptyline (doses unknown).

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

Pharmacotherapeutic group: Other Antidepressants, ATC code: NO6A X18

Mechanism of action
Reboxetine is a highly selective and potent inhibitor of noradrenaline reuptake. It has only a weak effect on the 5-HT reuptake and does not affect the uptake of dopamine.

Noradrenaline reuptake inhibition and the consequent increase of noradrenaline availability in the synaptic cleft and modification of noradrenergic transmission, reportedly is among the most relevant mechanisms of action of known antidepressant drugs.

Pharmacodynamic effects
In vitro, studies have shown that reboxetine has no significant affinity for adrenergic (α_1, α_2, β) and muscarinic receptors; antagonism of such receptors has been described to be associated with cardiovascular, anticholinergic and sedative side effects of other antidepressant drugs. Reboxetine is devoid of *in vitro* binding affinity for either α_1 or α_2 adrenoceptors, however, a functional interference with α-adrenoceptors at high doses *in vivo* cannot be excluded.

Clinical efficacy
In a post hoc stratified analysis of data from 11 placebo-controlled trials involving 2400 patients, there was no statistical difference in response rates on the primary endpoint (HAMD 21 item scale) for reboxetine versus placebo patients with mild to moderate severity of depression. Efficacy was only clearly demonstrated in patients with severe or very severe depression. From these trials there are limited efficacy data available in the use of reboxetine in patients with mild to moderate severity of depression.

5.2 Pharmacokinetic properties

Absorption
After oral administration of a single 4 mg reboxetine dose to healthy volunteers, peak levels of about 130 ng/ml are achieved within 2 h post-dosing. Data indicate that absolute bioavailability is at least 60%.

Distribution
The drug appears to be distributed into total body water. Reboxetine is 97% bound to human plasma proteins in young and 92% in elderly (with affinity markedly higher for α_1 acid glycoprotein than albumin), with no significant dependence of the concentration of drug.

Biotransformation and elimination
The amount of radioactivity excreted in 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 metabolites excretion is limited by their formation. 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 sulpho-conjugation.

The drug is available as a racemic mixture (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 enantiomer 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.

Increases in systemic exposure and half-life of approximately two-fold are observed in patients with renal insufficiency and hepatic insufficiency. Similar or somewhat greater (3-fold) increases in systemic exposure also occur in elderly patients relative to young healthy volunteers.

Linearity/non-linearity
Reboxetine plasma levels decreased monoexponentially with a half-life of about 13 h. 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.

Pharmacokinetic/pharmacodynamic relationships
Reboxetine is predominantly metabolised *in vitro* via cytochrome P4503A (CYP3A4). *In vitro* studies have shown that reboxetine does not inhibit the activity of the following isozymes of cytochrome P450: CYP1A2, CYP2C9, CYP2C19, and CYP2E1. Reboxetine inhibits both CYP2D6 and CYP3A4 with low binding affinities, but has shown no effect on the *in vivo* clearance of drugs metabolised by these enzymes. Reboxetine should be co-prescribed with caution with potent inhibitors of CYP3A4.

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 tumor incidence in carcinogenecity 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 compound on global reproductive performance. In fertility studies in rats, reboxetine did not alter mating behavior, 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

Cellulose microcrystalline
Calcium hydrogen phosphate dihydrate
Crospovidone
Silica, colloidal hydrated
Magnesium stearate

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store above 25°C.
Bottle: Keep the container tightly closed in order to protect from moisture.

6.5. Nature and contents of container

The tablets are contained in aluminium-PVDC/PVC-PVDC opaque blisters or high-density polyethylene (HDPE) bottle with a cylinder containing silica gel desiccant, closed with a polypropylene child-resistant, squeeze-and-turn closure cap.

Each pack contains: 10, 20, 50, 60, 100, 120, and 180 tablets in blisters, or 20 and 60 tablets in bottles.

Multipacks of 3x60, 5x60 and 10x60 tablets in blisters.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3
Ireland

8. MARKETING AUTHORISATION NUMBER

PA 822/127/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th November 1997
Date of last renewal: 10th April 2007

10. DATE OF REVISION OF THE TEXT

04/2025

Ref: 22_3