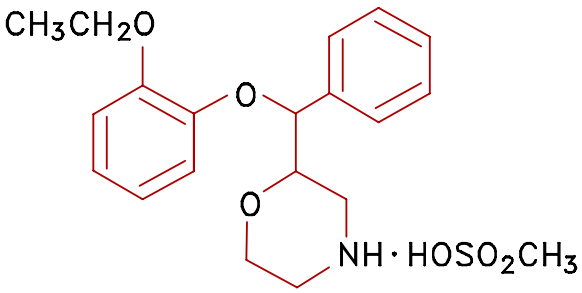
PRODUCT INFORMATION

EDRONAX®

Reboxetine mesilate

DESCRIPTION

Structural Formula:



Tablets containing 5.2 mg reboxetine mesilate corresponding to 4 mg reboxetine free base.

Inactive ingredients: magnesium stearate, cellulose microcrystalline, silicon dioxide, crospovidone and calcium hydrogen phosphate.

Chemical name: (2RS, αRS)-2-[α-(2-ethoxyphenoxy)benzyl] morpholine methanesulfonate.

Reboxetine mesilate has the empirical formula $C_{19}H_{23}NO_3$-CH_4O_3S, and a molecular weight of 409.50.

CAS Number: 141425-90-3

Reboxetine mesilate is freely soluble in water (>20% w/v).

PHARMACOLOGY

Pharmacodynamics

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, is among the most relevant mechanisms of action of known antidepressant drugs.

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

In healthy volunteers the administration of reboxetine single doses of 1 and 3 mg was followed by dose-dependent CNS effects with EEG modifications (decreased power of theta and fast beta-waves in the fronto-central derivative) and performance improvement (peg-board test).

Pharmacokinetics

The pharmacokinetics of reboxetine after single and multiple oral doses have been studied in healthy young and elderly volunteers, in depressed patients, and in subjects with renal or liver insufficiency.

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 hours post-dosing. The administration of reboxetine with food delayed the rate of absorption by approximately 2 hours while not affecting the extent of absorption. Reboxetine displays linear pharmacokinetics in a dose range of up to 4 mg twice daily. Data indicate that absolute bioavailability is approximately 94%. Reboxetine plasma concentrations 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.

Distribution

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 clinically relevant dependence on the concentration of the drug. The volume of distribution of reboxetine at steady state following intravenous administration is 26 L and 63 L for the RR and SS diastereomers, respectively.

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.

Metabolism

Reboxetine is extensively metabolised after oral administration. The drug is predominantly metabolised through hydroxylation of the ethoxyphenoxy ring, o-dealkylation and oxidation of the morpholine ring. *In vitro* studies indicate that CYP3A4 is the isozyme of cytochrome P-450 that is primarily responsible for the metabolism of reboxetine. *In vitro* studies show that reboxetine has no effect on the activity of the following isozymes of cytochrome P-450: CYP1A2, CYP2C9, CYP2C19 and CYP2E1. At high concentrations, reboxetine inhibits CYP2D6. *In vitro* studies show that reboxetine is a weak inhibitor of CYP3A4. *In vitro* studies have shown that the major circulating metabolite, the 3-morpholine oxidation product of reboxetine, has little or no activity on noradrenergic or seratonergic uptake, and is unlikely to contribute to the pharmacological activity of reboxetine.

The drug is available as a racemic compound: the SS enantiomer is two times more potent than the racemate, and the RR enantiomer is 10 times less potent than the racemate. No chiral inversion or reciprocal pharmacokinetic interferences between enantiomers have been observed. Plasma concentrations 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.

Elimination

The systemic clearance of reboxetine is 43 mL/min. About 10% of the dose of reboxetine is excreted unchanged in urine. The renal clearance of SS and RR diastereomers of reboxetine is 9.3 mL/min and 2.0 mL/min, respectively.

Elimination of reboxetine is mainly via hepatic metabolism (by cytochrome P450 3A4) with a mean terminal half-life of about 12 hours. No significant difference was observed in the terminal half-lives of the RR and SS diastereomers.

Special Populations

Elderly (> 65 years)

The pharmacokinetics of reboxetine were assessed in three studies of elderly volunteers. In the first study, middle-aged (50 to 63 years) and elderly (68 to 77 years) subjects showed only moderate differences in area under the plasma concentration time curve and half-life. The AUC increased by 20 to 25% and half-life was 3 to 5 hours longer in the elderly compared to healthy young volunteers given the same 4 mg dose. In the second study, elderly subjects (66 to 98 years) showed a 4-fold increase in AUC and 2-fold increase in half-life compared to young healthy males following a single 4 mg reboxetine oral dose. In the third study, the mean AUC in elderly depressed females (75 to 87 years) was approximately three times higher than in young males. A reduction in dose is warranted in elderly patients. (See Dosage and Administration).

Children

There have been no pharmacokinetic studies in children.

Gender

In a study in six males and six females, no differences in reboxetine pharmacokinetics were observed between genders following a 1 mg oral reboxetine dose.

Race

The effect of race on reboxetine pharmacokinetics has not been studied.

Hepatic Impairment

Compared with young healthy volunteers receiving the same 4 mg reboxetine dose, AUC and $t_{1/2}$ were approximately doubled in patients (n=6) with alcoholic liver disease (moderate, i.e. Child-Pugh score of 7 to 9, and severe i.e., Child-Pugh score of 10 to 13). A reduction in dose is warranted in patients with hepatic insufficiency (See Dosage and Administration).

Renal Impairment

An increase in systemic exposure and $t_{1/2}$ up to threefold was observed in patients (n=6) with severe renal insufficiency (creatinine clearance = 10 to 20 mL/min) following a 4 mg oral dose of reboxetine. A reduction in dose is warranted in patients with compromised renal function (See Dosage and Administration).

CLINICAL TRIALS

The EDRONAX clinical program consists of 15 phase II and III clinical trials that were conducted in adult (aged 18 – 65 years) and elderly (aged > 65 years) patients diagnosed with Major Depressive Disorder (MDD).

The Hamilton Depression Rating Scale (HAMD) was used as the primary instrument for the assessment of the change in depressive symptoms in all clinical trials. The Montgomery and Asberg Rating Scale for Depression (MADRS) and the Clinical Global Impressions Scales (CGI) were used as secondary efficacy parameters. For the short-term studies in non-elderly patients (i.e. those 18 to 65 years of age), the study endpoint was defined as the absolute decrease of the mean HAMD total score or as the frequency of response, (defined as ≥50% decrease of the HAMD total score), as measured at the last available assessment. This allowed for a global evaluation of the consistency of the results of the studies and for conclusions on the antidepressant efficacy of EDRONAX to be drawn.

The clinical program has demonstrated that EDRONAX is effective in the therapy of acute episodes of depression as well as in the prevention of relapses and recurrences of depressive illness when administered for long-term therapy. The results of the studies indicate that the primary effect of EDRONAX is on the primary symptom (depressed mood) of depressive illness. The remission of the acute phase of the depressive illness is associated with an improvement in the patient's quality of life in terms of social adaptation.

Short-term Placebo-Controlled Studies

The results of the analysis of the HAMD total score for the five short-term (4 to 8 weeks), placebo-controlled studies in non-elderly patients (18 to 65 years) with MDD are summarised in Table 1.

Table 1 - Mean Absolute Decrease of HAMD Total Score at Last Assessment

	Reboxetine		PLC		IMI		FLX		DMI	
Ref	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N
27	15.3	80	8.8	81					13.1	82
28	23.1	27	4.5	25						
29	13.4	124	8.7	128			13.3	126		
30	13.5	110	11.3	111	13.8	111				
16	9.2	106	8.2	104						

Abbreviations: DMI = desipramine; HAMD = Hamilton Depression Rating Scale; FLX = fluoxetine; IMI = imipramine; PLC = placebo

The mean HAMD total score improvement associated with EDRONAX treatment ranged from 9.2 to 23.1 points. The mean HAMD improvement associated with placebo was always lower than that associated with EDRONAX, with an average decrease of 4.5 to 11.3 points. The difference between EDRONAX and placebo was statistically significant in three of the five studies above. In two studies, the difference between EDRONAX and placebo was not statistically significant on the mean HAMD total score. In one of these studies, the active comparator imipramine also failed to show a statistically significant difference over placebo. In the other study, a number of secondary efficacy measures demonstrated statistically significant differences in favour of EDRONAX over placebo.

The frequency of clinically relevant improvement with EDRONAX was, on the average, 16% greater than with placebo, providing unequivocal indication of the efficacy of EDRONAX in the acute treatment of depressive illness.

Active-Controlled Studies

Imipramine-Controlled Studies

Two 6-week studies were conducted to determine the benefits of EDRONAX relative to those of imipramine in the treatment of patients with MDD. A total of 237 patients were treated with EDRONAX compared to 233 receiving imipramine. The mean HAMD score improvement associated with EDRONAX treatment ranged from 13.5 – 15.8, compared to 13.8 – 14.3 for imipramine. The results of both these studies therefore confirmed equivalent efficacy for EDRONAX and imipramine.

Fluoxetine-Controlled Studies

Two 8-week studies were conducted to determine the benefits of EDRONAX relative to those of fluoxetine in the treatment of patients with MDD. A total of 200 patients were treated with EDRONAX compared to 213 receiving fluoxetine. The mean HAMD score improvement associated with EDRONAX treatment ranged from 13.4 – 19.2, compared to 13.3 – 16.8 for fluoxetine. The results of both these studies confirmed equivalent efficacy for EDRONAX and fluoxetine.

Long-Term, Placebo-Controlled Study

The long-term efficacy of EDRONAX for the treatment of patients with MDD was investigated in a 1-year, double-blind, randomised, parallel-group, placebo-controlled study. In this study, patients received open-label treatment with EDRONAX (8 mg/day) for 6 weeks; thereafter, the patients who responded to therapy (minimum 50% decrease of the HAMD total score) were randomised to receive treatment with EDRONAX or placebo until relapse occurred or for up to 1 year. Two hundred and eighty-three patients participated in the double-blind, long-term portion of the study: 143 were treated with EDRONAX and 140 were treated with placebo.

This study demonstrated the efficacy of EDRONAX in the maintenance therapy of depressive illness. 61% and 40%, respectively, of the responder patients on EDRONAX and placebo remained relapse-free during the initial 6 months following randomisation, and 88% and 59%, respectively, of the patients on EDRONAX and placebo who entered the last 6 months of treatment remained relapse-free up to the end of the study. EDRONAX showed a 29% advantage in relapse rate over placebo, thus confirming the efficacy of EDRONAX in the prevention of recurrences of new depressive episodes.

INDICATIONS

EDRONAX is indicated for the treatment of major depression and is effective in preventing the relapse of depressive symptoms.

CONTRAINDICATIONS

Hypersensitivity to reboxetine or any of the excipients.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated.

Since reboxetine has a weak mydriatic effect, its use is not recommended in patients with narrow angle glaucoma.

PRECAUTIONS

Seizures

Since rare cases of seizures have been reported in clinical studies, EDRONAX should be given under close supervision to subjects with a history of convulsive disorder and it should be discontinued if the patient develops seizures.

Activation of Mania/Hypomania

As with all antidepressants, switches to mania/hypomania have occurred. Close supervision of patients with bipolar disorders is recommended.

Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. The risk of suicide must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines (SSRIs and others) in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the initial treatment period (generally the first one to two months) in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients treated with placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine). In addition, long-term safety data in children and

adolescents concerning growth, maturation, and cognitive and behavioural development are lacking.

A further pooled analysis of short-term placebo-controlled trials of antidepressant medicines (SSRIs and others) showed the increased risk of suicidal thinking and behaviour (suicidality) during the initial treatment period (generally the first one to two months) extends to young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. These studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Currently, data are insufficient to quantify an increased risk of suicidal thinking and behaviour associated with reboxetine treatment. Nevertheless, anyone considering the use of reboxetine in young adults must balance this potential risk with the clinical need.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for EDRONAX should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular

Patients (particularly those aged > 65 years) with a history of cardiac disease, including hypertension, should be closely supervised when being treated with reboxetine.

Orthostatic Hypotension

Orthostatic hypotension has been observed with greater frequency at doses higher than the maximum recommended. Close supervision is recommended when administering EDRONAX with other drugs known to lower blood pressure. EDRONAX should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions that would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

Hypertension

Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, e.g., those with pre-existing hypertension, heart failure or recent myocardial infarction.

Tachycardia

Reboxetine should be used with caution in patients whose underlying medical conditions might be compromised by increases in heart rate, e.g., patients with hyperthyroidism, heart failure or recent myocardial infarction.

Use in Patients with Concomitant Illness

Clinical experience with reboxetine in patients affected by serious concomitant illness is limited. Close supervision is recommended in patients with current evidence of urinary retention, prostatic hypertrophy and glaucoma.

Carcinogenicity and Mutagenicity

Carcinogenicity studies in mice and rats showed no drug-related increases in tumour incidences at oral reboxetine doses up to 45 and 90 mg/kg/day, respectively. Systemic exposure (plasma AUC) to unbound drug at the highest dose levels was approximately two fold higher than that in humans at the maximum recommended dose.

Both the reboxetine S,S-enantiomer and racemic reboxetine mesilate induce chromosomal aberrations in human lymphocytes *in vitro*. Racemic reboxetine mesilate did not induce gene mutations in bacterial or mammalian (Chinese hamster) cells *in vitro*, did not produce DNA damage in yeast cells or rat hepatocytes *in vitro*, and did not cause chromosomal damage in an *in vivo* mouse micronucleus test.

Impairment of Fertility

No effect on fertility of male or female rats was observed at oral dose levels up to 90 mg/kg/day. Systemic exposure (plasma AUC) to unbound drug at the highest dose levels was approximately two fold higher than that in humans at the maximum recommended dose.

Use in Pregnancy

Category B1

Development studies in rat and rabbits have not shown clear evidence of teratogenic effect at oral dose levels up to 320 and 100 mg/kg/day, respectively. However, in both species, there were increases in post-implantation loss, decreases in mean foetal weight and an increased incidence of skeletal anomalies, including delayed ossification. Compared with human exposure (plasma AUC at the maximum recommended dose), estimated exposure in rats was less than human exposure, and exposure in rabbits was approximately 6 fold (reboxetine, SS enantiomer) and 16 fold (RR enantiomer) higher at the highest dose tested. At the no-effect dose in rabbits (25 mg/kg/day), reboxetine exposure was similar to human exposure. Reboxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Reboxetine is excreted in milk in lactating rats. Oral doses of 25-125 mg/kg/day reduced survival of offspring and retarded postnatal growth and development. Plasma drug levels at these doses were similar to or lower than those in humans at the maximum recommended dose. Therefore, while no information on the excretion of reboxetine in maternal milk in humans is available, EDRONAX administration is not recommended in women who are breast feeding.

Use in Children and Adolescents (< 18 years)

The efficacy and safety of reboxetine has not been satisfactorily established for the treatment of children and adolescents (see Dosage and Administration).

Interactions with Other Medicines

In vitro studies show that reboxetine has no effect on the activity of the following isozymes of cytochrome P450: CYP1A2, CYP2C9, CYP2C19 and CYP2E1.

Specifically, *in vitro* and *in vivo* studies show that reboxetine is not metabolised by CYP2D6 and therefore no special precautions are necessary for individuals deficient in this enzyme.

Inhibitors of CYP2D6, such as fluoxetine and paroxetine, are unlikely to have an effect on EDRONAX pharmacokinetics. This was confirmed in a multiple-dose study performed in healthy volunteers where no clinically significant interaction between fluoxetine and EDRONAX was observed.

In vitro metabolism studies indicate that reboxetine is metabolised by the 3A4 isozymes of cytochrome P450. Therefore compounds that decrease the activity of CYP3A4 are 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%. Similar interactions are expected with other inhibitors of CYP3A4, such as azole antifungals, macrolide antibiotics and fluvoxamine.

In vitro studies show that reboxetine is a weak inhibitor of CYP3A4. However an *in vivo* study has shown that EDRONAX did not alter the clearance of alprazolam. This is expected to apply to other CYP3A4 substrates.

Carbamazepine induces CYP3A4 and is therefore expected to induce clearance of reboxetine and lower plasma concentrations. Therefore doses of EDRONAX may need to be increased if given concomitantly with carbamazepine.

Concomitant use of EDRONAX with lithium has not been evaluated in clinical trials but in view of the small degree of glomerular filtration of unbound reboxetine, no effect of EDRONAX on lithium elimination is expected. However, monitoring of lithium levels is recommended where the two drugs are co-administered.

Concomitant use of EDRONAX with tricyclic antidepressants and SSRIs has not been evaluated during clinical studies.

No significant reciprocal pharmacokinetic interaction has been found between EDRONAX and lorazepam.

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

The small degree of glomerular filtration of unbound reboxetine means there is little likelihood that EDRONAX will affect the renal clearance of cardiac glycosides such as digoxin.

Co-administration of antihypertensive agents may exacerbate the orthostatic hypotensive effects of EDRONAX.

Concomitant use of ergot derivatives and EDRONAX may result in increased blood pressure.

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

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

Effects on Ability to Drive and Use of Machines

Patients should be cautioned about driving or operating hazardous machinery until reasonably certain that their performance has not been affected.

ADVERSE EFFECTS

Clinical Trial Data

About 1700 patients have received EDRONAX in clinical studies, 216 of which received EDRONAX for at least 12 months.

Short-term clinical trials

Adverse events reported during the 4 – 8 week studies are reported below:

Table 2. Treatment-Emergent Symptoms (TES) Reported in ≥1% of Reboxetine-Treated Patients in the Short-Term Controlled Studies

Body System/Event	Reboxetine N = 892		Placebo N = 506	
	n	%	n	%
Body as a Whole	243	27.2	143	28.3
headache	153	17.2	90	17.8
asthenia	38	4.3	25	4.9
abdominal pain	22	2.5	8	1.6
infection	20	2.2	23	4.5
pain	14	1.6	7	1.4
reaction unevaluable	12	1.3	2	0.4
chills	11	1.2	1	0.2
flu syndrome	11	1.2	3	0.6
back pain	10	1.1	6	1.2
Cardiovascular	115	12.9	34	6.7
tachycardia	45	5.0	10	2.0
palpitation	20	2.2	2	0.4
vasodilatation	20	2.2	5	1.0
hypertension	16	1.8	2	0.4
hypotension	16	1.8	9	1.8
postural hypotension	14	1.6	1	0.2
Digestive	433	48.5	156	30.8
dry mouth	273	30.6	71	14.0
constipation	168	18.8	39	7.7
nausea	96	10.8	36	7.1
anorexia	35	3.9	15	3.0
vomiting	27	3.0	15	3.0
diarrhea	22	2.5	37	7.3
dyspepsia	20	2.2	7	1.4
Nervous	320	35.9	139	27.5
insomnia	141	15.8	37	7.3
dizziness	96	10.8	28	5.5
tremor	33	3.7	11	2.2

Body System/Event	Reboxetine N = 892		Placebo N = 506	
	n	%	n	%
paresthesia	28	3.1	13	2.6
somnolence	26	2.9	32	6.3
anxiety	25	2.8	14	2.8
agitation	24	2.7	14	2.8
CNS stimulation	16	1.8	12	2.4
nervousness	16	1.8	8	1.6
Respiratory	48	5.4	33	6.5
rhinitis	21	2.4	20	4.0
Skin	137	15.4	47	9.3
sweating	111	12.4	33	6.5
pruritus	10	1.1	3	0.6
rash	10	1.1	7	1.4
Special Senses	66	7.4	19	3.8
abnormality of accommodation	34	3.8	14	2.8
taste perversion	13	1.5	4	0.8
Urogenital	123	13.8	27	5.3
urination impaired	41	4.6	6	1.2
urinary retention	27	3.0	2	0.4
urinary tract infection	16	1.8	4	0.8
impotence	14	1.6	2	0.4
sexual function abnormal	12	1.3	2	0.4
urinary frequency	9	1.0	4	0.8

Abbreviations: n = Number of patients reporting a treatment-emergent symptom, % = Percentage based on number of intent-to-treat patients, N = Number of intent-to-treat patients.
Each patient is counted once per body system. Each patient is counted once per COSTART term.

The most relevant between-gender difference in adverse event rate was related to the frequency of urinary hesitancy/retention which occurred more often in male patients (10% *vs* 2% in females on short-term treatment; 14% *vs* 1% in females on long-term treatment).

There was an increase in heart rate upon standing 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). In all short-term controlled studies in depression, the mean change in pulse (in beats per minute) for reboxetine treated patients was 2.9, 8.3 and 3.0 in the supine, sitting and standing positions respectively, compared with –0.5, 0 and 0 for placebo-treated patients in the corresponding positions.

In the short-term controlled studies in depression, no significant mean change in blood pressure was observed. Diastolic blood pressures > 105 mm Hg were observed in 5.6%, 1.0% and 3.8% of reboxetine treated patients in the supine, sitting and standing positions, respectively compared with 1.5%, 1.0% and 2.8% for placebo-treated patients in the corresponding positions. Analyses of data from the phase 2 and 3 studies in depression have demonstrated no increase in systolic blood pressure.

Impotence was mainly observed in patients treated with doses higher than 8 mg/day.

Long-term clinical trials

Based on data from long-term studies which included 328 patients who were treated with EDRONAX for longer than 6 months, the frequency of the most common adverse events (e.g., dry mouth, constipation, tachycardia, hypotension) did not increase over time but, rather, decreased or remained constant over time. Table 3 summarises the treatment-emergent symptoms (TES) that

were reported in ≥1% of the reboxetine-treated patients by duration of therapy (≤6 months or >6 months). Although small, the placebo group is provided for reference purposes.

Table 3. Treatment-Emergent Symptoms (TES) Reported in ≥1% of Reboxetine-Treated Patients in the Long-Term Studies by Duration of Therapy

	Reboxetine		Placebo	
Body System/Event	**≤6 mo N=94**	**>6 mo N=328**	**≤6 mo N=60**	**>6 mo N=80**
Nervous				
Insomnia	37 (39.4%)	70 (21.3%)	14 (23.3%)	5 (6.3%)
CNS Stimulation	9 (9.6%)	11 (3.4%)	0	0
Anxiety	5 (5.3%)	9 (2.7%)	0	0
Paresthesia	5 (5.3%)	9 (2.7%)	0	1 (1.3%)
Tremor	2 (2.1%)	10 (3.0%)	0	7 (8.8%)
Dizziness	3 (3.2%)	7 (2.1%)	0	3 (3.8%)
Decreased Libido	1 (1.1%)	8 (2.4%)	0	3 (3.8%)
Agitation	6 (6.4%)	2 (0.6%)	0	0
Cerebral Ischaemia	0	5 (1.5%)	0	0
Vertigo	0	5 (1.5%)	0	0
Digestive				
Constipation	20 (21.3%)	47 (14.3%)	7 (11.7%)	16 (20.0%)
Dry Mouth	14 (14.9%)	51 (15.5%)	3 (5.0%)	15 (18.8%)
Nausea	4 (4.3%)	25 (7.6%)	0	0
Diarrhoea	2 (2.1%)	11 (3.4%)	1 (1.7%)	3 (3.8%)
Anorexia	0	5 (1.5%)	0	0
Liver Function Tests Abnormal	2 (2.1%)	3 (0.9%)	0	0
Vomiting	1 (1.1%)	4 (1.2%)	0	2 (2.5%)
Body As a Whole				
Headache	9 (9.6%)	30 (9.1%)	1 (1.7%)	3 (3.8%)
Asthenia	3 (3.2%)	12 (3.7%)	1 (1.7%)	0
Abdominal Pain	5 (5.3%)	8 (2.4%)	0	0
Flu Syndrome	0	8 (2.4%)	0	0
Infection Viral	1 (1.1%)	6 (1.8%)	0	0
Chest Pain Substernal	1 (1.1%)	4 (1.2%)	0	0
Cardiovascular				
Tachycardia	12 (12.8%)	24 (7.3%)	4 (6.7%)	4 (5.0%)
Hypertension	3 (3.2%)	10 (3.0%)	2 (3.3%)	0
Myocardial Ischaemia	9 (9.6%)	4 (1.2%)	0	0
Hypotension	2 (2.1%)	7 (2.1%)	1 (1.7%)	0
Urogenital				
Urination Impaired	2 (2.1%)	17 (5.2%)	1 (1.7%)	6 (7.5%)
Sexual Function Abnormal	2 (2.1%)	4 (1.2%)	1 (1.7%)	2 (2.5%)
Urinary Tract Infection	3 (3.2%)	3 (0.9%)	0	0
Dysuria	0	5 (1.5%)	0	0
Urinary Retention	1 (1.1%)	4 (1.2%)	0	0
Skin				
Sweating	12 (12.8%)	28 (8.5%)	1 (1.7%)	6 (7.5%)
Rash	3 (3.2%)	6 (1.8%)	0	0
Metabolic & Nutritional				
Hyperlipemia	0	7 (2.1%)	0	0
Hypercholesteremia	2 (2.1%)	4 (1.2%)	0	0
GGT Increased	0	5 (1.5%)	0	0
Respiratory				
Bronchitis	1 (1.1%)	5 (1.5%)	0	0
Pharyngitis	1 (1.1%)	5 (1.5%)	0	0
Special Senses				
Abnormality of Accommodation	2 (2.1%)	8 (2.4%)	1 (1.7%)	3 (3.8%)

For long-term tolerability, 143 EDRONAX 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 EDRONAX 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 EDRONAX and placebo. Among events seen more than occasionally, no individual events not seen on short-term treatment were apparent.

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%).

Apart from tachycardia no consistent changes in ECG tracings were observed during EDRONAX treatment in adult patients. Similarly, no consistent changes were observed at the opthalmological examination, carried out upon long-term treatment. In the elderly population, newly observed rhythm disorders (mainly tachycardia) and conduction disorders were apparent in the ECG in approximately 15% of cases.

In a long-term study, treatment-emergent rhythm disorders (including sinus tachycardia, occasional atrial and ventricular ectopics), conduction disorders, ischaemic changes (including myocardial ischaemia, repolarisation changes and non-specific ST-T changes) and other changes (including left ventricular hypertrophy) occurred more frequently in elderly patients with a history of cardiovascular disease at baseline than in elderly patients without such a history. A similar pattern was also observed in a short-term study in elderly patients.

Abnormal laboratory test values were uncommon during EDRONAX therapy.

Side-effects occurring in < 1% of patients treated with reboxetine from phase II and III studies:

Systemic:

≥0.1% - <1%: fever, backache, attempted suicide, self-harm, generalised oedema, shock, cold extremities.

Cardiovascular:

≥0.1% - <1%: myocardial ischaemia, bundle-branch block, ventricular extrasystoles, AV block, ventricular fibrillation, cardiomegaly, myocardial infarction-phlebitis, supraventricular extrasystoles.

<0.1%: angina pectoris, arterial thrombosis.

Gastrointestinal tract:

≥0.1% - <1%: flatulence, increased salivation, dysphagia, gastritis, gastroenteritis, stomatitis, yellow colouration of mucosa, moniliasis of oral mucosa, increased liver enzymes.

<0.1%: gallbladder pain, colitis, enterocolitis, increased appetite.

Blood and lymphatic system:

≥0.1% - <1%: anaemia, leukocytosis, granulocytosis, lymphocytosis.

<0.1%: leukopenia, thrombocytopenia.

Metabolism and gastrointestinal system:

≥0.1% - <1%: weight increase or decrease, peripheral oedema.

<0.1%: cyanosis.

Muscular and skeletal system:

≥0.1% - <1%: myalgia, arthralgia, myasthenia.

Nervous system:

≥0.1% - <1%: acathisia, hyperkinesia, confusion, hypokinesia, cerebral ischaemia, muscle spasm, ataxia, abnormal dreams, hemiplegia, paraplegia, difficulties concentrating, migraine.

<0.1%: apathy, cerebral haemorrhage, cerebral infarction, dyskinesia, emotional instability, extrapyramidal syndrome, hypaesthesia, neuritis, polyneuritis.

Respiratory:

≥0.1% - <1%: dyspnoea, pharyngitis, epistaxis.

Skin:

≥0.1% - <1%: urticaria.

<0.1%: eczema, erythema multiforme, vesiculobullous rash.

Senses:

≥0.1% - <1%: tinnitus, opthalmalgia (pain in the eyeball) mydriasis, allergic reactions (e.g. allergic conjunctivitis or hay fever).

<0.1%: dry eyes.

Urogenital system:

≥0.1% - <1%: dysuria, albuminuria, urinary incontinence, cystitis, glycosuria, haematuria, changes in the penis (e.g. penile retraction, pain or swelling of the penis), abnormal ejaculation (e.g. delayed or painful ejaculation).

<0.1%: epididymitis, oliguria, testicular pain, testicular retraction.

Post-Marketing Experience

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

Metabolism and nutrition disorders: Hyponatremia.

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.

DOSAGE AND ADMINISTRATION

The onset of clinical effect is usually seen after 14 days of treatment.

Use in Adults

The recommended therapeutic dose is 4 mg twice daily (8 mg/day) administered orally. After 3 weeks the dose can be increased up to 10 mg/day in case of incomplete clinical response.

Use in Children and Adolescents (< 18 years)

There are no data available on the use of reboxetine in children or adolescents under 18 years of age.

Use in the Elderly (> 65 years)

The recommended therapeutic dose is 2 mg twice daily (4 mg/day) administered orally. After 3 weeks the dose can be increased up to 6 mg/day in case of incomplete clinical response.

Use in Renal or Hepatic Impairment

The starting dose in patients with renal or moderate to severe hepatic insufficiency should be 2 mg twice daily, increased according to patient tolerance.

OVERDOSAGE

Clinical effects in overdose are expected to be an exaggeration of known adverse events, including seizures. In a few cases, doses higher than those recommended (12 to 20 mg/day) were administered to patients during the clinical studies for a period ranging from a few days to a few weeks. Treatment-emergent adverse events included postural hypotension, anxiety and hypertension.

There are minimal reports of overdosage with reboxetine. One patient ingested 52 mg as the sole agent and developed minimal toxicity and doses up to 240 mg have been ingested with survival reported. No fatalities have been reported with reboxetine alone and there have been no reports of ECG abnormalities, coma, or convulsions following overdose with reboxetine alone. One fatal overdose was reported in a patient who ingested reboxetine in combination with amitriptyline (doses unknown).

Reboxetine serum levels are not clinically useful.

In case of overdose, treatment should consist of those general measures employed in the management of overdose with any antidepressant. Treatment is symptomatic and supportive. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs.

Activated charcoal may reduce absorption of the drug if given within one hour after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange perfusion are unlikely to be of benefit. No specific antidotes for reboxetine are known.

Induction of emesis is not recommended.

In managing overdosage, consider the possibility of multiple-drug involvement.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

4 mg EDRONAX tablets (containing 5.2 mg reboxetine mesilate) are white, convex, round tablets with a breakline on one side and engraved 'P' on the left of the breakline and 'U' on the right side of the breakline, and '7671' on the opposite side.

The tablets are available in blister packs of 60 tablets.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38 – 42 Wharf Road
West Ryde NSW 2114

POISON SCHEDULE

Schedule 4 – Prescription Only Medicine

DATE OF APPROVAL

Approved by the TGA on 28 June 2005.

Date of most recent amendment: 10 December 2009.

*Please note changes to Product Information.

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