

EU Core Safety Profile

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| Active Substance: | Reboxetine |
| Brand Names: | EDRONAX, REBOXETINE |
| Pharmaceutical form(s)/strength: | Tablets |
| RMS: | UK |
| Date: | 31 st January 2011 |
| Supersedes: | NA |

4.3. Contraindications

Known hypersensitivity to reboxetine or any of the components of the product.

4.4. Special warnings and precautions for use

Use in children and adolescents under 18 years of age

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.

Concomitant use of MAO-inhibitors 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.

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.

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 metabolized 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.

Concomitant use of MAO-inhibitors 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. 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.

LACTATION

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 breastfeeding can be considered if the potential benefits outweigh the risk for the child.

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.

Common adverse events causing withdrawal at least twice as often on reboxetine than placebo include insomnia, dizziness, dry mouth, nausea, sweating, sensation of incomplete bladder emptying (males only), urinary hesitancy (males only) and headache.

The information below refers to short-term controlled studies. Very common or common adverse events that are at least two times higher on reboxetine than placebo are listed below.

Table 1: The following undesirable effects have been observed and reported during treatment with reboxetine with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$).

| System Organ Class | Frequency | Undesirable effects |
|---|-------------|--|
| Nervous system disorders | Very common | insomnia |
| | Common: | vertigo |
| Eye disorders | Common | abnormality of accommodation |
| Cardiac disorders | Common | tachycardia, palpitation, vasodilation, postural hypotension |
| Gastrointestinal disorders | Very common | dry mouth, constipation |
| | Common | lack or loss of appetite |
| Skin and subcutaneous tissue disorders | Very common | sweating |
| Renal and urinary disorders | Common | urinary hesitancy, sensation of incomplete bladder emptying, urinary tract infection |

| | | |
|---|--------|---|
| Reproductive system and breast disorders | Common | erectile dysfunction, ejaculatory pain, ejaculatory delay, testicular disorder-primarily pain |
| General disorders and administration site conditions | Common | chills |

In addition there have been spontaneous reports of agitation, anxiety, irritability, aggressive behaviour, hallucination, peripheral coldness, nausea, vomiting, allergic dermatitis/rash, paraesthesia, hypertension, Raynaud's phenomenon, hyponatremia and testicular pain.

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

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, urinary hesitancy 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 on abrupt discontinuation were infrequent and less frequent in patients treated with reboxetine (4%) than in those treated with placebo (6%). 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.

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.