MHRA UK PUBLIC ASSESSMENT REPORT

Reboxetine: a review of the benefits and risks

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PLAIN-LANGUAGE SUMMARY

KEY MESSAGE: A European review of scientific evidence has shown that the balance of benefits and risks for reboxetine remains positive.

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency responsible for regulating medicines and medical devices. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses an analysis of the effectiveness and safety of a medicine called reboxetine.

Reboxetine (brand name Edronax) belongs to a group of important prescription medicines called antidepressants. It has been licensed in the UK since 1997, for the treatment of depression[1], and for maintaining the improvement of depressive symptoms in patients who initially respond to reboxetine treatment.

The MHRA reviews the benefits and risks of a medicine if a possible safety concern over its use has been raised. In 2010, a published analysis of reboxetine data conducted by a scientific institute in Germany raised concerns, as the authors concluded that the risks of reboxetine outweighed the benefits. Because of these concerns, the MHRA and the European Pharmacovigilance Working Party[2] conducted their own review of all available scientific and clinical data on the benefits and risks of reboxetine, and compared the results to the German analysis.

Results

The European review noted that there were limitations to the German analysis, including that it did not analyse all of the available studies on reboxetine when reviewing efficacy[3] (only 7 out of a possible 11 placebo-controlled studies).

From analysing this selection of studies, the authors of the German paper concluded that there was no difference in effectiveness against depression between reboxetine and placebo[4] (odds ratios[5] and 95% confidence intervals[6] for response rates to treatment: 1·24 [0·98 – 1·56]). However, the European review, which analysed all 11 relevant placebo-controlled studies, showed that reboxetine was statistically significantly more effective than placebo (odds ratios and 95% confidence intervals for response rates: 1·47 [1·10 – 1.97]).

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[1] A clinical mental health disorder characterised by symptoms such as depressed mood, loss of interest or pleasure in life, and disturbed sleep and appetite. The condition can become chronic or recurrent, and substantially impair everyday life.

[2] A group which provides recommendations on pharmacovigilance matters to the Committee for Medicinal Products for Human Use in the European Medicines Agency

[3] The effectiveness of a drug measured under laboratory conditions or in clinical trials

[4] Inactive treatment given in a clinical trial to a particular patient group so their responses can be compared with the group receiving the test medicine

[5] A measure of risk for one group compared to another. A value close to or equal to 1 suggests no change in risk. A value greater than 1 suggests an increased risk.

[6] Difference in risk between two groups

It is questionable whether an overall analysis is the best way to look at the data as the results were inconsistent between patient groups (ie, inpatients versus outpatients, etc.)

When the results were organised by severity of disease, the European review showed that reboxetine was more effective in patients with severe clinical depression, with no evidence of benefit in patients with mild/moderate depression. This finding is in line with current clinical guidance, which states that antidepressants are not recommended for first-line treatment[1] of mild or moderate depression.

The German analysis suggested that reboxetine was associated with a higher rate of safety risks than placebo; however, the authors of this paper also stated that the rates of serious adverse events were low and did not differ between reboxetine and placebo. The European review of all available safety data did not identify any new safety concerns and confirmed that the benefit-risk balance for reboxetine was unchanged.

Conclusions

- A European review of data has shown that reboxetine is an effective medicine for patients with severe clinical depression. These results are in line with current clinical guidance on antidepressant use

- The balance of benefits and risks for reboxetine in the treatment of depression remains positive

[1] The initial, or first treatment recommended for an illness or disease

1. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK government agency responsible for regulating medicines and medical devices. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report discusses a European analysis of the efficacy and safety of reboxetine in the treatment of depression. The European analysis was conducted in response to the publication of an analysis of reboxetine conducted in Germany.

2. BACKGROUND

Reboxetine is a selective noradrenaline reuptake inhibitor antidepressant. It has been licensed in the UK since 1997 for the acute treatment of depressive illness/major depression, and for maintaining the clinical improvement in patients initially responding to treatment.

Reboxetine is also licensed as an antidepressant in Germany, and was assessed for efficacy and safety in 2010, along with two other antidepressants (mirtazapine and bupropion) by the German Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]). The Institute conducts health technology assessments of all medicines licensed in Germany. The report is available online[1], and a meta-analysis presenting the main findings of the Institute's assessment was published in the *British Medical Journal* in October 2010[2].

The paper generated significant public interest as the authors concluded from the data that the risks of reboxetine in the treatment of depression outweighed the benefits. These conclusions raised concerns in other countries where reboxetine was available, including in the UK. The MHRA and the European Pharmacovigilance Working Party[1] therefore conducted their own review of reboxetine efficacy and safety, and compared the results to the German analysis. The results and conclusions from the European review are summarised below.

[1] A group which provides recommendations on pharmacovigilance matters to the Committee for Medicinal Products for Human Use in the European Medicines Agency

3. DATA CONSIDERED AND METHODOLOGY

3.1. Efficacy

The European review of reboxetine efficacy compared reboxetine to placebo and examined 'response rates to treatment' as an efficacy outcome in 11 placebo-controlled studies.

The German analysis had reviewed data from 13 differentially-controlled clinical studies of reboxetine (to either placebo alone; a selective serotonin re-uptake inhibitor (SSRI) alone; or both placebo and an SSRI). This analysis also examined reboxetine efficacy compared to placebo, but however excluded four of the 11 relevant placebo-controlled studies that were included in the European review (the excluded studies are marked '*' in table 1).

'Response rates' were defined as the number of patients who showed a 'response to treatment', out of the total number of patients in the study. A 'response to treatment' was defined as a ≥50% reduction in the Hamilton depression rating score[1] from baseline to end of study.

Table 1. Clinical studies of reboxetine which included a placebo comparator, and examined response rates as an efficacy outcome, which were included in the European review.

Study	Initiated	Completed	Placebo control	Active control	Duration	Daily dose	Other relevant information
009*	1987	1989	Yes	None	4 weeks	4-8mg	Hospitalised patients
008*	1988	1989	Yes	desipramine	4 weeks	4-8mg	Hospitalised patients
091*	1989	1990	Yes	None	6 weeks	6-10mg	In-patients
032b*	1991	1991	Yes	None	8 weeks	4-10mg	Mainly hospitalised elderly patients
015	1991	1992	Yes	imipramine	6 weeks	8-10mg	Mainly hospitalised
014	1991	1993	Yes	fluoxetine	8 weeks	8-10mg	Mainly hospitalised
049	1997	1998	Yes	None	8 weeks	8-10 mg	Out-patients
045	1997	1999	Yes	None	8 weeks	8 mg	Mainly out-patients

[1] A questionnaire used by clinicians to rate the severity of a patient's depression

050	1998	1999	Yes	fluoxetine	8 weeks	8-10 mg	Out-patients
046	2000	2000	Yes	paroxetine	8 weeks	4-10 mg	Mainly out-patients
047	2000	2000	Yes	paroxetine	8 weeks	2-10 mg	Mainly out-patients

All studies in the table were included in the European review. Studies marked '*' were excluded from the German analysis.

3.2. Safety

For the assessment of reboxetine safety, the European review examined adverse event data from 13 differentially-controlled clinical trials with reboxetine (either compared to placebo, another antidepressant, or both).

The German analysis had also examined safety data from 13 differentially-controlled clinical trials with reboxetine (either compared to placebo, an SSRI, or both).

4. RESULTS OF EUROPEAN REVIEW

4.1. Efficacy

Table 2 shows the response rates compared to placebo in 11 placebo-controlled reboxetine clinical studies that were included for efficacy assessment in the European review. Seven of these studies were included for assessment of the same efficacy endpoint in the German analysis. The four studies that were excluded from the German analysis are marked '*' in table 2.

Table 2. Reboxetine efficacy compared to placebo: Response rates to treatment from 11 clinical studies included in a European review of data.

Study	**Dose (mg/day)**	**Duration**	**Reboxetine response rate (n /N) [%]**	**Placebo response rate (n/N) [%]**
009*****	4 – 8	4 weeks	14/26 (53·8)	9/24 (37·5)
008*****	4 – 8	4 weeks	50/84 (59·5)	30/85(35·3)
091*****	6 – 10	6 weeks	20/27 (74·1)	5/25 (20·0)
014	8 – 10	8 weeks	69/124 (55·6)	43/128 (33·6)
015	8 – 10	6 weeks	65/110 (59·1)	58/111 (52·3)
032b*****	2 – 6	8 weeks	4/24 (16·7)	5/26 (19·2)
045	8	8 weeks	38/88 (43·2)	39/86 (45·3)
049	8 – 10	8 weeks	40/101 (39·6)	34/101 (33·7)
050	8 – 10	8 weeks	60/144 (41·7)	63/143 (44·1)
047	2 – 10	8 weeks	120/238 (50·4)	108/239 (45·2)
046	4 – 10	8 weeks	144/252 (57·1)	136/247 (55·1)
Total			**624/1218 (51·2)**	**530/1215 (43·6)**

Treatment responses in all studies were measured using the Hamilton Depression Scale. n=number of patients who responded to treatment; N=the total number of patients in the study; *****=the studies which were not assessed in the published German analysis

A random effects model was used to compare the efficacy results between the German analysis and the UK analysis (table 3).

Table 3. Statistical assessment of reboxetine efficacy compared to placebo in the German analysis versus the European review of data.

	Reboxetine response rates (n/N) [%]	Placebo response rates (n/N) [%]	OR (95% CI)	p-value
German analysis of reboxetine data (Eyding et al, 2010[2])	539/1064 (50·7%)	482/1058 (45·6%)	1·24 (0·98, 1·56)	0·071
European review of reboxetine data	624/1218 (51·2%)	530/1215 (43·6%)	1·47 (1·10, 1·97)	0·0101

n=number of patients who responded to treatment; N=the total number of patients in the study; OR=odds ratios; CI=confidence intervals

The German analysis which assessed the results from seven placebo-controlled trials led the authors to conclude that there was no significant difference in response rates between patients receiving reboxetine and those receiving placebo (OR 1·24 [95% CI: 0·98 – 1·56]; p=0·07). However the European review, which assessed results from 11 placebo-controlled studies, showed that reboxetine was statistically significantly more effective than placebo: OR 1·47 [1·10 – 1·97]; p=0·01).

Despite the results from the European review showing statistical significance and the German analysis not showing significance, these two results are actually fairly similar. They both point to a small benefit of reboxetine (approximately 51% with reboxetine compared to 44 – 46% with placebo [5 – 7% difference in response rates]; lower bounds of confidence intervals: German analysis: 0.98; European review: 1.10).

It is questionable whether an overall meta-analysis is the most appropriate way to look at the data as the results were inconsistent between patient groups.

The European review subsequently stratified the studies by baseline depression severity (mild/moderate/severe) measured using the Hamilton Depression Scale, to examine whether there were any differences in treatment efficacy related to disease severity.

Patients in almost all of the studies had severe depression at baseline; the exceptions were studies 046 and 047 which included patients with a range of baseline severity. The responses rates to treatment in these studies in patients divided by disease severity are shown in table 4.

Table 4. Studies 046 and 047: Treatment response rates to reboxetine or placebo in patients divided by baseline depression severity

Study	**Reboxetine response rates (n/N) [%]**	**Placebo response rates (n/N) [%]**

046 (mild/moderate depression)	32/72 (44·4)	42/72 (58·3)
046 (severe depression)	111/180 (61·7)	94/175 (53·7)
047 (mild/moderate depression)	19/41 (46·3)	28/54 (51·9)
047 (severe depression)	101/197 (51·3)	80/186 (43·0)

n=number of patients responding to treatment; N=total number of patients in study

In both studies there was a consistent pattern with a substantial trend favouring placebo over reboxetine in the mild and moderate patients, while the trend favoured reboxetine in the severe patients, with a difference of about 8% in favour of reboxetine. Therefore, reboxetine was markedly more effective in patients with severe depression at baseline, compared to its efficacy in patients with mild or moderate depression. There was no evidence of any benefit for reboxetine in mild/moderate patients.

4.2 General safety data

German analysis

The German analysis looked at the safety data of eight placebo-controlled reboxetine trials and found that reboxetine was associated with higher event rates of patients with at least one adverse event (OR 2.14; 1.59-2.88) and a higher rate of discontinuations due to adverse events (OR 2.21, 95% CI 1.45 to 3.37) than placebo.

Out of 13 treatment trials which compared reboxetine with placebo, an SSRI, or both, there were 18 suicide related events: 6 associated with reboxetine, 8 SSRI, 4 placebo. The only completed suicide was in the placebo group. There were no statistically significant differences between reboxetine, SSRIs or placebo for the rate of serious adverse events or suicide-related adverse events.

There was no statistically significant differences between the reboxetine or the SSRI treatment groups for reporting rates of ≥1 non-serious adverse event, or rates of discontinuations due to non-serious adverse events (OR 1.06 [0.82-1.36]; p=0.667).

European review

Data were available for a total of 218 patients in the 13 trials examined which compared reboxetine with placebo, another antidepressant, or both; 173 adverse events were tabulated.

The most common adverse events occurring with the use of reboxetine were: dry mouth (n=67), nausea (n=34), insomnia (n=23), headache (n=16), hypotension (n=12), and increased sweating (n=10). These adverse events were already known and are all listed in the product information for reboxetine (the Summary of Product Characteristics [SPC] and the Patient Information Leaflet [PIL]). No new safety signals were identified.

5. DISCUSSION

The European review of reboxetine efficacy and safety data was triggered by the publication of a German data analysis in which reboxetine was concluded to be 'overall, an ineffective and potentially harmful antidepressant.' The German analysis calculated that efficacy for reboxetine (measured as response rates to treatment) was not significantly different compared to placebo: OR 1.24, 95% CI 0.98 to 1.56; p=0.071. However this calculation was based on data from only seven out of a total 11 placebo-controlled reboxetine studies.

The European review, which analysed data from all 11 placebo-controlled studies, showed that response rates for reboxetine were statistically significantly higher than placebo: OR 1.47, 95% CI 1.10 to 1.97; p=0.01, providing evidence efficacy for reboxetine.

The German analysis found that reboxetine was inferior to placebo for safety measures; however the European review of all available data, which included all 11 placebo-controlled trials, did not identify any previously unrecognised safety concerns associated with reboxetine, and confirmed the currently recognised side effect profile.

In conclusion, the European review provides evidence that reboxetine is an effective medicine for patients with moderate or severe clinical depression, and that the balance of benefits and risks for reboxetine in the treatment of depression remains positive.

It is questionable whether an overall meta-analysis is the most appropriate way to look at the data as the results were inconsistent between patient groups. Factors which may affect the magnitude of the reboxetine treatment effect include:

Care setting

The early studies conducted between 1987 – 1991 predominantly included inpatients, while the later studies (1997 – 2000) were mainly in outpatients. Studies that were conducted in an inpatient setting consistently showed better efficacy results than studies conducted in outpatients, though favourable trends were still seen in the outpatient studies. Therefore, care setting may affect the magnitude of reboxetine treatment effect, and it may be more effective in hospitalised patients. This could be because of differences in the type of patients likely to be hospitalised compared to those who are not, or because of the way patients are cared for in the hospital setting compared to outpatients. The four studies that were excluded by the German analysis were early studies which were mainly conducted between 1987 – 1991 in inpatients.

Baseline severity of depression

Baseline severity of depression also seemed to affect treatment effectiveness, and it is clear that greater reboxetine efficacy compared to placebo was only demonstrated in patients with severe depression, not those with mild-moderate severity. This is in line with current clinical guidance, which already recommends that pharmacological treatment of depression is reserved for those with severe depression.

Safety

The selective noradrenaline reuptake inhibition of reboxetine does confer a different risk profile than the SSRIs, with more well-recognised cardiac and urinary adverse reactions that are contained in the product information. Men in particular more frequently report more than one adverse event taking reboxetine compared to fluoxetine and these events tend to be urogenital as one would expect from the pharmacology of the drug.

However, the European review of available safety data did not identify any previously unrecognised safety concerns associated with reboxetine and the vast majority of adverse events presented in the clinical study reports are those that are labelled in the SPC and PIL for reboxetine.

Premature discontinuations

Premature discontinuations were also generally lower for reboxetine in the earlier studies than the later studies, which could also be a function of the hospital setting. Adverse events that cause a discontinuation for an out-patient may not cause discontinuation for a patient in hospital – the smaller number of withdrawals in the hospital setting would give reboxetine a greater chance to show efficacy.

There were consistently lower rates of discontinuation due to adverse events in the inpatient trials compared with outpatient trials, supporting the hypothesis that inpatients may tolerate adverse events in hospital better because of increased care and support, and are more likely to comply with medication given the level of supervision and monitoring provided in the hospital setting.

The lower rates of treatment discontinuations due to adverse events coupled with the more favourable efficacy in hospital patients might lead us to form the opinion that perhaps reboxetine is best placed restricted in use in a hospital setting only. To restrict the use of reboxetine to patients in a hospital setting only however would prove an unjustifiable burden on the healthcare system and it is not considered necessary to admit patients already taking reboxetine to hospital for the duration of treatment.

For patients already receiving reboxetine experiencing good clinical effect there is no reason to stop or switch medication from these data. There are no new safety concerns which would necessitate discontinuation of reboxetine in patients with mild to moderate depression already receiving reboxetine, if it is considered by their prescriber to be the most appropriate treatment.

6. CONCLUSIONS

Reboxetine is an effective antidepressant. A comprehensive European review of data has shown it has a clear clinical benefit. The results of the review stratified by baseline disease severity show that reboxetine efficacy is greater in patients with severe depression and has not been shown in patients with mild/moderate disease, which is in line with current clinical guidance.

There are no safety data to suggest any change to the benefit-risk balance of reboxetine. Overall, it is considered the balance of risks and benefits of reboxetine remains favourable.

7. REFERENCES

1. Buproprion, mirtazapine, and reboxetine in the treatment of depression. Published by Institut für Qualität und Wirtschaftlichkeit im Geesundheitswesen, IQWiG, 2009. (See https://www.iqwig.de/index.582.en.html?random=49969f)

2. Eyding D, Lelgemann M, Grouven U, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ* 2010; **341**: c4737

8. GLOSSARY

Adverse events
Side effects to a drug that are unintended, and harmful or unpleasant

Anorexia
Loss of appetite

Antidepressant
A medicine used to treat clinical **depression**

Asthenia
Lack of strength or energy

Buproprion
A prescription medicine given to help people stop smoking

Clinical trials
A research study that tests the effectiveness and safety of medicines in humans

Depression
A clinical mental health disorder characterised by symptoms such as depressed mood, loss of interest or pleasure in life, and disturbed sleep and appetite.

Desipramine
An antidepressant medicine belonging to the tricyclic class of medicines

Diaphoretic
A drug or agent that induces sweating

Double-blind study
A **clinical trial** in which the identity of the test medicine is hidden from both the volunteers and the study investigators (to remove any possible bias from the results)

Dysuria
Painful or difficult urination

Efficacy
The effectiveness of a drug measured under laboratory conditions or in clinical trials

Electrocardiogram (ECG)
A reading from a machine used to show the electrical activity of the heart

Fluoxetine
An **antidepressant** belonging to the **SSRI** class of medicines

Hamilton depression rating score
A questionnaire used by clinicians to rate the severity of a patient's depression

Hypertension
High blood pressure

Hypoesthesia
Partial loss of sensation or reduced sensitivity to touch

Hypomania
A mood disorder characterised by persistent euphoria or irritability

Hypotension
Low blood pressure

Imipramine
An antidepressant medicine belonging to the tricyclic class of medicines

In-patients
A patient admitted to, and staying in, a hospital or clinic

Insomnia
Inability to fall asleep or remain asleep for an adequate length of time

Meta-analysis
An analysis of data that statistically combines the results from several studies

Micturition
Urination

Mirtazapine
An antidepressant medicine belonging to the tetracyclic class of medicines

Nausea
Feeling of sickness or an urge to vomit

Noradrenaline reuptake inhibitor (NRI)
A class of medicines that are often used as antidepressants

Orthostatic dizziness
Another term for **postural hypotension**

Out-patients
A patient who attend a hospital or clinic for treatment, who does not require an overnight stay

Palpitations
Irregular or forceful heartbeat

Paroxetine
An **antidepressant** belonging to the **SSRI** class of medicines

Peripheral vascular disorder
A disease of the arteries supplying the arms and legs

Placebo
Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

Postural hypotension
A form of low blood pressure accompanied by dizziness that occurs when moving from a sitting or lying position to a standing position.

QT interval
Part of the electrical signal produced by the heart, which can be seen on an **electrocardiogram**

Randomised study
A **clinical trial** in which the study participants are randomly assigned to receive a test medicine, or a **placebo** or comparator medicine

Reboxetine
An **antidepressant** belonging to the **noradrenaline reuptake inhibitor (NRI)** class of medicines

Response rate (medicine)
The number of patients who respond to treatment

Selective serotonin reuptake inhibitor (SSRI)
A class of antidepressant drugs

Somnolence
Sleepiness

Statistical outlier
An observation that lies an abnormal distance from other values in a random sample from a population

Statistical significance
An statistical interpretation of data that indicates that a result is unlikely to have occurred by chance

Stratified
A method of separating patients in a study into groups based on different characteristics

Treatment discontinuation
To discontinue or withdraw from receiving treatment in a **clinical study**

Treatment-emergent signs and symptoms
An **adverse event** that was not present prior to the initiation of the treatments

Vasodilatation
Widening of the blood vessels which causes an increase in blood flow