Studie 083

(950E-CNS-0005-083)

Studienberichtssynopse

Reboxetine
Clinical Study Report 950E-CNS-0005-083

EFFECTS OF THE USE OF REBOXETINE AS A SUBSTITUTE FOR SELECTIVE SEROTONIN REUPTAKE INHIBITOR ANTIDEPRESSANTS IN THE TREATMENT OF DEPRESSION IN PATIENTS WITH SECONDARY SEXUAL DYSFUNCTION.

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1. SUMMARY

Company Name: Pharmacia
Finished Product: norebox
Principal Active Ingredient: reboxetine

Study Title:
Effects of the use of Reboxetine as a substitute for Selective Serotonin Reuptake Inhibitor antidepressants in the treatment of depression in patients with secondary Sexual Dysfunction.

Protocol Number: 950ECNS0005-083

Investigator(s):
This study was participated in by 39 investigators in Spain. Of those, 32 investigators included patients in this study.

Study Sites:
39 sites located in Spain participated in the study. The study was conducted principally in Mental Health Centers as well as hospitals and private centers.

Reference Publications:
At the date of this report, no work has been published in relation to this study.

Study Period (years):
February 12th, 2001 to March 5th, 2002

Development Phase:
Phase IV

Objectives
Principal:
To study changes in the sexual dysfunction of patients transferred to reboxetine (8 mg/day) for the treatment of clinically stable depression due to sexual dysfunction induced by SSRI antidepressants.

Secondary:
To analyse whether reboxetine is capable of sustaining the antidepressive effect achieved with the previous treatment for a period of 2 months using associated measures of efficacy. The frequency of adverse events, and the severity of these, was evaluated throughout the study.

Methodology:
Open, multi-center, fixed dose, observational study.

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Number of Patients (planned and enrolled):
To fulfil the objectives of the study, the inclusion of a minimum of 100 patients was planned for treatment over a minimum period of 14 days with an open treatment with reboxetine (Intention-to-Treat) in at least 50 sites

A total of 143 patients in 39 sites have been included in the study. Of these 141 received treatment with reboxetine; 93 patients were treated for a minimum of 14 days and 85 completed the 8 week period of treatment.

For the safety assessment 141 patients were considered, i.e. all those patients who received at least one dose of reboxetine.

For the efficacy assessment the groups included were the Intention-to-Treat patient population composed of 98 patients and the per protocol population composed of 93 patients.

Diagnosis and Main Inclusion Criteria:
Patients of both sexes, both out-patients and in-patients, aged between 18 and 70, capable of cooperation and with a diagnosis of Major Depressive Disorder according to DSM-IV either single episode or recurrent.

The included patients must have been in treatment with an SSRI antidepressant and with a stable clinical condition, with a Hamilton Depression Rating Scale score of <10 , or a clinical global impression of less than 2 points, and presence of sexual dysfunction developed within 2 months of beginning antidepressant treatment. An association with low doses of benzodiacepine (less than 20 mg of clorazepate or equivalent) was permitted.

The inclusion was not permitted of patients: with sexual dysfunction previous to antidepressant treatment (except certain types of previous reduction in libido), who required or who were in treatment with neuroleptics, hormone treatment, or any other medication with the potential to interfere in sexual relations, or who were suffering from any significant intercurrent illness which clearly affected their sexual function.

Product Under Investigation, Dose and Method of Administration, Batch Number:
The dosage of the study was of 8-10 mg/day of reboxetine in 2 doses. 4 mg reboxetine tablets were used.

Reference Treatment, Dose and Method of Administration, Batch Number:
No reference treatment or other comparative was used. The study was not controlled with any other treatment.

Duration of Treatment:
The treatment period of the study with reboxetine lasted 8 weeks (56 days).

Final Objectives and Evaluation Criteria

Efficacy:
The evaluation criteria for efficacy are:

- The mean change since inclusion in the total score of the Psychotropic-Related Sexual Dysfunction Questionnaire.

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- The mean change since inclusion in the total score on the Hamilton Depression Rating Scale (HAM-D, 17-item).

- The Clinical Global Impression (CGI) in terms of severity and improvement.

Safety:
The frequency of adverse events, and the severity of these, was evaluated throughout the study.

Statistical Methods:
Descriptive statistics are presented for the variables of safety and efficacy. The primary analysis of efficacy was based on patients who were treated with reboxetine for a period of at least 14 days (considered as the Per Protocol Population, PPP). Hypothesis testing are also presented to confirm the statistical significance of the clinical change in terms of Sexual Dysfunction on completion of the treatment compared to the initial condition of the patient, and also the clinical state in terms of depression.

All patients who received at least one dose of reboxetine have been included in the safety assessment, with the efficacy analysis including those patients who in addition, had fulfilled the criteria for inclusion considered to be most relevant (score of ≤ 10 on the Hamilton Depression Rating Scale, HAM-D, 17-item, or a score on the CGI severity scale of <2).

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2. SUMMARY OF RESULTS:

2.1. Distribution of Patients and Basal Characteristics:

The study included 143 patients, of which 141 patients received treatment with reboxetine, 93 patients were treated for a minimum of 14 days and 85 patients completed the treatment period of 8 weeks (56 days).

For the safety assessment 141 patients were taken into consideration, i.e. all those patients who received at least one dose of reboxetine.

The efficacy assessment considered the **Intention-to-Treat** analysis population composed of 98 patients and the **Per Protocol** Population composed of 93 patients.

The study includes 45.2% women and 54.9% men, the mean age of the patients was 43.9 with a standard deviation (SD) of 9.4.

For all groups analysed, the mean **duration** of the depressive disorder was 4 years. References to previous episodes of Major Depression (MD) existed in 50% of the patients. **Previous treatments** for MD with SSRI were: paroxetine 39.9%, fluoxetine 25.8%, sertraline 16.3%, citalopram 14%, fluvoxamine 5.4%.

All patients included in the study had previous **diagnosis** of Major Depressive Disorder according to DSM-IV criteria, were undergoing **antidepressive treatment with SSRI** and were in a **stable clinical condition**. The clinical situation of the MD was confirmed during the enrolment visit by associated measures of efficacy, the HAM-D 17-item scale and the CGI severity scale.

On the HAM-D 17-item scale the sample analysed showed, on the first visit, a mean score of 6.6 and a SD of 2.7, with a 95% CI (6.1 to 7.2) in accordance with the inclusion criteria. In the CGI severity scale the mean obtained was 1.9 and a SD of 0.9, indicating, in general, a condition classified as good, normal, or borderline illness in accordance with the inclusion criteria.

In the study, the Psychotropic-Related Sexual Dysfunction Questionnaire was used, as a tool which enables screening of sexual dysfunction in patients undergoing treatment with antidepressants. The maximum score for the version of the scale used in this study is 14 points.

In the population analysed, 96.9% of the patients referred to **alterations in sexual activity** during their first visit. 79.6% of the patients referred to this in a spontaneous manner. The overall mean in the questionnaire on the first visit was 10 and a SD of 3 with a 95% CI (9.4 to 10.7). In general it can be stated that on the first visit, all of the studied sample of patients displayed varying degrees of alteration in their sexual activity in accordance with the selection criteria.

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2.2. Efficacy Results:

In patients with clinically stable depression and secondary sexual dysfunction linked to their treatment with SSRI, the change to reboxetine 8-10 mg produced an overall reduction of 72.7% in the sexual dysfunction questionnaire after 2 months of treatment, without producing any worsening in the patient's depressive condition, as measured on the HAM-D and CGI scales.

Of the 141 patients, 93 have been included in the principal efficacy assessment and of those, a total of 83 patients completed the full reboxetine treatment period of 8 weeks duration.

The efficacy of the reboxetine treatment in patients with stabilised MD and SSRI induced secondary sexual dysfunction demonstrates that after the transfer to reboxetine, the sexual dysfunction improved significantly in each visit with respect to the basal evaluation.

At the start of the study, 96.8% of the patients made spontaneous reference to **alterations in sexual activity**, while after 2 months of treatment with reboxetine 8-10 mg/day, this percentage had dropped to 57.5%.

The total sample studied displayed an ***absolute change*** in the questionnaire of -7.5 points with a SD of 3.6 and a 95% CI (-8.2 to -6.7) and a ***percentage change*** of a reduction of -72.7% in the scale with a SD of 31.5 and a 95% CI (-79.5 to -65.8). The changes reached statistical significance in all visits in comparison to the basal evaluation with $p<0.0001$.

This clinical improvement in sexual activity is produced while maintaining the **clinical state** of the patient's depression. This has been evaluated using the HAM-D scale and CGI severity scale in each visit. In patients already displaying a stable clinical condition, the change to reboxetine 8-10 mg maintained or improved the clinical state of the patient's depression.

At the end of the study, the total mean score on the **HAM-D** scale was 2.9 with a SD of 2 and a 95% CI (2.5 to 3.4). The absolute mean change observed with respect to the start of the study is of -3.6 points on the HAM-D scale, with a SD of 2.4 and a 95% CI (-4.1 to -3.1), this represents a mean reduction of -54.7% on the HAM-D.

The changes in the patient's clinical state were also evaluated on the **CGI severity scale** and displayed improvement, indicating that the clinical state of the patients was maintained during the 2 month treatment with reboxetine.

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2.3. Safety Results:

In the study of reboxetine in patients with MD resistant to treatment with SSRI, with a study population of 143 patients, an incidence rate of AEs of 21.3% was observed. The AEs observed were those described in previous studies resulting from administration of reboxetine, the most frequent being; dryness of the mouth, constipation, dizziness, agitation and restlessness. In most cases, the AEs appeared during the first month of treatment and were considered by the investigator to be related to reboxetine. In 17.3% of the AEs, it was decided to modify the treatment regime, and in 30.8% it was necessary to cease treatment.

49.9% of the AEs recovered by the end of the study while 13.5% were not recovered in the final follow-up check. Those AEs not recovered at the end of the study were tachycardia, constipation, agitation, increased sweating and increased libido. For the rest no follow-up information is available.

SAEs were observed in 2 patients, representing 3.8% of all AEs, and the diagnoses were dizziness and agitation in one patient and manic reaction in the other. All these were recorded and related to the treatment. One of the patients experienced a full recovery at the end of the study while for the other patient no follow-up information was recorded.

The results of the study show that reboxetine is, in general, a well tolerated treatment, with a relatively low incidence of AEs related to the product, which are quick to appear following the start of treatment and which in a small proportion of patients make an adjustment of the dose or withdrawal of the treatment necessary.

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3. CONCLUSIONS

In the study undertaken of the efficacy of reboxetine treatment in patients with SSRI induced secondary sexual dysfunction , the transfer to treatment with reboxetine for a period of 8 weeks demonstrates a 72.7% reduction in the Psychotropic-Related Sexual Dysfunction Questionnaire score, indicating an improvement in sexual activity (referred to spontaneously or through questioning), without producing any worsening in the clinical state of the patient's depression, evaluated using the HAM-D and the CGI.

At the start of the study, 96.8% of the patients made spontaneous reference to alterations in sexual activity, while after 2 months of treatment with reboxetine, this percentage had dropped to 57.5%.

The first signs of efficacy can be observed 14 days after commencing the treatment, but are more pronounced after 8 weeks. At the end of this period, a reduction was observed in the Psychotropic-Related Sexual Dysfunction Questionnaire score of -7.5 points with a SD of 3.6 and a 95% CI (-8.2 to -6.7). The maximum score that can be achieved on the scale is 14 points. The reduction on the scale is statistically significant in all visits during the study with $p<0.0001$ compared to the initial values.

There is a percentage of patients that did not experience improvement with the change of treatment to reboxetine. At the end of the study, 57.6% of the sample population continued to make spontaneous reference to alterations in sexual activity during the final visit following 2 months of treatment.

The results of the study show that reboxetine is, in general, a well tolerated treatment, with an incidence of AEs of 21.3%. The AEs observed are those described in previous studies with reboxetine. The AEs related to the product are quick to appear following the start of treatment and made necessary an adjustment of the dose in 17.3% of cases and a withdrawal of the treatment in 30.8% of the AEs observed

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