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Superintendencia de Industria y Comercio
E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00067212 00000006 Folios: 16
Fecha (AMD): 2006-03-15 16:55:10
Tramite : 002 PATENTES D 1 REGISTRO/ 444 RESPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Trámite :002
Evento :001
Actuación :444

Referencia	:	Expediente No. 00067212
Asunto	:	Solicitud de patente para **SOLUCIONES FARMACEUTICAS DE LEVOSIMENDAN**
Solicitante	:	ORION CORPORATION
Fecha de solicitud	:	6 de septiembre DE 2000

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al oficio número 2087 notificado por fijación en lista del 23 de febrero de 2005.

2. Mediante el oficio número 2087 se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1 Requerimiento de acuerdo al Art. 46 de la Decisión 486 de la Comisión de la Comunidad Andina:

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Adjunto a este escrito presento el documento requerido por su Despacho de acuerdo con el Artículo 46. Manifiesto que el artículo requerido por ese Despacho no es relevante para el estudio de patentabilidad de la presente solicitud puesto que no está dirigido a la materia aquí reivindicada.

3. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

Anexos:

1. European Neuropsychopharmacology, 7, suppl.1, 1997, s37-s47

Bogotá, 15 MAR. 2006
Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO 08962-801-002-0
ZCA/ZCA/ID-000086/WPCL8962

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European Neuropsychopharmacology 7 Suppl. 1 (1997) S37–S47

EUROPEAN NEURO-PSYCHOPHARMACOLOGY

Efficacy and tolerability of reboxetine compared with imipramine in a double-blind study in patients suffering from major depressive episodes

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Abstract

A 6-week, randomised, double-blind, multicentre study in 256 patients with a DSM-III-R diagnosis of major depression was carried out to compare the selective noradrenaline reuptake inhibitor (NARI), reboxetine, with the reference standard tricyclic antidepressant, imipramine. The efficacy of reboxetine, as measured by the extent of improvement of Hamilton Depression Rating Scale, Montgomery and Asberg Depression Rating Scale and the Clinical Global Impression Scale, was similar to that of imipramine. The improvement was observed in the overall population and in severely depressed and melancholic patients. Reboxetine tolerability compared favourably with that of imipramine. Frequency of discontinuation due to adverse events was lower in the reboxetine-treated group (10.0%) than in the imipramine-treated group (14.3%), and the cumulative risk of development (Kaplan–Meier analysis) of dry mouth, hypotension and/or related symptoms and tremor was significantly higher on imipramine than on reboxetine.

Keywords: Selective noradrenaline reuptake inhibitors (NARIs); Reboxetine; Major depression

1. Introduction

Reboxetine is a selective noradrenaline reuptake inhibitor (NARI), highly potent in animal models predictive of antidepressant efficacy (Melloni et al., 1984; Riva et al., 1989). Pharmacodynamic studies in humans confirm the animal findings. In placebo-controlled conditions, single oral doses of 1 and 3 mg of reboxetine had dose-related effects on the CNS, with modifications at quantitative power spectrum analysis of the human electroencephalogram similar to 75 mg imipramine in the fronto-central, but not in the occipito-temporal derivative (data on file). There was also increased growth hormone release (data on file), probably due to hypothalamic noradrenergic stimulation (Laakmann, 1983). A dose-ranging study in patients with major depression showed that reboxetine is well tolerated when administered for 4 weeks at fixed doses up to 10 mg/day. Daily doses of 8 or 10 mg provided the largest safety margin (data on file). The controlled study reported in this paper compared the efficacy and tolerability of reboxetine with the tricyclic antidepressant (TCA) imi-

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0924-977X/97/$17.00
PII S0924-977X(97)00418-5

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2. Experimental procedures

2.1. Study design and patients

This prospective, double-blind, randomised, parallel-group, multicentre trial was carried out in 22 centres located in Germany, Belgium and South Africa. Patients of either sex, of any race, aged 18–65 years, under in-patient care or attending out-patient or day-hospital clinics for a major depressive episode (DSM-III-R, American Psychiatric Association, 1987) were included. Patients with a pre-treatment total score for the 21-item Hamilton Depression Rating scale (HAMD) of ≥22 (Hamilton, 1960), and with the depressive episode present for at least 1, but no more than 4 months were recruited. Informed consent was obtained from each patient prior to screening.

At screening, a full medical history review and physical examination (including chest X-ray, electrocardiogram (ECG) and vital signs) were carried out and laboratory tests for the assessment of haematopoietic, hepatic, renal, thyroid (TSH and T_4) and glucose handling function were performed. Exclusion criteria included: history of major depressive episodes associated with endocrine disorders or of drug hypersensitivity; pregnancy detected by a pregnancy test at the end of the wash-out period; refusal by female patients of childbearing age to use effective contraception during the study period; participation in another clinical study in the 4 weeks preceding the study; evidence of Substance Use Disorder (DSM-III-R), currently or within the past 6 months; chronic respiratory insufficiency (determined by physical examination and X-ray); history or presence of gastrointestinal, hepatic or renal disease, or other conditions known to interfere with the absorption, distribution, metabolism and excretion of drugs; history of seizures or brain injury; current evidence of clinically important haematopoietic or cardiovascular diseases; current evidence of thyroid function disorders, urinary retention or glaucoma; symptoms of any other important clinical illness in the 4 weeks preceding the study; electroconvulsive therapy in the previous 6 months; clinically relevant abnormal findings in the physical examination, laboratory tests and ECG at admission; patients with high risk of suicide.

After an initial wash-out period of 4–14 days, patients were randomised to one of the following treatments: oral reboxetine 4 mg twice daily, or imipramine 50 mg in the morning and 100 mg in the evening (50 mg for the first 3 days), for 6 weeks. After 3 weeks of treatment, if the patient experienced an unsatisfactory response but tolerated treatment well, the daily dose was increased to 10 mg for reboxetine and 200 mg for imipramine. Individual patient treatments were supplied in indistinguishable capsules, packed in weekly cartons. Individual treatment information was supplied in sealed envelopes for emergencies necessitating treatment identification.

With the exception of hypnotics such as chloral hydrate (0.5–1 g) used for sleep induction on a pro re nata basis, no concomitant medication was allowed on entry and during the course of the study. In the case of events arising during the course of the study, non-psychotropic medications needed for the patient's welfare could be administered, and were recorded on the case report form. Approval from the Ethics Committees or Institutional Review Boards of the participating centres was obtained in accordance with the regulations and requirements of individual countries.

2.2. Assessments

Efficacy assessments, at baseline and at weekly intervals thereafter, included the HAMD, the Clinical Global Impression (CGI), (Guy, 1976), and the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The MADRS items were scored from 0 to 3, as in Asberg et al., 1978.

Safety and tolerability were assessed in the following way. Adverse events were reported, spontaneously and by a check-list. Body weight, blood pressure and heart rate (measured in lying position after 5 min rest, and in standing position, 1–2 min after standing up) were measured at baseline and at weekly intervals thereafter. ECG and laboratory tests (full blood count, serum electrolytes, liver enzymes, urinalysis, blood sugar, serum alkaline phosphatase, blood urea nitrogen, serum creatinine, uric acid, bilirubin, total serum protein and electrophoresis, serum cholesterol and triglycerides) were also performed, at baseline and on days 21 and 42.

2.3. GCP compliance, data quality assurance

The study was conducted in accordance with the Declaration of Helsinki 1974 (version of Venice, 1983) and according to standard operating procedures for study monitoring and co-ordination. For training purposes, reliability sessions on the instruments used for the assessment of change were carried out. These took place during investigator meetings and/or during monitoring visits.

2.4. Statistical analysis

The primary efficacy assessment was defined as the absolute decrease of the HAMD total score at last assessment vs. baseline. Ninety-five percent confidence intervals of the mean difference in each treatment arm were computed using the standard error (S.E.) obtained from the ANOVA, and the 95% confidence interval for the difference between treatments was calculated (Gill, 1978). The standard deviation of the outcome variable was expected to

be of approximately nine points (see, e.g. Stark and Hardison, 1985) and the drop-out rate before the first post-baseline assessment was expected to be 10%. Under such assumptions a sample size of 100 patients recruited in each treatment arm was expected to provide a confidence interval of the between-treatment difference of the outcome variable, of 5.3 points (2.65 points each side). The same analysis was carried out in two subsets of patients. One sub-set of patients were defined as those judged markedly (score 5) to severely (score 6/7) ill at entry according to the CGI-Severity of Illness scale (Guy, 1976). The second subset were melancholic patients defined retrospectively by applicable DSM-IV criteria (i.e presence of item 2, 'loss of pleasure in all or almost all daily activities' in the DSM-III-R classification at entry (American Psychiatric Association, 1994) and of at least three of the following in the baseline HAMD scale: *late insomnia* of maximal severity, agitation or retardation of at least moderate severity (score≥2), definite loss of weight or loss of appetite of maximal severity, diurnal variation with worsening in the morning, excessive or inappropriate guilt (score 2 or 3).

Secondary efficacy assessments were response (a decrease of at least 50% in the total HAMD score) and remission (a total HAMD score of 10 or less) at last assessment. Ninety-five percent confidence for within-treatment and between-treatment differences were calculated (Peace, 1988).

The cumulative probability of response (*time to onset* of response confirmed at all subsequent assessments) was calculated by the Kaplan–Meier method and the comparison of treatment groups was carried out using the log-rank test (Kalbfleisch and Prentice, 1980). Homogeneity of baseline HAMD-21 *total* scores as well as homogeneity of variances across treatment groups were tested by ANOVA. Summary statistics of the HAMD total score and of the secondary efficacy assessments (MADRS and CGI) at each visit and at the last valid observation were calculated. The data analysed included all patients entered into the trial, with the exception of patients who had no post-baseline evaluations.

Physical parameters measured at each assessment were summarised by descriptive statistics. The frequency of patients showing clinically relevant change (20% or more vs. baseline), accompanied by absolute critical values (≥160 or ≤100 mmHg for *systolic blood pressure*; ≥100 or ≤70 mmHg for diastolic blood pressure; ≥100 or ≤50 bpm for heart rate) at each assessment were calculated. ECG tracings were interpreted by cardiologists and the presence of pre-coded individual abnormalities identified. Frequency of individual abnormalities in each treatment group at baseline, during the trial period and at last assessment were calculated.

Laboratory test results were classified as normal or abnormal on the basis of the normal ranges provided by the performing laboratory. Changes of frequency distributions over time were tested by MacNemar or Stuart Maxwell test (Fleiss, 1973). Continuous values of laboratory tests were standardised according to a method proposed by Chuang-Stein (Chuang-Stein, 1992), and changes over time were tested by the Wilcoxon Rank Signed test for paired data (Hollander and Wolfe, 1973). Abnormal values of laboratory tests were identified as clinically relevant on the basis of standard criteria and their frequency over time calculated.

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Statistical analyses were carried out with SAS PROCs (version 6.07) (except Stuart–Maxwell test and confidence interval calculation).

3. Results

3.1. Patient population and treatment

Of the 256 patients in the study, 130 were randomised to reboxetine treatment and 126 were randomised to imipramine treatment. The majority of patients entering the trial were classified as markedly to severely ill (80% in the reboxetine group and 72% in the imipramine group (see Fig. 1a and b)). Demography, diagnosis and history of the depressive disorder in the two treatment groups are described in Table 1.

The majority of patients were Caucasian and female; the ratio of females to males was similar in both groups. The two treatment groups were well matched for age, height, weight and race. The proportion of recurrent cases was slightly higher in the reboxetine-treated group (60.8%) than in the imipramine-treated group (54.8%). The mean age of onset, median number of previous episodes of depression and mean duration of the index episode were similar in the two treatment groups. The onset of the index episode was acute or subacute in 70% of the reboxetine-treated patients and 65% of the imipramine-treated patients. Precipitating external stress was absent more frequently in the reboxetine-treated group (40.0%) than in the imipramine-treated group (28.6%).

Protocol violations, both at admission and during the treatment period, were rare in both treatment groups. The index-episode duration was shorter than 4 weeks in four of the reboxetine- and two of the imipramine-treated patients and was longer than 4 months only in one reboxetine-

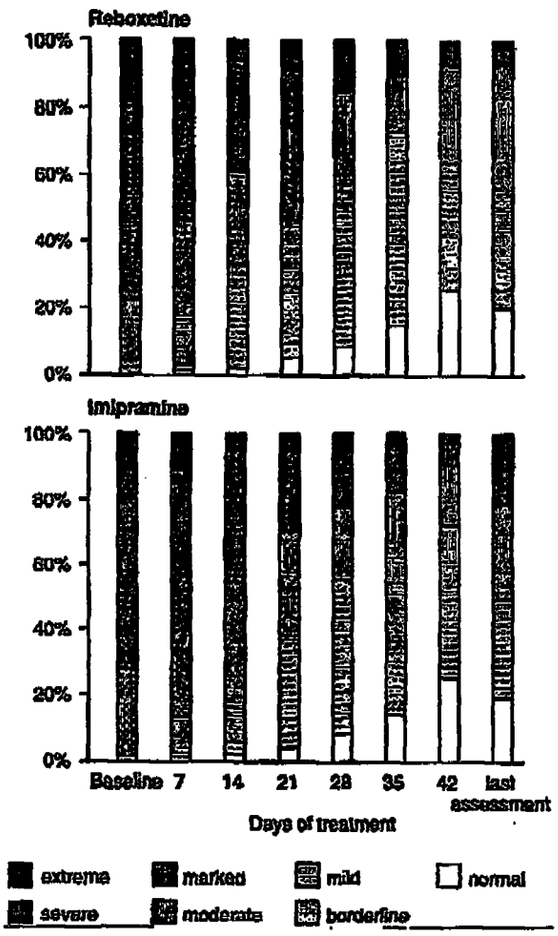

Fig. 1. CGI-severity of illness: score frequency distribution at each assessment interval and at last assessment in the reboxetine and imipramine groups.

group patient. Long-acting benzodiazepines were administered to five reboxetine-treated patients and six imipramine-treated patients. Additional psychotropic medications were administered to six patients in both treatment groups.

As shown in Table 2, a total of 188 patients (73.4%) completed the study and 68 (26.6%) withdrew; 32 (24.6%) in the reboxetine-treated group, and 36 (28.6%) in the imipramine-treated group. Adverse events or intercurrent illnesses newly emerged during the treatment period were the main reasons for withdrawal in 13 patients (10.0%) treated with reboxetine (including one suicide) and in 18 patients (14.3%) treated with imipramine. Deterioration was the main reason for withdrawal in eight patients in the reboxetine-treated group and seven patients in the imipramine-treated group. Remaining cases included mainly uncooperative patients (seven and five in reboxetine and imipramine treatment groups, respectively)

At the end of the initial 3 weeks of treatment, 13 patients (10%) in the reboxetine-treated group and 16 patients (12.7%) in the imipramine-treated group had their daily dose increased from 8 mg to 10 mg of reboxetine and from 150 to 200 mg of imipramine. Over the following period, nine additional patients on reboxetine and six on imipramine were switched to the higher dose level (as

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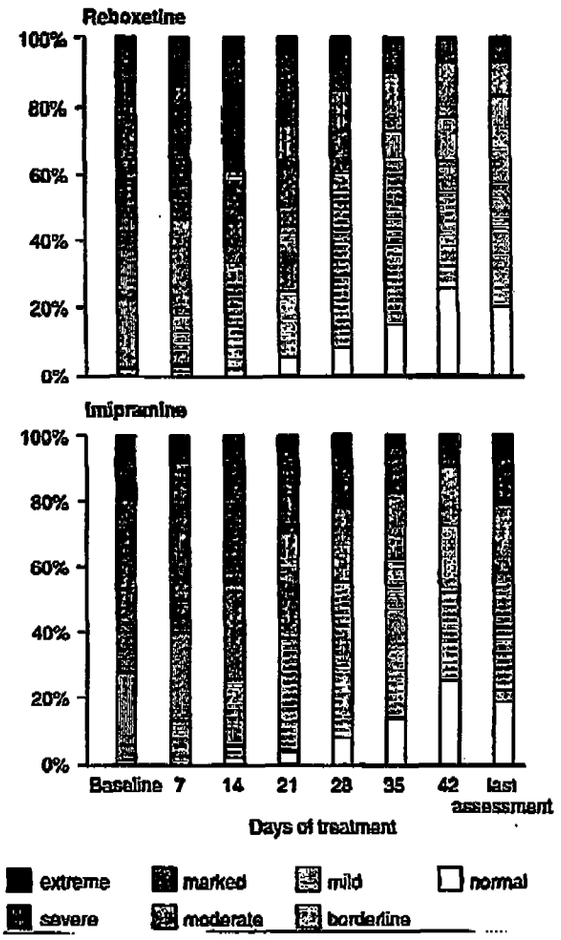

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Table 1
Demography, psychiatric diagnosis and history

Variable		Reboxetine (n=130)	Imipramine (n=126)
Sex (%)	Female/male	64.6/35.4	65.9/34.1
Race (%)	Caucasian	90.0	93.6
	Black	7.7	6.4
	Other	2.3	0.0
Age in years	Mean (±S.D.)	45.4 (±12.0)	42.4 (±13.6)
Height in cm	Mean (±S.D.)	167.4 (±8.0)	167.8 (±8.9)
Weight in kg	Mean (±S.D.)	68.7 (±11.4)	69.4 (±13.8)
DSM-III-R (%)	Recurrent	60.8	54.8
	Single episode	39.2	45.2
Age of onset in years	Mean (±S.D.)	39.6 (±13.2)	38.9 (±13.9)
Number of previous episodes	Median (range)	2 (1–11)	2 (1–40)
Duration of index episode in weeks	Mean (±S.D.)	8.2 (±5.2)	8.6 (±3.9)
Onset of index episode (%)	Acute	8.5	8.7
	Subacute	62.0	56.4
	Insidious	29.5	34.9
Presence of precipitating stress (%)	Absent	40.0	28.6
	Probable	34.6	40.5
	Definite	25.4	30.9

allowed in the protocol). During the treatment period the daily dose was occasionally decreased (in a maximum of five patients per study day in the reboxetine-treated group and in a maximum four patients in the imipramine-treated group), mainly due to missed doses, lost medication or emergence of signs/symptoms of intolerance. Occasionally patients had their daily dose gradually increased to a maximum of 20 mg/day reboxetine and to a maximum of 350 mg/day imipramine (in a maximum of four patients per day in the reboxetine-treated group and five patients per day in the imipramine-treated group). This led to side-effects including headache, nausea and fatigue in some of the patients taking the high dose of reboxetine. Dry mouth, headache, dizziness, tremor, somnolence and abnormal vision occurred in some of the patients taking the high dose of imipramine.

3.2. Efficacy

3.2.1. Hamilton depression rating scale

The mean values (±S.E.) of the HAMD total score in patients with at least one assessment in addition to baseline are shown in Fig. 2. The mean (±S.D.) HAMD total scores at baseline were similar in both groups: 28.8(±4.8) in the reboxetine-treated group and 28.0(±5.2) in the imipramine-treated group. As the study progressed, there was similar improvement in reboxetine-treated patients (98 patients continuing to receive study medication) and imipramine-treated patients (92 patients continuing to receive study medication), with a minimum value of 9.6(±7.5) and 10.4(±8.2) on day 42 for reboxetine and imipramine treatment, respectively.

The mean decreases of the HAMD total score at last assessment are shown in Fig. 3. The mean decrease was 15.8 points (95% C.I., 14.0–17.5) in the reboxetine-treated group, and 14.3 points (95% C.I., 12.5–16.1), in the imipramine-treated group. There was a difference of 1.5 points in favour of the reboxetine-treated group (95% C.I., −1.0–4.0).

Response or remission by the last assessment is shown in Table 3. At the last assessment 68.5% of the reboxetine-treated patients and 56.2% of the imipramine-treated patients were classified as responders, while 52.0% and 45.5%, respectively, were in remission. The difference in the percentage of patients achieving response in the two

Table 2
Patient disposition

Disposition	Reboxetine (n=130)		Imipramine (n=126)	
	n	%	n	%
Completed study	98	75.4	90	71.4
Discontinued	32	24.6	36	28.6
Due to:				
Adverse event	13	10.0	18	14.3
Deterioration	8	6.1	7	5.6
Patient non-operative	7	5.4	5	4.0
Protocol violation	3	2.3	1	0.8
Other	1	0.8	5	4.0

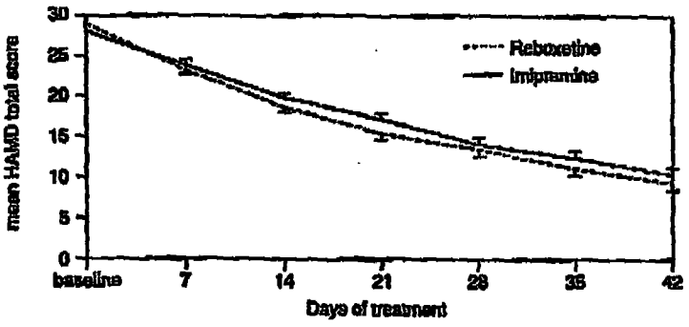

Fig. 2. Hamilton depression rating scale, mean±S.E.

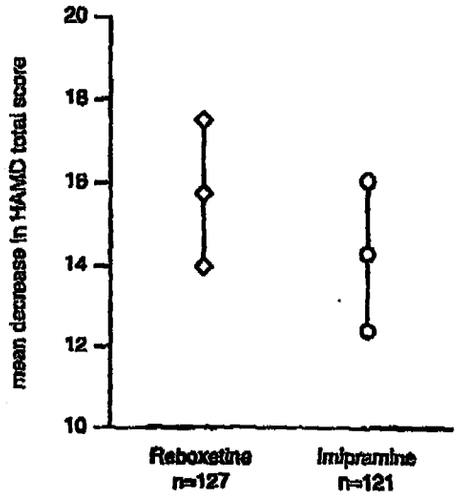

Fig. 3. Mean decrease in the Hamilton depression rating scale total score at last assessment (95% confidence intervals).

Table 3
Response (≥50% decrease of HAMD total score vs. baseline) and remission (HAMD total score≤10) rate at last assessment

Criterion		Reboxetine (n=127)	Imipramine (n=121)
Response	% patients	68.5*	58.2
	95% confidence interval	59.7–76.5	48.9–67.2
Remission	% patients	52.0	43.5
	95% confidence interval	42.9–60.9	34.4–54.8

*Statistically significant difference (12.3% in favour of reboxetine, 95% C.I. 0.3–24.3) compared with the imipramine-treated group.

treatment groups was 12.3% in favour of reboxetine, with a 95% C.I. of 0.3–24.3.

The cumulative probability of response is plotted by the Kaplan–Meier method in Fig. 4. Patients receiving reboxetine had a cumulative rate of response significantly higher than patients on imipramine (P=0.0126). At the end of the third week (Day 22), the cumulative probability of response was 39.7% on reboxetine, vs. 27.6% on imipramine.

Additional analyses were carried out on the patients classified as markedly to severely ill at admission (80% in the reboxetine group and 72% in the imipramine group, according to the CGI-Severity of Illness scale) and on those patients who could be characterised on the basis of available information as melancholic at admission (43% of the 219 patients where information was available for classification). The mean decrease at last assessment of the HAMD total score in patients classified as markedly to severely ill at admission (99 reboxetine-treated patients and 87 imipramine-treated patients) is shown in Fig. 5. Results are very similar to those reported for the total population (Fig. 2), the difference between the two treatments being 2.0 points (95% C.I., −1.0–5.0).

The mean decrease at last assessment of the HAMD total score in patients classified as melancholic at admission in the two treatment groups (51 reboxetine-treated patients, 44 imipramine-treated patients) is shown in Fig. 6. There was a difference between treatment groups of 1.6 points (95% C.I. −3.0–6.3) in favour of reboxetine treatment.

3.2.2. *Clinical global impression*

The percentage of patients scored as normal or borderline on the CGI severity of illness scale increased more rapidly in the reboxetine-treated group compared with the imipramine-treated group (Fig. 1a and b). A similar profile was seen for the CGI-Global Improvement Scores (Fig. 7a and b). The frequency distribution of CGI-Efficacy Index

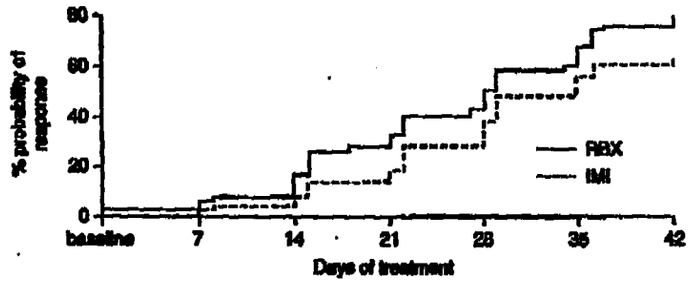

Fig. 4. Kaplan Meier analysis of the cumulative probability of response (>50% decrease of the Hamilton depression rating scale total score).

Score classes at last assessment is shown in Fig. 8. The most relevant difference between treatment groups is seen in the proportion of cases with marked efficacy in the absence of side-effects (index 4): 33.9% of the reboxetine-treated cases vs. 22.3% of the imipramine-treated cases.

3.2.3. Montgomery and Asberg depression rating scale

The MADRS total scores over time and at last assessment are shown in Fig. 9. The mean MADRS total scores at baseline were similar in both groups (17.2 (S.D.±3.3) and 16.9 (S.D.±3.3) in the reboxetine-treated and imipramine-treated patients, respectively). There was a similar improvement in both treatment groups with a minimum value of 5.9 (S.D.±4.6) and 6.0 (S.D.±4.9) for reboxetine and imipramine-treated patients, respectively. At last assessment no difference between treatment groups was apparent.

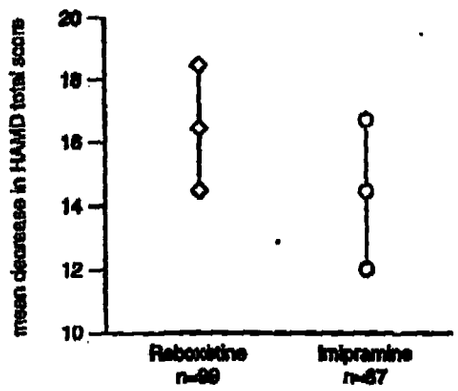

Fig. 5. Mean decrease of the Hamilton depression rating total score at last assessment in severely ill patients (as judged by CGI severity at baseline) (95% confidence intervals).

3.3. Tolerability and safety

3.3.1. Adverse events

81.5% of patients treated with reboxetine experienced an adverse event (an average of 2.5 events each), 31.9% were probably or definitely related to drug treatment. 81.7% of patients treated with imipramine experienced an adverse event (an average of 2.9 events each), 39.0% were probably or definitely related to drug treatment. Males suffered from adverse events more frequently than females when treated with reboxetine (87.0% vs. 78.6%) and imipramine (86.0% vs. 79.5%).

The most frequently reported adverse events are shown in Table 4. The cumulative risks of dry mouth, hypotension and related symptoms, or tremor, (estimated according to the Kaplan–Meier method and log-rank test) were

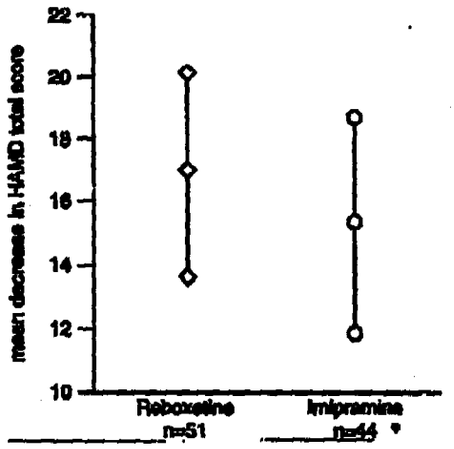

Fig. 6. Mean decrease of the Hamilton depression rating scale total score at last assessment in melancholic patients (as judged by DSM-IV criteria) (95% confidence intervals).

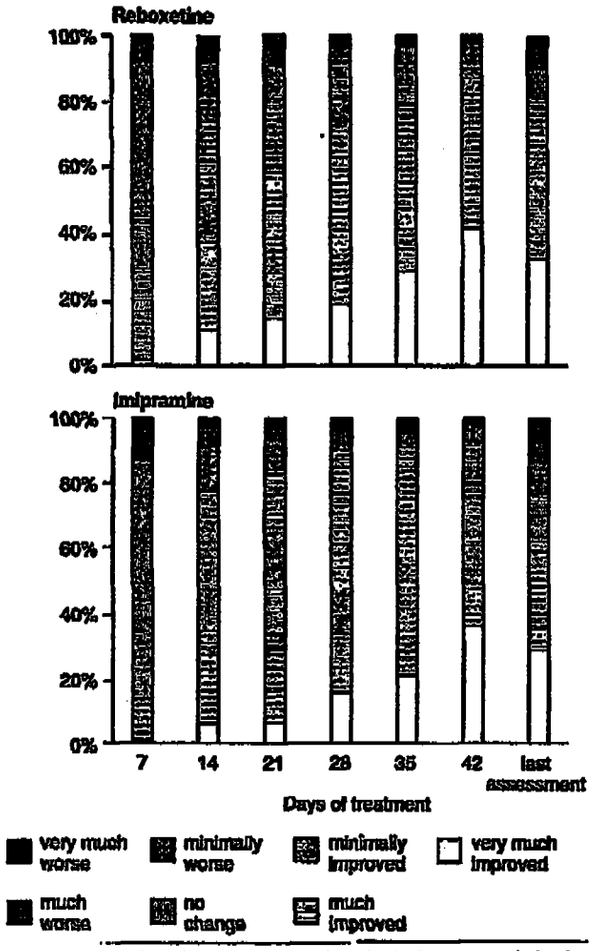

Fig. 7. CGI-global improvement: score frequency distribution at each assessment interval and at last assessment in the reboxetine and imipramine groups.

significantly higher for imipramine-treated patients than for reboxetine-treated patients ($P<0.05$).

The majority of adverse events were judged of mild or moderate severity in both groups with no clear differences in severity between the treatments.

Serious adverse events were reported in four patients. Among the reboxetine-treated patients, one case of suicide (death by firearm) and one of parasuicide were recorded. One imipramine-treated patient suffered from supraventricular tachycardia and another from first degree A–V block. Thirteen patients on reboxetine (10.0%) and 18 on imipramine, (14.3%) had adverse events or intercurrent illnesses as the main reason of withdrawal from the study. In the reboxetine group, events associated with discontinuation more than occasionally (two to three patients) were suicide attempt, insomnia, dizziness, headache, nausea, increased sweating and urinary retention. In the imipramine group, events associated with discontinuation more than occasionally (two to five patients) were tachycardia, headache, dry mouth, tremor, fatigue, dizziness, agitation, asthenia, nausea, confusion, insomnia, somnolence, increased sweating and urinary retention.

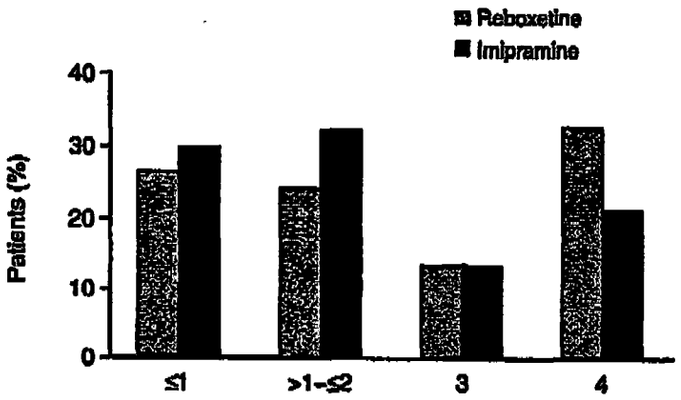

Fig. 8. CGI-efficacy index: frequency distribution of score classes at last assessment in reboxetine- and imipramine-treated patients.
≤1=no advantage of efficacy vs. side-effects.
>1 2=marginal efficacy advantage vs. side-effects.
3=moderate efficacy in the absence of side-effects.
4=marked efficacy in the absence of side-effects.

3.3.2. Physical parameters

These were not modified to any significant extent by either treatment. The only differences concerned the frequency of clinically relevant decreases of both systolic and diastolic blood pressure on standing. This was lower in reboxetine- compared with imipramine-treated patients (4.0% vs. 10.8% of patients, respectively). The frequency of heart rate values which increased ≥20% vs. baseline to ≥100 bpm was slightly higher for reboxetine-treated patients than for imipramine-treated patients, particularly on standing (27.6% vs. 21.2% of patients, respectively). However, the majority of these changes in blood pressure and heart rate occurred only once. Body weight and temperature were not affected by either treatment.

3.3.3. Electrocardiogram

No effect on cardiac function was indicated by ECG recordings. At last assessment, abnormalities newly

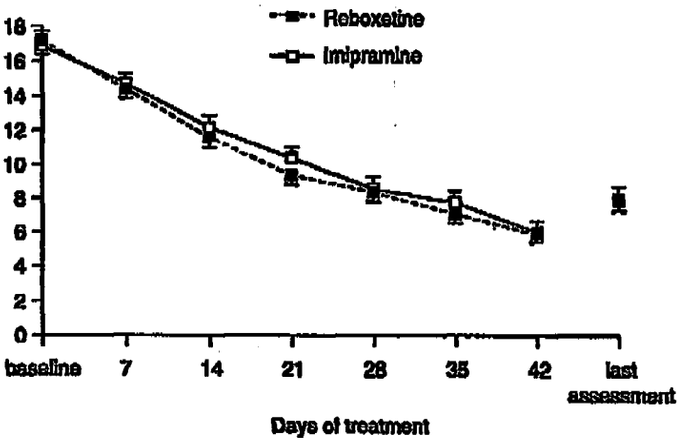

Fig. 9. Montgomery–Asberg depression rating scale; mean values and standard errors at each assessment interval and at last assessment.

Table 4
Frequency of adverse events occurring in 5% or more of patients in at least one treatment group

Adverse event	Reboxetine (n=130)		Imipramine (n=126)	
	n	%	n	%
Dry mouth	32	24.6	45	35.7
Headache and/or migraine	21	16.2	18	14.3
Nausea and/or related symptoms	19	14.6	14	11.1
Increased sweating	18	13.8	18	14.3
Constipation	13	10.0	13	10.3
Hypotension and/or related symptoms	13	10.0	23	18.3
Insomnia	10	7.7	14	11.1
Urinary hesitancy and/or retention	10	7.7	6	4.8
Agitation and/or anxiety and/or nervousness	9	6.9	9	7.1
Tachycardia	8	6.2	13	10.3
Somnolence	4	3.1	9	7.1
Tremor	2	1.5	13	10.3

emerged in more than one patient included sinus tachycardia (8.4% of reboxetine-treated patients and 4.2% of imipramine-treated patients); disorders not classifiable as rhythm, conduction or ischaemic disorders (1.8% of reboxetine-treated patients); and occasional ventricular ectopic beats (3.1% of imipramine-treated patients).

3.3.4. Laboratory tests

There were no clinically significant changes in laboratory test values in either treatment group.

4. Discussion

This comparative, controlled study was undertaken to estimate the difference in efficacy, measured by the change of the HAMD total score, between reboxetine and imipramine. The results for the imipramine-treated patients were similar to those from studies comparing imipramine treatment and placebo. For example, Stark and Hardison (1985), in a large multicentre outpatient study, found a similar mean HAMD total score at baseline, and a mean improvement in HAMD (after a 6-week course of treatment with imipramine) of 12 points (S.D.±10.1). This was only slightly lower than the 14.3 points improvement (S.D.±9.6) seen in our study. In their study the mean HAMD improvement in patients receiving placebo was 8.2 points (S.D.±9.0). In the study described here, the difference in efficacy, as measured by the HAMD, between treatment groups was of 1.5 points and the 95% C.I. (−1.0, 4) in favour of reboxetine indicates that the true difference ranges from a lower 'clinically irrelevant' limit in favour of imipramine to an upper 'clinically relevant' limit in favour of reboxetine. This indicates that reboxetine is at least as effective as imipramine in the extent of improvement of major depression.

The sub-analysis of severely ill and melancholic patients, confirms the effectiveness of reboxetine in the most difficult cases within major depression, a population reported to respond less well to antidepressant therapy (Kocsis et al., 1990). Severe depression is an experimental condition required for the demonstration of the efficacy of new antidepressant agents (CPMP, 1994).

The percentage of patients showing clinically-relevant improvement was higher in the reboxetine-treated group compared with the imipramine-treated group. In agreement with this, the cumulative probability of response (Kaplan–Meier analysis) was significantly higher (P=0.0126) indicating an earlier onset of response in reboxetine-treated patients. Results from the CGI-Severity of Illness and CGI-Global improvement ratings also show a quicker response in reboxetine-treated patients.

The tolerability of reboxetine was high, as shown by the results of laboratory tests, ECG recordings and physical parameter measurements. Serious adverse events were infrequently reported in either group. The newly emerged adverse event rate was quite high, as expected when using a check list to record adverse events (Spilker, 1984). However, these were judged probably or definitely related to study medication in only a minority of cases.

A significant difference was found in the cumulative risk of individual adverse events (dry mouth, hypotension and/or related symptoms and tremor) in favour of reboxetine. When the investigators were asked to weight efficacy vs. side-effects according to the CGI-Efficacy Index, more of the reboxetine-treated patients than imipramine-treated patients were judged to show evidence of marked efficacy in the absence of side-effects at the last assessment.

The advantage for reboxetine in the cumulative risk of development of hypotension and/or related symptoms was confirmed by blood pressure measurements. The only clinically relevant difference between the two treatment groups was the frequency of decrease in both systolic and diastolic blood pressure on standing which was less frequent in reboxetine-treated patients. The advantage of reboxetine over imipramine in frequency of hypotension is likely to be due to the absence of α_1 noradrenergic receptor-blocking properties of reboxetine (Riva et al.,

1989; Cookson, 1993). The advantage for reboxetine in the frequency of dry mouth and tremor may be due to the relative weakness of its muscarinic cholinergic receptor blocking properties as demonstrated in animal and human models (Beaumont, 1989; Riva et al., 1989; Cookson, 1993; Theofilopoulos et al., 1995).

In conclusion, the efficacy of reboxetine was similar to that of imipramine in the overall population and in severely depressed and melancholic patients. Reboxetine was also better tolerated than imipramine.

References

American Psychiatric Association. (1987) Mood disorders. In: Diagnostic and Statistical Manual of Mental Disorders. Third edition revised, American Psychiatric Association, Washington DC.

American Psychiatric Association. (1994) Mood disorders. In: Diagnostic and Statistical Manual of Mental Disorders. Fourth edition, American Psychiatric Association, Washington DC.

Angst, J., Bech, P., Boyer, P., Bruinvels, J., Engel, R., Helmchen, H., Hippius, H., Lingjaerde, O., Racagni, G., Saletu, B., Sedvall, G., Silverstone, J.T., Stefanis, C.N., Stoll, K. and Woggon, B. (1989) Consensus conference on the methodology of clinical trials of antidepressants, Zurich, March 1988: Report of the Consensus Committee. Pharmacopsychiatry 22, 3–7.

Asberg, M., Montgomery, S.A., Perris, C., Schalling, D. and Sedvall, G. (1978) A comprehensive psychopathological psychiatric rating scale (CPRS). Acta Psychiatr. Scand. 271, 5–27.

Beaumont, G. (1989) The toxicity of antidepressants. Br. J. Psychiatry 154, 454–458.

Chuang-Stein, C. (1992) Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Inf. J. 26, 77–84.

Cookson, J. (1993) Side-effects of antidepressants. Br. J. Psychiatry 163 (Suppl. 20), 20–24.

CPMP. (1994) Guidelines on psychotropic drugs for the EC. Eur. Neuropsychopharmacol. 4, 61–77.

Fleiss, J.L. (1973) Statistical Methods for Rates and Proportions. John Wiley and Sons, New York.

Gill, J.L. (1978) Design and Analysis of Experiments in the Animal and Medical Sciences. The Iowa State University Press, Ames, Iowa, USA.

Guy, W. (1976) ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, Rockville, Maryland.

Hamilton, M. (1960) A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Hollander, M. and Wolfe, D.A. (1973) Nonparametric Statistical Methods. John Wiley and Sons, New York.

Kalbfleisch, J.D. and Prentice, R.L. (1980) The Statistical Analysis of Failure Time Data. John Wiley and Sons, New York.

Kocsis, J.H., Croughan, J.L., Katz, M.M., Butler, T.P., Secunda, S., Bowden, C.L. and Davis, J.M. (1990) Response to treatment with antidepressants of patients with severe or moderate nonpsychotic depression and of patients with psychotic depression. Am. J. Psychiatry 147, 621–624.

Laakmann, G. (1983) Antidepressants. In: Hippius, H. and Winokur, G. (Eds.), Psychopharmacology 1-Part 2: Clinical Psychopharmacology. Excerpta Medica, Amsterdam, pp. 83–86.

Melloni, P., Carniel, G., Della Torre, A., Bonsignori, A., Buonamici, M., Pozzi, O., Ricciardi, S. and Rossi, A.C. (1984) Potential antidepressant agents. α-Aryloxy-benzyl derivatives of ethanolamine and morpholine. Eur. J. Med. Chem.-Chim. Ther. 19, 235–242.

Montgomery, S.A. and Asberg, M.A. (1979) New depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Peace, K.E. (1988) Biopharmaceutical Statistics for Drug Development. Marcel Dekker, New York.

Riva, M., Brunello, N., Rovescalli, A.C., Galimberti, R., Carfagna, N., Carminati, P., Pozzi, O., Ricciardi, S., Roncucci, R., Rossi, A. and Racagni, G. (1989) Effect of reboxetine, a new antidepressant drug, on the central noradrenergic system: behavioural and biochemical studies. J. Drug Dev. 1, 243–253.

Stark, P. and Hardison, C.D. (1985) A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. J. Clin. Psychiatry 46 (3, Sec 2), 53–58.

Spilker, B. (1984) Guide to Clinical Studies and Developing Protocols. Raven Press, New York.

Theofilopoulos, N., McDade, G., Szabadi, E. and Bradshaw, C.M. (1995) Effects of reboxetine and desipramine on the kinetics of the pupillary light reflex. Br. J. Clin. Pharmacol. 39, 251–255.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Doctor
EMILIO FERRERO
(Apoderado)

ASUNTO	Radicación	00067212
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	3951
	Folios	002

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 2 a 25) y las reivindicaciones modificadas 1 a 16 (Folios: 78 y 79), las cuales no representan una ampliación del objeto inicialmente presentado.

La presente solicitud reivindica prioridad finlandesa N° FI19991925 de 10 de septiembre de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de invención:

La presente solicitud se titula: "Soluciones farmacéuticas de levosimendan".

El objeto de la presente solicitud se refiere a soluciones de levosimendan para uso farmacéutico, y particularmente para administración intravenosa. Las soluciones de la solicitud tienen estabilidad mejorada y son particularmente útiles como infusión o soluciones de inyección o concentrados para infusión. El levosimendan o (-)-[[4-(1,4,5,6-tetrahidro-4-metil-6-oxo-3-piridazinil)fenil]hidrazono]propanodinitrilo, es útil en el tratamiento de falla cardiaca congestiva.

Según la descripción, el levosimendan y métodos para su preparación se describen en la EP 565546 y WO 97/35841. El levosimendan es potente en el tratamiento de falla cardiaca y tiene enlace significativo dependiente de calcio a la troponina. Los efectos hemodinámicos del levosimendan, la farmacocinética en el hombre después de dosis vía IV y oral y el uso en el tratamiento de isquemia del miocardio se describen en el estado de la técnica (ver folio: 3). Los estudios clínicos han confirmado efectos benéficos del levosimendan en pacientes con falla cardiaca.

La elaboración de las soluciones de levosimendan y particularmente las soluciones adecuadas para uso intravenoso, involucra numerosos problemas que son causados por la sensibilidad del levosimendan a las influencias químicas y físicas. En soluciones el levosimendan es sensible a la degradación química que limita la vida

media de las soluciones y puede producir productos de degradación indeseables. El levosimendan también es pobremente soluble en agua y precipita fácilmente en las soluciones intravenosas es extremadamente peligrosa en razón a que el material es partículas puede ocluir los vasos sanguíneos. La solubilidad del levosimendan se disminuye adicionalmente en forma severa cuando el pH se baja en neutro, de tal forma que un pH bajo parecería en principio desfavorablemente. De esta forma existe la necesidad de formulaciones acuosas mejoradas de levosmendan que sean química y físicamente estables durante un almacenamiento prolongado y adecuadas para administración intravenosa.

Lo que se reivindica como novedoso es lo siguiente: una solución acuosa farmacéutica que comprende levosimendan o una sal de este como ingrediente activo, caracterizada porque el valor del pH de la solución es inferior a 5.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/50.

Claridad de la solicitud:

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción. Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

Aun cuando se hicieron modificaciones en el capítulo reivindicatorio, de todas maneras se considera que las reivindicaciones 1 a 5 (folio: 78) continúan siendo muy generales, ya que no se especifica una composición o formulación farmacéutica de levosimendan, sino que a partir de la reivindicación 6 ya se habla de una solución farmacéutica más particular. De hecho, tal reivindicación 6 y sus dependientes, no dependen de las anteriores 1 a 5.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 06 ABR. 2006

CONCEPTO TÉCNICO N°: 492	EXAMINADOR TÉCNICO Código N°: 202005	EXAMINADOR JURÍDICO Código N°: