Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

Exploratory study of the efficacy and safety of flexible doses of milnacipran and venlafaxine administered in outpatients with Major Depressive Disorder.

Investigational product	Milnacipran (F2207).
Study Design	Exploratory 24-week, national multicentre, randomised, double-blind, venlafaxine-controlled, parallel group study.
Protocol number	F02207 GE303.
Phase of development	III.
Date of first enrolment	February 22, 2007.
Date of last completed	April 15, 2008.
Coordinator	Pr. J.-P. Olié Centre Hospitalier Sainte-Anne 1, rue Cabanis F-75674 – Paris cedex 14
Sponsor Representatives for study report	Clinical Monitor B. Froger-Gaillard (0 149 108 243). Medical advisor M.T. Petrissans, MD (0 562 242 757). Project Statistician S. Roye (0 562 242 749). Medical Writer C. Touzet, MD (0 562 242 736).

Date of report: June 26, 2009

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: IXEL®	**Referring to Module 5 of the Dossier**	
Name of active substance: milnacipran HCL	**Vol.: .....Page: .....**	

Title of study	**Exploratory study of the efficacy and safety of flexible doses of milnacipran and venlafaxine administered in outpatients with Major Depressive Disorder.**
Investigators	This multicentre study was conducted by 50 psychiatrists and coordinated by ***Pr. Jean-Pierre OLIÉ.***
Study centres	This multicentre study was conducted in 21 centres.
Publication (reference)	Not applicable.
Studied period **date of first enrolment** **date of last completed**	**Phase of development: III** February 22, 2007 April 15, 2008
Objectives:	**Primary objective** **To assess the percentage of responders in both treatment groups, milnacipran or venlafaxine administered up to 200 mg.day^{-1} in flexible doses,** during a treatment period of 8 weeks including a 4-week up-titration period, in outpatients suffering from Major Depressive Disorder. Secondary objectives To assess – clinical response in both treatment groups when treated up to 24 weeks, – safety in each treatment group, – physical pain symptoms / somatic complaints and anxiety symptoms when associated with Major Depressive Disorder.
Methodology:	Randomised, double-blind, venlafaxine-controlled, parallel group study with progressive flexible doses up to 200 mg.day^{-1}, for 24 weeks including a 4-week up-titration period and a down-titration (≤ 15 days). Ten (10) visits: selection, randomisation, Day 14, Day 28, Day 42, Day 56, Day 84, Day 126, Day 168, study end visit (Day 178).
Number of patients (planned and analysed):	195 patients were randomised. 181 patients composed the safety data set (90 on milnacipran, 91 on venlafaxine), 177 composed the Full analysis set (FAS) (90 and 87 respectively) and 166 composed the per protocol data set (82 and 84 respectively).
Diagnosis and main criteria for inclusion:	– Patient having signed the written informed consent, – Outpatient, aged 18 to 70, male or female, – With a MDD episode of moderate or severe score, recurrent, unipolar, without psychotic features (MINI), – With a total MADRS score ≥ 23 at both the selection visit (V1) and visit V2, – Without any clinically relevant abnormalities on clinical examination, laboratory tests and ECG parameters.
Test product, Dose, Mode of administration, Batch number:	Flexible doses: 100 mg.day^{-1} (50 mg *b.i.d.*), 150 mg.day^{-1} (50 mg *a.m.*, 100 mg *p.m.*) or 200 mg.day^{-1} (100 mg *b.i.d.*) per os. F2207 capsules 25 mg: Batch: SB0506 expiry date: September 2008. F2207 capsules 25 mg: Batch: SB0556 expiry date: December 2008. F2207 capsules 50 mg: Batch: SB0507 expiry date: September 2008. F2207 capsules 50 mg: Batch: SB0557 expiry date: December 2008.
Reference therapy, Dose, Mode of administration, Batch number:	Flexible doses: 100 mg.day^{-1} (50 mg *b.i.d.*), 150 mg.day^{-1} (50 mg *a.m.*, 100 mg *p.m.*) or 200 mg.day^{-1} (100 mg *b.i.d.*) per os. Venlafaxine capsules 25 mg: Batch: SB0508 expiry date: September 2008. Venlafaxine capsules 25 mg: Batch: SB0558 expiry date: December 2008. Venlafaxine capsules 50 mg: Batch: SB0509 expiry date: September 2008. Venlafaxine capsules 50 mg: Batch: SB0559 expiry date: December 2008.
Duration of treatment:	24 weeks (168 days).

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Criteria for evaluation:
- MADRS at each visit.
- HAM-D_{17} at the selection visit, on Day 1, Day 56 and Day 168.
- CGI – severity at the selection visit, on Day 1, Day 56, Day 168 and Day 178.
- CGI global improvement on Day 56, Day 168 and Day 178.
- VAS associated symptoms, on Day 1, Day 56 and Day 168.
- Covi scale at the selection visit, on Day 1, Day 14, Day 28, Day 42, Day 56 and Day 168.
- Adverse events at each visit.
- Laboratory parameters haematology, haemostasis, biochemistry and hormonology at the selection visit (V1), on Day 56 (V6) and Day 168 (V9).
- Vital signs and physical findings at each visit.
- Electrocardiogram at the selection visit, on Day 28, *(Day 42, Day 56)*, Day 168.

Statistical methods:

Demography: Descriptive statistics.

Efficacy

- MADRS on Day 56 and Day 168.
  - . responders and remitted patients (confidence interval from normal approximation of the binomial distribution on FAS and PP,
  - . factors potentially predictive of the study drug response using a multiple factor logistic regression analysis,
  - . average total score using an OC approach and repeated measurement analysis overtime using a MMRM approach,
  - . average total score using an LOCF approach and an analysis of covariance,
  - . item 6 and 7 descriptive statistics.
- HAM-D17 on Day 56 and Day 168.
  - . responders and remitted patients (confidence interval from normal approximation of the binomial distribution on FAS,
  - . average total score using a using an LOCF approach.
- CGI, Covi scale, VAS on Day 56 and Day 168 descriptive statistics.
- Between group tests (χ^2) for MADRS and HAM-D17 responders and remitted patients on Day 56 and Day 168 according to LOCF approach,
- Analyses on patients with a suicidal risk and patients with a severe major depressive episode on Day 56 and Day 168.
  - . responders and remitted patients according to both the MADRS and the HAM-D17 (confidence interval from normal approximation of the binomial distribution on FAS).

Safety

- Adverse events: frequencies, tabulated individual data.
- Laboratory findings:
  - . tabulated individual data for clinically noteworthy abnormal laboratory values (CNALV), scatter plots including predefined potentially clinically significant changes and CNALV,
  - . descriptive statistics (values and changes) for all parameters,
- Vital signs: descriptive statistics for values and changes, predefined potentially clinically significant changes (PC) and, among them, those leading to clinically significant changes (CSC), orthostatic hypotension.
- ECG / QTc_B and QTc_F: descriptive statistics and frequencies by CHMP classes for values and changes.
- Concomitant treatments: frequencies by ATC classes.

Summary - Conclusions:

The patient's disposition accross the different data sets was well balanced between both treatment groups.

	Milnacipran	Venlafaxine	Total
Randomised data set	97	98	195
Safety data set	90	91	181
Full analysed set	90	87	177
Per protocol data set	82	84	166

The safety data set was composed of 90 patients on milnacipran and 91 patients on venlafaxine. 60.8% of patients were women (61.1% on milnacipran and 60.4% on venlafaxine) with a mean age of 43.7 (sd = 12.1) years. The population studied suffered from major depressive disorders for about 12.6 years with a moderate (41.2%) to severe without psychotic feature (58.8%) current episode. More patients on milnacipran (63.3%) presented a severe major depressive episode than patients on venlafaxine (54.0%). Patients presented a median of 2 previous episodes. This population was in accordance with the target population defined in the protocol.

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Summary – Conclusions *(continued)*:

The study completion from randomisation to study completion was the following:

Number of patients (N)	[Day 1 – Day 56] Milnacipran N	[Day 1 – Day 56] Venlafaxine N	]Day 56 – Day 168] Milnacipran N	]Day 56 – Day 168] Venlafaxine N	Total
Randomised	97	98	-	-	195
Withdrawn	19	15	18	9	61
Safety reason	*12*	*8*	*7*	*2*	*29*
Lack of efficacy	*6*	*5*	*7*	*2*	*20*
Patient' decision or other	*1*	*2*	*4*	*5*	*12*
Completers	-	-	60	74	134

Before Day 56, the imbalance between milnacipran and venlafaxine groups was mainly due to a safety reason. A lack of efficacy (means "worsening" + "insufficient response") was observed similarly in both groups. From Day 56 onwards, the imbalance between milnacipran and venlafaxine groups was due to both a safety reason and a lack of efficacy.

Efficacy results

At the end of an 8-week treatment period, the efficacy of milnacipran and venlafaxine was similar. On the FAS, the main analysis of the primary criterion, *i.e.*, the percentage of MADRS responders on Day 56 in patients on milnacipran and on venlafaxine, evidenced similar results (64.4% and 65.5% respectively) confirmed by the per protocol analysis (68.3% and 66.7% respectively). The percentage of MADRS remitted patients on milnacipran and on venlafaxine was similar (42.2% and 42.5% respectively). The analyses on the secondary parameters strengthened those obtained on the primary criterion. Improvement observed at 8 weeks persisted and even increased until 24 weeks in both groups, but on a more pronounced manner on venlafaxine whatever the parameter concerned.

Efficacy parameters [min max] for quantive parameters	Day 56 Milnacipran N = 90	Day 56 Venlafaxine N = 87	Day 168 Milnacipran N = 90	Day 168 Venlafaxine N = 87
MADRS responders (FAS)	64.4%	65.5%	70.0%	77.0%
MADRS responders (PP)	68.3%	66.7%	-	-
MADRS total score change (LOCF)	-16.8 (sd = 9.3) [-37.0 +11.0]	-16.8 (sd = 8.9) [-37.0 +7.0]	-18.1 (sd = 10.5) [-38.0 +11.0]	-19.6 (sd = 9.8) [-37.0 +7.0]
MADRS remitted	42.2%	42.5%	52.2%	62.1%
HAM-D17 responders	64.0%	55.3%	61.8%	73.3%
HAM-D17 total score mean change	-12.5 (sd = 8.0) [-33.0 +6.0]	-12.6 (sd = 7.8) [-31.0 +10.0]	-13.2 (8.8) [-34.0 +6.0]	-14.7 (8.7) [-31.0 +10.0]
HAM-D17 remitted	31.5%	31.8%	42.7%	45.3%
CGI global improvement mean score	+2.4 (sd = 1.1) [+1.0 +6.0]	+2.2 (sd = 1.1) [+1.0 +6.0]	+2.4 (sd = 1.3) [+1.0 +6.0]	+2.0 (sd = 1.2) [+1.0 +6.0]
CGI global improvement *improved patients*	84.2%	87.2%	80.9%	88.4%
CGI severity *mean change*	-2.0 (sd = 1.4) [-5.0 +2.0]	-2.3 (sd = 1.2) [-5.0 0]	-2.3 (sd = 1.5) [-5.0 +2.0]	-2.7 (sd = 1.4) [-5.0 0]
Covi scale *mean change*	-2.5 (sd = 2.3) [-8.0 +3.0]	-2.8 (sd = 2.6) [-9.0 +3.0]	-2.7 (sd = 2.3) [-9.0 +3.0]	-3.2 (sd = 2.7) [-9.0 +3.0]
VAS back pain *mean change*	-22.8 (sd = 25.1) [-88.0 +20.0]	-26.2 (sd = 27.0) [-100 +28.0]	-25.5 (sd = 26.4) [-84.0 +15.0]	-31.3 (sd = 25.5) [-100.0 +19.0]
VAS joint pain *mean change*	-25.6 (sd = 25.8) [-88.0 +6.0]	-31.2 (sd = 31.4) [-82.0 +45.0]	-28.2 (sd = 23.8) [-81.0 +1.0]	-35.3 (sd = 32.1) [-100.0 +40.0]
VAS weakness *mean change*	-25.3 (sd = 28.4) [-88.0 +43.0]	-24.6 (sd = 29.1) [-95.0 +35.0]	-27.3 (sd = 29.7) [-100.0 +22.0]	-32.1 (sd = 33.1) [-100.0 +35.0]
VAS dizziness *mean change*	-20.4 (sd = 25.7) [-65.0 +21.0]	-16.3 (sd = 24.0) [-94.0 +41.0]	-18.9 (sd = 28.8) [-65.0 +50.0]	-20.0 (sd = 28.9) [-94.0 +41.0]
VAS heart beating *mean change*	-20.7 (sd = 32.5) [-92.0 +72.0]	-22.3 (sd = 26.2) [-88.0 +10.0]	-15.3 (sd = 34.1) [-92.0 +81.0]	-29.5 (sd = 27.5) [-88.0 +10.0]
VAS chest pain *mean change*	-42.3 (sd = 24.2) [-94.0 +6.0]	-27.5 (sd = 29.5) [-79.0 +27.0]	-41.2 (sd = 23.3) [-90.0 –1.0]	-26.8 (sd = 31.6) [-79.0 +30.0]

In the subgroup of patients with a suicidal risk (MINI), the percentage of MADRS responders was more important on milnacipran than on venlafaxine at the end of an 8-week treatment period as well as at the end of a 24 week treatment period.

In the subgroup of patients with a severe current major depressive episode (MADRS), the percentage of MADRS responders, whatever the period, was similar between milnacipran and venlafaxine.

MADRS response rate	Day 56		Day 168	
(% - number of patients analysed)	Milnacipran	Venlafaxine	Milnacipran	Venlafaxine
patients with a suicidal risk (39 /milna; 37 /venla)	66.7% - 39	59.5% - 37	71.8% - 39	64.9% - 37
patients with a severe current major depressive episode(57 /milna; 47 /venla)	61.4% - 57	61.7% - 47	71.9% - 57	74.5% - 47

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Safety results

During the whole study period, 15 serious adverse events were reported in 13 patients: 1 pregnancy (notified as a serious adverse event during the selection period), 6 serious adverse events in 5 patients on milnacipran (uterine abscess, depression, lower limb fracture, multiple drug overdosage associated with anxiety, aneurysm ruptured, inducing the death of the patient, not related to milnacipran) and 8 in 7 patients on venlafaxine (3 depressions, diabetes mellitus inadequate control, overdose associated with anxiety, transaminases increased, biliary colic).

Among the 181 patients from the safety data set, 65 patients on milnacipran reported 271 adverse events and 67 patients on venlafaxine reported 298 adverse events. Patients with at least one treatment emergent adverse event considered by the investigator as related to the study drug or unassessable and with a frequency on study treatment (*i.e.* milnacipran or venlafaxine) higher than 5% was the following:

Preferred terms (MedDRA)	**Milnacipran (N=90)**		**Venlafaxine (N=91)**	
Nausea	18	20.0%	22	24.2%
Headache	16	17.8%	15	16.5%
Dizziness	15	16.7%	20	22.0%
Constipation	12	13.3%	9	9.9%
Hyperhidrosis	12	13.3%	15	16.5%
Palpitations	9	10.0%	7	7.7%
Dry mouth	7	7.8%	10	11.0%
Dysuria	7	7.8%	3	3.3%
Vomiting	5	5.6%	8	8.8%
Poor quality sleep	5	5.6%	2	2.2%
Fatigue	5	5.6%	3	3.3%
Tachycardia	5	5.6%	3	3.3%
Male orgasmic disorders	-	-	6	6.6%
Tremor	4	4.4%	5	5.5%
Tension	2	2.2%	5	5.5%
Decreased appetite	4	4.4%	5	5.5%

Thirty-three (33) adverse events on milnacipran and 20 on venlafaxine induced a premature study drug discontinuation in respectively 20 and 12 patients, dispatched by SOC in the following table (a patient could have more than 1 reason of premature study drug discontinuation).

SOC (MedDRA) or TEAE/study drug discontinuation	**Milnacipran (n = 90)**	**Venlafaxine (N = 91)**
Gastrointestinal disorders	5	5
Psychiatric disorders	4	4
Nervous system disorders	3	3
Renal and urinary disorders (2 dysuria, 1 pollakiuria)	3	-
Reproductive system and breast disorders (2 testicular pains, 1 ejaculation failure)	3	-
Skin and subcutaneous tissue disorders	2	1
Vascular disorders (2 hypertensions, 1 aneurism ruptured)	3	-
Cardiac disorders (1 palpitation, 1 tachycardia)	2	-
Metabolism and nutrition disorders	1	1
Investigations	1	1
Injury, poisoning and procedural complications	1	1
General disorders and administration site conditions	-	1

Among the patients (51/milnacipran and 43/venlafaxine) who reached the highest dosage (200 $mg.day^{-1}$), 4 (7.8%) patients on milnacipran (pain for ejaculation, nervousness, anxious raptus and overdosage, testicular pain, all of them of mild or moderate intensity) and 2 (4.7%) patients on venlafaxine (moderate thoracic pain due to anxiety, diabetes mellitus inadequate control) prematurely discontinued the study treatment due to a safety reason.

The time profiles of haematology, biochemistry or lipid parameters did not show any clinically relevant abnormalities except for 3 patients on milnacipran and 3 on venlafaxine (increase in ASAT/ALAT up to 11N and 8.6N respectively).

A cardiovascular signal was observed in both groups but more pronounced on milnacipran with a mean increase at endpoint in both supine SBP (+3.9 and + 0.7 mm Hg) and DBP (+ 4.0 and +1.0 mm Hg), as well as heart rate (+6.3 and +4.4 bpm) on milnacipran and venlafaxine respectively.

ECG parameters did not show any clinically relevant abnormalities, except QT_{cF} value > 500 ms with QT_{cF} increase > 60 ms in 1 patient on milnacipran and 1 patient on venlafaxine had a QT_{cF} increase > 60 ms.

No unexpected tolerability/safety concerns were reported on both SNRI treatments.

Conclusions

This study shows the efficacy of milnacipran up to 200 $mg.day^{-1}$ in patients with MDD as assessed by the proportion of responders and the rate of remitted patients at 8 and 24 weeks, and shows consistent results on a range of other efficacy measures.

The safety profile of milnacipran in this study is in line with the safety profile described and known for this drug in MDD patients.

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