European Medicines Agency
Evaluation of Medicines for Human Use

REFUSAL ASSESSMENT REPORT

FOR

IMPULSOR

International Non-proprietary Name:
milnacipran

Procedure No. EMEA/H/C/001122

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1. Submission of the dossier

The applicant Pierre Fabre Médicament submitted on 5 June 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Impulsor, through the centralised procedure under Article 3 (2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 23 October 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / Known active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies

The applicant applied for the following indication: treatment of Fibromyalgia syndrome.

Scientific Advice
The applicant received Scientific Advice from the CHMP on 23 June 2005. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:
The product was not licensed for the proposed indication in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Dr. Karl Broich **Co-Rapporteur :** Dr. Ian Hudson

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 05 June 2008.
- The procedure started on 25 June 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 September 2008.
- During the meeting on 20 - 23 October 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 October 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 January 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 March 2009.
- During the CHMP meeting on 16 – 19 March 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 19 March 2009.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 May 2009.
- The Rapporteurs circulated the Second Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 09 June 2009.

- During the CHMP meeting on 22 – 25 June 2009, the CHMP agreed on the second list of outstanding issues to be addressed in writing and in an oral explanation by the applicant. The final consolidated Second List of Outstanding Issues was sent to the applicant on 25 June 2009.
- The applicant submitted the responses to the second CHMP consolidated List of Outstanding Issues on 07 July 2009.
- During the CHMP meeting on 20 – 23 July 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20 – 23 July 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Impulsor on 23 July 2009.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP for the re-examination were:

Rapporteur: Dr. Gonzalo Calvo **Co-Rapporteur:** Dr. Martin Votava

- The applicant submitted a written notice to the EMEA on 28 July 2009 to request a re-examination of the Impulsor CHMP opinion of 23 July 2009.
- During its written procedure on 17 - 20 August 2009, the CHMP appointed Dr Gonzalo Calvo as Rapporteur. Dr. Martin Votava was appointed as Co-Rapporteur.
- The detailed grounds for the re-examination request were submitted by the applicant on 22 September 2009 (Appendix 2 of Final Opinion). The re-examination procedure started on 23 September 2009.
- During its meeting on 19 - 22 October 2009, the CHMP adopted the List of Questions and List of Participants to the SAG on CNS to be held on 5 November 2009.
- The Rapporteur's Assessment Report was circulated on 23 October 2009. The Co-Rapporteur's Assessment Report was circulated on 23 October 2009.
- During a meeting of the CHMP Scientific Advisory Group on CNS on 5 November 2009, experts were convened to consider the grounds for re-examination. During this meeting the applicant presented an oral explanation. A report of this meeting was forwarded to the CHMP.
- The Rapporteurs' Joint Assessment Report was circulated on 12 November 2009.
- During the CHMP meeting on 16 - 19 November 2009, the grounds for refusal were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 16 - 19 November 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final Opinion recommending the refusal of the Marketing Authorisation for Impulsor.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

This application concerns a centralised procedure for Impulsor 25 mg, 50 mg, 100 mg hard capsules (EMEA/H/C/1034) submitted for Marketing Authorisation in the EU and is submitted under Article 8(3) of Directive 2001/83/EC (as amended) as a known active substance.

Milnacipran belongs to the class of nor epinephrine serotonin reuptake inhibitors (NSRIs) that exert their effects by preferentially inhibiting the reuptake of NE over 5-HT and is indicated for the treatment of Fibromyalgia syndrome (FMS), a chronic rheumatological disorder characterized by widespread musculoskeletal pain, tenderness, fatigue, sleep disorders and a constellation of symptoms such as cognition troubles, morning stiffness and mood disturbances.

2.2. Quality aspects

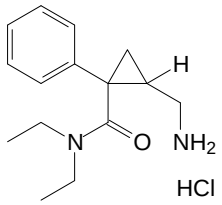
Introduction
Impulsor medicinal product contains the known active substance Milnacipran hydrochloride.
The product is available as hard capsules in the following strengths: 25 mg, 50 mg and 100 mg. The hard capsules are packed into either polypropylene bottles or PVC/ACLAR/Al blisters.

Active Substance

The active substance is not reported in any pharmacopoeia.

The active substance Milnacipran hydrochloride has been developed by Pierre Fabre Médicament. Its manufacture is performed since more than ten years by Pierre Fabre Médicament. The manufacturing process, the specifications and the analytical methods have been transferred to another manufacturer. Complete Active Substance Master Files for both manufacturers have been submitted (no. 2024 and no. 2025, version May 2008). Letters of access as well as the applicant parts of the ASMF have been included in the dossier.

Milnacipran (INN) or $C_{15}H_{23}ClN_2O$ possesses the following structure as described below. Physical and chemical characteristics such as appearance, solubility, hygroscopicity (non hygroscopic), pKa-value, potential isomerism, partition coefficient, polymorphism and particle size have been studied.



- Manufacture

The details of the manufacture and the process controls of milnacipran hydrochloride have been described in the restricted part of the ASMF.

Elucidation of structure
The structure of Milnacipran hydrochloride has been confirmed by elemental analysis (C, H and N), spectroscopic analyses (IR-, UV-, ^{1}H-NMR-, ^{13}C-NMR-, mass spectrometry) and X-ray diffraction studies. Satisfactory spectra have been provided.

Potential isomerism: The manufacturing process can only generate the required *cis* racemic isomers (milnacipran). The *trans* isomers can only be obtained using a different synthesis pathway or by stress studies under forced exposure to light

Polymorphism: Milnacipran does not show any polymorphism showing that the obtained crystalline form is thermodynamically stable. X-ray diffraction studies for batches synthesised by both manufacturers are identical. This has been confirmed by X-rray diffraction and DCS analysis.

Impurities: Potential impurities of Milnacipran hydrochloride such as starting materials, synthesis intermediates, synthesis impurities, degradation products, inorganic impurities, residual solvents and microbiological contamination have been comprehensively discussed. Investigations have been performed in order to detect, identify and quantitate impurities present in Milnacipran hydrochloride.

The microbiological contamination was carried out on ten consecutive industrial batches using Ph.Eur. methods 2.6.12 and 2.6.13. All the industrial batches meet the Ph.Eur. requirements. Based on those results it is justified not to include a routine test of microbiological contamination.

- Specification

Appropriate specification has been set for the active substance and includes the following parameters: appearance, solubility (PhEur), identification (chloride, IR, optical rotation), appearance of the solution (PhEur), water content (PhEur), sulfated ash (PhEur), heavy metals (PhEur), residulal solvents (GC), related substances (TLC and HPLC), assay (HPLC). The specification is considered adequate to control the quality of the drug substance.

The methods used for analysing the active substance have been appropriately described and the validations of the analytical procedures are adequate and in accordance with EU/ICH validation guidelines.
Results from three consecutive production batches of Milnacipran hydrochloride have been presented from each manufacturer. All batches comply with the proposed specification and demonstrate the consistent quality of material.

Adequate justification of specification has been provided. The specifications have been set based on commercial batch data and in accordance with guideline ICH Q6A and with Ph.Eur. In particular the limits sets for the related substances are in line with the guideline ICH Q3A. Also, the limits for the residual solvents are fully in line with ICH recommendations.

For each manufacturer, description of the container used for the active substance has been presented. Adequate tests including appearance and identification of the packaging material have been carried out. The packaging materials comply with relevant EU Directives (food contact requirements in 2002/72/EC) and with Ph.Eur. monographs 3.1.3, 3.1.4 and 3.2.2. Furthermore a certificate stating that materials did not use substances of animal or human origin has been provided and therefore no TSE risk is foreseen.

- Stability

Forced degradation studies
Stability under forced degradation conditions (temperature, light, humidity, oxidation, acid, basic) were performed on one industrial batch. Results showed that the active substance was sensitive to humidity, acid and basic conditions but stable when exposed to temperature and oxidation.
Photostability studies were performed on one batch in line with ICHQ1B conditions and the results show that the active substance is stable when exposed to light.

Long term and accelerated storage conditions

Stability data are presented for three industrial batches kept in the commercial packaging after storage at 25°C/60%RH (up to 48 months) and 40°C/75%RH (6 months) in line with ICH guidelines. The following parameters were monitored: appearance, appearance of the solution, water content, related substances, and assay. The analytical methods used for the stability studies are the same are those used for the control of the active substance and been validated.

The stability data show that the drug substance is stable under long term and accelerated storage conditions over the period tested. All parameters tested in the stability studies remained within the specified limits. Based on the stability data for both manufacturers, a re-test period of 48 months is proposed when stored in the proposed packaging.

Medicinal Product

Impulsor 25 mg, 50 mg and 100 mg hard capsules contain milnacipran hydrochloride as the active substance and the following excipients: calcium hydrogen phosphate dihydrate as diluent, carmellose calcium as disintegrant, povidone as binder, silica hydrophobic colloidal as glidant, magnesium stearate as lubricant, and talc as anti-adherent. All the excipients used are commonly used as pharmaceutical excipients in solid dosage forms.

The capsules shell contain titanium oxide (E171), quinoline yellow (E104), sunset yellow (E110) and gelatin for the cap, and the body.

All excipients are compendial and controlled according to the requirements of the respective Ph. Eur. except for gelatin capsules. Certificates of analysis of each excipient have been provided. Satisfactory specifications for the capsule shells are provided and the test procedures are in line with Ph Eur. The colouring agents of the capsule comply with the specifications of the European Directive 95/45/EC of July 25, 1995 and amendments thereafter.

The hard capsules are packed into either polypropylene bottles or PVC/ACLAR/Al blisters.

- Pharmaceutical Development

The pharmaceutical development has been adequately described

The choice of the active substance based on its physicochemical properties and the excipients were justified. The excipients selected in the proposed formulation demonstrated no incompatibility and ensure good stability. The levels used for the excipients are typical for fast-dissolving capsule formulations. During the pharmaceutical development, all the formulations were found to be bioequivalent with no food effect. The formulation used in pivotal Phase III studies is identical to the proposed commercial formulation.

For convenience of administration and precision of dosage, the capsule was the selected dosage form. Capsules usually exhibit good stability, a high dosage precision and ensure taste masking.

Due to the physical properties of milnacipran hydrochloride (very poor flowability, and low bulk density) the use of a wet granulation process was preferred.

There are no manufacturing overages.

Due to high aqueous solubility of the drug substance and chosen manufacturing process (wet granulation) there is no impact of particle size on dissolution profiles. This is accepted.

- Adventitious Agents

The magnesium stearate used is of vegetable origin. Gelatin used for the manufacture of the hard capsules is obtained by three possible suppliers. For each of the suppliers a valid TSE-Certifcate of suitability is presented. Therefore it is not anticipated to have any risk in relation to the TSE.

A satisfactory TSE declaration for magnesium state is provided. Satisfactory current certificates of suitability for gelatin are provided.

- Manufacture of the Product

Manufacturing process
The manufacture of the hard capsules consists of a wet granulation process. Satisfactory flow diagram detailing the manufacturing process and in-process control testing has been provided as well as a summary of the process. In brief, the API and excipients are mixed by and wet granulated, sieved, and lubricating agents added and filled into capsules.

In-process controls
The control of critical steps in the manufacture is highlighted in the manufacture flow diagram. The critical acceptance criteria include drying, mass uniformity and disintegration. This is accepted.

Process validation
Process validation for three commercial batches of each strength has been conducted in accordance with the EU guideline and Note for guidance ICH Q8. All process data are within specifications and showed that the manufacturing process is reliable and consistent.

- Product Specification

Satisfactory product specification at release and shelf-life for the 25mg, 50 mg, 100mg have been established and the following tests are included: appearance, identification of the active substance (HPLC/TLC), average mass (PhEur), dissolution (PhEur), uniformity of dosage unit by content uniformity (PhEur), assay of the active substance (HPLC), related substances (HPLC), microbial examination (PhEur).

Full justifications are provided for all specifications which are in line with Ph Eur and limits are in compliance with ICH guidelines.

Methods have been fully described and validated in accordance with ICH guidelines.

Satisfactory batch data for three batches for each strength have been provided. All data are within specifications.

The finished product is packed in either
- polyvinylchloride (PVC)/chlorotrifluoroethylene (ACLAR) aluminum blister or
- a polypropylene pill bottle with a LDPE cap.

The secondary packaging is a printed cardboard box, including the leaflet.

Satisfactory specifications and certificates of analysis have been provided. The primary packaging components are conform to the EU food contact requirements in Directive 2002/72/EC and the PhEur. The compatibility of the capsules with the primary packaging systems has been demonstrated by stability data.

- Stability of the Product

Stability studies have been carried out on on two industrial scale batches of Impulsor 20 mg, 50 mg and 100 mg hard capsules kept in the two different commercial packaging (blisters or bottle) under

ICH conditions (up to 12 months at 25 °C/60% RH, 30 °C/65% RH , with bottles: 30°C/75%RH and for 6 months at 40 °C/75% RH).

Stability samples were tested for: characteristics, identification of milnacipran hydrochloride (HPLC), average mass of content, disintegration, dissolution, uniformity of dosage unit, related substances, microbiological examination, and assay of milnacipran hydrochloride content.
The methods used were those used in the release specification for the finished product.

No significant changes were observed after storage under long term conditions and no essential trends were detectable. The product remained stable throughout the stability studies.

Forced degradation studies (heat, humidity) were conducted on one batch (25 mg) and showed that milnacipran is sensitive to heat and humidity.
Photostability studies in accordance with ICH Q1B requirements were carried out on two batches (25 mg and 100 mg). The characteristics, dissolution test, assay of milnacipran hydrochloride and impurities contents were tested and demonstrated the product is stable for 1 month.

In use stability for the pill bottle were carried on one batch (25 mg). Conditions of use were simulated (daily opening of the pill bottle stored at 30°C/75 % RH during 7 days). The characteristics, dissolution test, assay of milnacipran hydrochloride and impurities contents were tested and demonstrated the product is stable for 1 month.

It can be concluded that the stability results support the shelf-life and storage conditions as defined in the SPC when the product is kept in the commercial packaging.

Discussion on chemical, pharmaceutical and biological aspects
The information presented is acceptable and sufficient to guarantee the quality of Impulsor 25, 50, 100 mg capsules. The data submitted on the quality of the drug substance and drug products reflect well researched and well defined products. The development program has taken into account the current directives and CHMP guidelines relevant to this application.

2.3. Non-clinical aspects

Introduction

Milnacipran is intended to be used for the treatment of fibromyalgia, a disorder which is characterized by the presence of chronic musculoskeletal pain, allodynia, sleep disturbances and a variety of other symptoms. At present no validated preclinical models of the fibromyalgia syndrome exists. Therefore, preclinical evaluation of milnacipran in FMS is directed to assess the drug effect on leading symptoms of the disease, i.e. chronic pain, sleep disturbances and mood abnormalities.

GLP
Most of the safety pharmacology studies were done more than 25 years ago which also means that they are not compliant with GLP. Among the 31 studies presented in this section only 14 fulfil the GLP requirements. However, the most critical studies were done in accordance with GLP requirements. Taking into account that data quality and integrity of safety pharmacology studies were ensured and are documented by quality assurance statements included in the respective studies, concerns due to non-compliance in some of these studies do not arise.
All pivotal toxicity studies were conducted in compliance with GLP regulations.

Pharmacology

- Primary pharmacodynamics

Milnacipran was shown to inhibit effectively the uptake of both NE and 5-HT in neuronal as well as non-neuronal tissues. These properties were demonstrated both in vitro and in vivo in a number of

experimental setups, and many of the therapeutic effects of milnacipran, including its analgesic properties, are possibly based on this mechanism of action.
Milnacipran was tested in a variety of animal models of pain. Generally, the analgesic activity of the drug in rats and mice was moderate at best. The effect was more pronounced in models were chronic (neuropathic) pain was investigated.
Similar to clinically established NE and 5-HT reuptake inhibitors, milnacipran showed strong antidepressant activities in a variety of animal models (e.g. bulbectomized rats, PORSOLT test, tail suspension test, helplessness behaviour of mice).
Milnacipran caused only slight modifications in sleep parameters in rats and did not show any anorectic activity.
Summarizing it can be concluded that milnacipran displayed pharmacological activities which were similar to clinically established antidepressants. Whether the observed moderate activity found in chronic pain models is of clinical relevance is a matter of clinical evaluation. With respect to the mechanism of action some data were reported which suggest that the analgesic effects might be related to inhibition of NE and 5-HT uptake at the supraspinal level. Primary pharmacodynamic data obtained from non-clinical species do not allow concluding safely that milnacipran alleviates symptoms of FMS.

- **Safety pharmacology programme**

Safety pharmacology of milnacipran was extensively studied in a variety of in vivo and in vitro tests.
Most of these studies were done more than 25 years ago which also means that they were not GLP compliant. Among the 31 studies presented in this section only 14 fulfil the GLP requirements. However, the most critical studies were done in accordance with GLP requirements. Taking into account that data quality and integrity of safety pharmacology studies were ensured and are documented by quality assurance statements included in the respective studies, concerns due to non-compliance in some of these studies do not arise.
Binding affinities of milnacipran were investigated on a variety of molecular targets (receptors, enzymes, ion channels, transporters). High affinity binding (taking 50% inhibition as a criterion) was only found to NE and 5-HT-transporters.
At the behavioural level milnacipran was evaluated in different species and routes of administration. The general behaviour of mice, rats and monkeys was not affected in therapeutically relevant doses.
Moreover, milnacipran showed no major effects on convulsions or memory, and no adverse cholinergic activity was observed. Furthermore, milnacipran exhibited no psychological or physical dependence liability in monkeys.
The effect of milnacipran on blood pressure and heart rate has been studied in rats, dogs and monkeys under various conditions. Milnacipran exhibited complex effects on the cardiovascular system. In rats milnacipran increased blood pressure during intravenous infusion. In dogs and monkeys, lower milnacipran doses usually increased blood pressure, while at higher doses, a decrease was noted. The observed hypertensive activity of milnacipran was thought to be related to the inhibition of neurotransmitter reuptake (i.e., the proposed mechanism of action of milnacipran). A concomitant decrease in heart rate was attributed to reactive response of the vagus. Changes in QTc interval in dogs and monkeys were minor or not related to milnacipran dosing.
The effect of milnacipran on HERG channel activity was studied in stable transfected HEK293 cells by patch-clamp technique. Up to 10 µM milnacipran was without any effect; however, a statistically significant inhibition in HERG tail current was observed at target concentration of 30 µM. This concentration is far higher than the efficacious concentration determined for the inhibition of NE and 5-HT uptake in vitro (10-200 nM). Taken together, the pronounced effects on blood pressure and heart rate in therapeutically relevant doses might compromise cardio-vascular safety. However, in the monkey there exists a sufficient safety margin with respect to side effects on blood pressure and heart rate. Additionally, special warnings and precautions for use were included in the SPC recommending close monitoring of blood pressure and heart rate in all patients.

Milnacipran showed no significant respiratory and urogenital effects at therapeutically relevant doses. A prokinetic effect on the gastrointestinal tract of dogs and sheep may be attributed to inhibition of 5-HT uptake by milnacipran. In monkeys, milnacipran showed no effects on the gastrointestinal system.

- **Pharmacodynamic drug interactions**

Milnacipran was also tested for drug-drug interactions with of drugs that exhibit central nervous system or cardiovascular activity. In most studies, no prohibitive interactions were observed. In mice, milnacipran exacerbated motor impairment induced by TCAs and other compounds that affect the NE and 5-HT systems and also potentiated the activity of pentobarbital and haloperidol. Furthermore, milnacipran lowered the dose of digoxin that produced extra systoles, tachyarrhythmias, and cardiac arrest in anaesthetised guinea pigs. However, in a clinical trial in healthy human volunteers, no interactions were observed between milnacipran and digoxin at therapeutic levels of both compounds.

Pharmacokinetics

Pharmacokinetic profile of milnacipran was evaluated in vitro as well as in vivo. In vivo studies were performed in mouse, rat, rabbit, dog and monkey.
The bioanalytical methods used for the determination of plasma (mice, rats, monkeys) or urine (monkeys), concentrations of milnacipran and its potential metabolites have been fully validated and were developed for the quantification of either unchanged milnacipran (as racemate or single enantiomers) and potential metabolites. Most of the pharmacokinetic studies in non-clinical species were performed using ^{14}C-milnacipran. Total radioactivity (including parent compound and metabolites) was quantified through liquid scintillation counting.

Absorption of milnacipran was evaluated in mice, rats, dogs and monkeys. Results of these studies suggest rapid absorption of milnacipran after oral administration to animals. The rate of absorption varied from 63 to 77% depending on the species. Following single oral administration of milnacipran to mice, rats and monkeys, plasma concentrations of milnacipran increased to reach concentration peaks between 0.17 and 0.5 hours in rodents and between 1.6 and 4 hours in monkeys. The absolute bioavailability was 61% in rats. Plasma concentrations of unchanged milnacipran decreased rapidly in non-clinical species with corresponding elimination half-lives ranging from 0.9 to 1.9 in rodents and from 2.1 to 3.4 hours.
The pharmacokinetic parameters of milnacipran were compared across gender in rats, rabbits and dogs. No substantial differences were found. Repeat-dose administration does not result in accumulation.

Tissue distribution of milnacipran and/or its metabolites was assessed after ^{14}C-milnacipran single dose orally administered to mice, rats, monkeys and intravenously to rats.
After administration of ^{14}C-milnacipran, tissue distribution was rapid and large, all anatomical and biological structures except bones being radiolabelled. Corresponding highest concentrations were generally observed in the organs and tissues associated with absorption, metabolism and elimination (gastrointestinal tract, liver, kidneys, bile) and in various glands (testes, thyroid, pituitary, pancreas, thymus and adrenal). Cerebral tissues showed labelling in all nonclinical species.In monkeys, uptake of radioactivity into the eyes suggested that milnacipran and/or metabolites have affinities for melanin-rich structures (uveal tract, skin, eyes). It has been demonstrated that milnacipran can cross placental barrier in animals. Excretion into milk was observed. In all species the binding of milnacipran to plasma protein (albumin) was found to be low (15 – 26%).

Metabolic profile of milnacipran was assessed in plasma, urine and feces after oral administration of ^{14}C-milnacipran to mice, rats, monkeys and humans. Additionally, biotransformation by human hepatic microsomes and hepatozytes was investigated.
Generally, the results of in vitro metabolism of milnacipran were in good agreement with the results obtained in vivo. Both in human and non-clinical species the three major metabolites were two glucuronides (d-and l-milnacipran carbamoyl O-glucuronides) and N-desethyl milnacipran. Whereas the major circulating substance in all species was milnacipran, the plasma profile was different with respect to the metabolites: In human the predominant metabolites were the two glucuronides, whereas in non-clinical species the phase I metabolite N-desethyl milnacipran was dominating. These data reflect the fact that from a metabolic point of view non-clinical species and men differ to some extent. Among the rodents, rats are the most suitable species for toxicological studies of milnacipran.

Milnacipran biotransformation by human hepatic microsomes and hepatocytes was limited, less than 14.8% of the milnacipran being transformed by the microsomes. The IC_{50} of milnacipran on the activity of cytochrome P_{450} isozymes was always greater than 84 µM, indicating it is likely that therapeutic usage of milnacipran will not have inhibitory potential on the activity of these isozymes.

The rate and routes of excretion of total radioactivity have been studied following single oral administration of ^{14}C-milnacipran hydrochloride in mice, rats, monkeys and humans.. Radioactivity excretion was rapid, with 70% (monkeys) to 90% (mice and rats) of the administered dose recovered in the excreta within 24 hours after dosing. The route of excretion of total radioactivity was similar in all the studied non-clinical species with the radioactivity of the dose being predominantly excreted in urine.
After oral administration of ^{14}C-milnacipran, the dose was predominantly excreted in urine as unchanged milnacipran both in mice, rats, monkeys and in human.
Taken together, appropriate exposure of milnacipran and its metabolites in the safety evaluation has been demonstrated in the species studied. Absorption, metabolism, distribution and excretion of milnacipran have been adequately described in the studies. Contrary to the situation found in non-clinical species hepatic cytochrome P_{450} enzyme system does not contribute much to the metabolism of milnacipran in humans, which suggests low potential for drug-drug interactions under clinical conditions.

Toxicology

- Single dose toxicity

The oral single-dose toxicity of milnacipran or its enantiomers seemed to be similar in mice and rats with approximate lethal doses of 140 to 215 mg/kg.

- Repeat dose toxicity (with toxicokinetics)

Pivotal repeat-dose toxicity studies were conducted in rats and monkeys with oral application of milnacipran racemate. Milnacipran racemate was also studied after repeated dietary application to mice. The single enantiomers of milnacipran, F2695 and F2696, were investigated in separate repeat-dose studies in rats only. Toxic effects of milnacipran on the liver were observed in all animal species, predominantly in males. In one repeat-dose study in male rats, reversibility of liver effects was shown. However, concerning female rats and other animal species investigated a definite conclusion on reversibility of liver findings cannot be drawn. Decreases in male reproductive organ weights were seen in two long-term studies in rats. Decreases in male reproductive organ weights were also noticed in a fertility study in rats. Irreversible histopathological changes of the spinal cord and male reproductive organs were observed in one study in the monkey. However, these findings were not reproduced in other repeat-dose studies in monkeys. Comparative toxicity studies on the single milnacipran enantiomers and the racemate in the rat revealed qualitatively no major differences in the toxicity profile of both enantiomers. Beside the liver, the ovaries were noted as target organs of F2695 and F2696 toxicity. However, quantitatively, F2696 seemed to be less toxic than milnacipran or F2695.

- Genotoxicity

Milnacipran was tested in a standard battery of genotoxicity test, revealing no evidence for any relevant genotoxic potential of milnacipran.

- Carcinogenicity

Life time carcinogenicity studies in mouse and rat showed slight increases in relative liver weights and centrilobular hypertrophy and vacuolation but no increasing tumor incidence compared to control groups. In a second mouse study in transgenic Tg.rasH2 mice performed to achieve higher exposure levels than in the 2 years study a slight increase in haemiangiosarcomas in different tissues compared to controls was observed in females only. This effect was considered to be accidental as the control

group was unusually negative for this common type of tumor in this species when compared with historical controls. Calculations of safety margins based on plasma exposure levels were only done in the transgenic mouse study (resulting in safety margins of 6 for males and 9 for females) but no comparative data were provided for the conventional life time studies. Pierre Fabre justified this with quality of exposure data from life time studies not deemed sufficient for quantitative analyses. Measurements were only done to ensure absorption of the drug. However the exposure data from life time studies nevertheless gave sufficient evidence that exposure of rodents in these studies was far below human therapeutic exposure levels.

- Reproduction Toxicity

Reproductive and developmental toxicity of milnacipran were evaluated in two fertility studies in rats, embryotoxicity studies in mice and rabbits and two studies on pre/postnatal development in rats. Toxicokinetic parameters were obtained for pregnant mice and rabbits. Otherwise exposure margin calculations are made difficult by missing toxicokinetic data. General toxic effects of milnacipran became evident by decreases in body weight gain, in food consumption and by salivation. In the fertility studies a lower fertility index was observed for high dose groups. Decreases in epididymides and ovary weights were observed in treated F_0 animals. Similar findings were made in repeat-dose studies in rats. Furthermore, effects on corpora lutea counts and histopathological changes in male reproductive organs were observed in repeat-dose studies and/or reproductive toxicity studies in rats or monkeys. In embryotoxicity studies, no effects of milnacipran treatment were seen on fetal viability or development, and examinations revealed no external, visceral, or skeletal anomalies attributable to milnacipran in mice and rabbits. Fetal weights were decreased after milnacipran treatment in mice, which was considered to be incidental by the applicant. A safety margin of 2 for the rabbit and of 7 for the mice towards human therapeutic exposure was calculated for the embryotoxicity studies. In pre-/postnatal development studies, a NOAEL for maternal reproductive performance and for the offspring was established at 2.5 mg/kg/day, which is probably below human therapeutic exposures (proper toxicokinetic data are missing). At higher milnacipran doses, offspring toxicity was evidenced mainly by a reduced number of offspring, decreased pup survival, decreases in pup weight, delays in pup development and impaired fertility of F_1 females. The results of the pre-/postnatal development studies did not yield a clear indication as to whether reduced pup viability was directly due to treatment or was just secondary to impaired maternal care during lactation.
Juvenile toxicity studies have not been performed. The use of milnacipran in children is therefore not supported by any juvenile toxicity studies.

- Toxicokinetic data

Toxicokinetic data for milnacipran racemate are available for all animal species investigated. Toxicokinetic studies differentiating between the single enantiomers have only been performed for the rat. Milnacipran did not accumulate following repeated oral administration in animal species investigated. No clear gender effect was observed in nonclinical species, except for a higher plasma exposure in female rats compared to males. This may be a consequence of a lower biotransformation rate in females. The enantiomeric participation of F2695 and F2696 in the milnacipran pharmacokinetic pattern was found to be globally similar to the one observed with the racemate in the rat. Since no data on the single enantiomers are available for the other nonclinical species, a similar pharmacokinetic behaviour of the single enantiomers can only be assumed for these animal species, too. Unfortunately, no toxicokinetic data are available for lower dose groups where mostly NOAELs were established. Therefore, a calculation of exposure margins is hampered by missing toxicokinetic data. In most of the repeat-dose studies no safety margins to human exposures are obtained and reversibility of toxic effects (liver and reproductive organ tract findings) has not clearly been shown.

- Local tolerance

No studies on local tolerance were performed. This is acceptable.

- Other toxicity studies

In antigenicity study performed in guinea pig milnacipran did not demonstrate an allergenic potential. No immunotoxic potential of milnacipran was identified in standard toxicity studies. According to ICH S8, the immunotxic potential of milnacipran has been adequately evaluated.

On the basis of LD_{50} values, the self-inducing effect of milnacipran was evaluated. After pre-treatment of rats with milnacipran similar LD_{50} values were obtained compared to rats without pre-treatment. Accordingly, in relation to LD_{50} values no potential for a self-inducing effect was found.

Acute toxicity testing of some milnacipran metabolites and a repeat-dose toxicity test for the metabolite F2782 was performed. F1612 has been identified as a degradent of milnacipran in finished drug product at levels exceeding 0.2 %. To qualify the safety of F1612 at a maximum level of 0.3 % in finished drug product, additional studies for acute toxicity, repeat-dose toxicity and genetic toxicity of F1612 were conducted. The stomach and the female reproductive tract were identified as target organs of F1612 toxicity with a NOAEL of 15 mg/kg/day. A 73-fold margin of safety (based on body surface area) for a maximum daily dose of 1 mg F1612 in the milnacipran drug product at the MRHD was calculated. A complete standard battery of genotoxicity tests for F1612 was provided showing only a slight not convincingly reproducible increase in chromosome aberrations in vitro at doses near or exceeding the 10 mM dose level. All other tests including the in vivo study with high plasma exposure levels were negative and therefore the in vitro effects are regarded as artificial due to the extremely high dose.

Rats were pre-treated with phenobarbital (liver enzyme activator), piperonyl butoxide (liver enzyme inhibitor) or diethyl maleate (glutathione depletion) and successively with a single dose of milnacipran. Liver toxicity was assessed by measuring liver enzymes and by necropsy observations. No evidence of hepatotoxicity was noticed under these test conditions. However, this study seems to be of minor relevance concerning the evaluation of hepatic toxicity of milnacipran.

Milnacipran was examined for its phototoxic potential in male albino guinea pigs. No treatment related, severe phototoxic reaction were seen. No exposure data are provided.

Ecotoxicity/environmental risk assessment

The applicant provided a detailed environmental risk assessment on the medicinal product. The environmental risk assessment follows Phase I and Phase II of the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00, June 2006). The CHMP agrees with the applicant that there is no risk to the aquatic compartment (surface water and groundwater) due to Milnacipran hydrochloride. No final conclusion on the risk to sediment organisms was possible.

2.4. Clinical aspects

Introduction

GCP
Statements have been submitted confirming that clinical studies were conducted in accordance with the Ethical guidelines and in compliance with the principles of Good Clinical Practice (GCP).

Pharmacokinetics

- Absorption

Milnacipran hydrochloride (also coded F2207) is a racemate composed of d-milnacipran also coded F2695 and l-milnacipran also coded F2696. Achiral and enantiomeric selective studies have been used in across the different studies.
There were no differences in the pharmacokinetics of d-milnacipran and l-milnacipran when administered alone or as racemate, indicating no interconversion between the two enantiomers.

After intravenous and oral administration of 50 mg milnacipran HCl, the absolute bioavailability of milnacipran was 85% - 90%. After single and repeated oral administration, milnacipran was rapidly absorbed and Tmax averaged 2 to 4 hours after dosing across studies. Tmax was independent of the dose.

- Distribution

Satisfactory studies have been performed to assess the distribution of milnacipran in the blood and its binding properties to blood components and plasma proteins.

- Elimination

Milnacipran is predominantly renally excreted, it is therefore anticipated that impaired renal function will have a significant effect on its pharmacokinetic parameters.

- Dose proportionality and time dependencies

Milnacipran is a racemate. *d*-milnacipran has a longer terminal half-life than *l*-milncipran, 8 to 10 hours and 4 to 6 hours respectively. There were no differences in the pharmacokinetic properties of milnacipran when administered as sole enantiomers and as the racemate suggesting no interconversion between the enantiomers.

Linear pharmacokinetics is demonstrated in the dose range 25 mg to 300 mg.

- Special populations

Terminal half-life and plasma exposure are similar in healthy subjects and those with mild and moderate hepatic impairment. An increase of approximately 30% was seen in $AUC_{0-\infty}$ and a 55% increase in $T_{1/2}$ was seen in patients with sever hepatic impairment. Based on these results the applicant considers that no dosage adjustment is warranted in patients with hepatic impairment.

Severe renal impairment resulted in a 59% increase in Cmax, 199% increase in AUC and 122% increase in T1/2.

Moderate renal impairment resulted in a 26% increase in Cmax, 52% increase in AUC and 41% increase in T1/2. A difference in results was seen between studies and in a second study (M045) a 21% increase in Cmax, 110% increase in AUC and 44% increase in T1/2 was observed.

After oral administration of milnacipran to elderly healthy subjects (aged > 65 years), values for maximum concentration (C_{max}), plasma exposure ($AUC_{0-\infty}$) and terminal half-life ($T_{1/2}$) for milnacipran were higher compared with those in healthy young subjects.

In elderly subjects pharmacokinetic parameters of both d-milnacipran and l-milnacipran after multiple dosing were similarly affected with a 31% and 38% increase in C_{max} and a 27% and 39% increase in $AUC_{0-\infty}$. The differences were attributed to the reduced renal function of elderly subjects. No age-related dose adjustments are considered necessary unless renal function is reduced to values for which dose adjustment is recommended.

- Pharmacokinetic interaction studies

Concomitant use of milnacipran with drugs that affect serotonin reuptake should be maintained contraindicated in milnacipran SPC for FMS patients since interaction has not been systematically studied. Since serotonin syndrome has been reported in the postmarkering experience in MDD usage of milnacipran with other serotinergic agents such as MAOIs, SSRIs, Tramadol and St-John´s Wort and triptans is contraindicated. Milnacipran should further be contraindicated when used with adrenaline and noradrenaline and with clonidine and related compounds.

Special warning (caution) when used with products leading to hyponatremia and bleeding like: NSAIDs, aspirin and other anti-coagulant agents, and diuretics or other treatments known to induce hyponatremia are implemented in SPC.

Pharmacodynamics

Pharmacodynamic studies in human volunteers were coherent with the putative mechanism of action and the pharmacological profile of milnacipran demonstrated in *in vitro* and *in vivo* in animal studies. In general, and in comparison with TCAs, such as amitriptyline, milnacipran has a low pharmacodynamic impact. All of the observed effects are compatible with its only known pharmacological actions, namely the inhibition of the reuptake of serotonin and noradrenaline in the brain and in the periphery and the subsequent stimulation of serotonergic and noradrenergic neurotransmission. The Applicant has addressed the potential for pharmacodynamic interactions with other medicinal products and has provided details of drugs/classes that could or could not interact with the proposed product. The Applicant has provided the principal clases of drugs that could interact with milnacipran.
Concomitant use of milnacipran with drugs that affect serotonin reuptake should be maintained contraindicated in milnacipran SPC for FMS patients since interaction has not been systematically studied. Since serotonin syndrome has been reported in the postmarkering experience in MDD usage of milnacipran with other serotinergic agents such as MAOIs, SSRIs, Tramadol and St-John´s Wort and triptans is contraindicated. Milnacipran should further be contraindicated when used with adrenaline and noradrenaline and with clonidine and related compounds.

Special warning (caution) when used with products leading to hyponatremia and bleeding like: NSAIDs, aspirin and other anti-coagulant agents, and diuretics or other treatments known to induce hyponatremia are implemented in SPC.

The only PK/PD study that examined the effects of milnacipran 200 mg on pain perception in FMS patients showed only a modest effect in favour of milnacipran as compared to placebo. The 5.2 mm VAS downward shift of the stimulus response curve for pressure pain assessment is neither statistically significant (p=011) nor clinically relevant.

Clinical efficacy

The clinical phase II and III studies performed in the target indication are summarized in the following table:

Study number	Design/objective	Treatment groups Daily dose (regimen)	Patients in efficacy analysis	Treatment duration
Phase II				
FMS 021	Randomised, double-blind, placebo-controlled, parallel-group, flexible-dose, Initial safety, efficacy, and tolerability	Milnacipran 25-200 mg/day (QD) Milnacipran 25-200 mg/day (BID) Placebo	46 51 28	12 weeks
Phase III				
FMS-031	Randomised, double blind, placebo controlled, parallel group, fixed dose, Pivotal safety and efficacy	MLN 200 mg/day (BID) MLN 100 mg/day (BID) Placebo	441 224 223	27 weeks
MLN-MD-02	Randomised, double blind, placebo controlled, parallel group, fixed dose, Pivotal safety and efficacy	MLN 200 mg/day (BID) MLN 100 mg/day (BID) Placebo	396 399 401	Up to 29 weeks
F2207 GE 302	Randomised, double blind, placebo controlled, parallel group, fixed dose, Pivotal safety and efficacy	MLN 200 mg/day (BID) Placebo	430 446	17 weeks and 2 days (114 days)
MLN-MD-04	Randomised, double blind, , parallel group, fixed dose, Long-term safety and persistence of efficacy	MLN 100 mg/day (BID) MLN 200 mg/day (BID)	54 330	up to 39 weeks
FMS034	Randomised, double blind, parallel group, Long-term safety and persistence of efficacy	MLN 100 mg/day (BID) MLN 200 mg/day (BID)	48 401	28 weeks

Dose-response studies:
The doses used to evaluate the efficacy and safety of milnacipran were derived from the phase II study FMS021. Based on these results, milnacipran 100 mg/d (BID) and 200 mg/d (BID) were investigated in the phase III studies in the claimed indication. No real dose finding studies have been performed as the previously examined doses for depressive disorder were used in these studies. This was considered adequate.

Main clinical studies:

Treatments and study design
All studies were double-blind, randomised, parallel group studies. The phase II study and the phase III pivotal studies were placebo-controlled while the phase III extension studies were not placebo-controlled.
Phase II study and the 3 pivotal phase III studies: after a washout period which varied in duration depending on the previously used drugs, a 2-week baseline period followed, during which pain and further characteristics of FMS were assessed. Patients then entered a dose escalation phase, followed by a fixed-dose phase. Regarding study GE 3 02, the fixed dose phase was followed by a 9-day down-titration phase, followed by a 2-week follow-up phase without treatment.

	Study	Study design	Objective	Treatment groups	Randomisation ratio placebo: active group(s) (200:100 mg/day)	Duration (weeks)			
						Washout	Baseline	Dose escalation	Fixed dose
Phase 2 study	FMS021	Randomised, double-blind, placebo-controlled, parallel, flexible-dose	Initial safety, efficacy and tolerability	Placebo Milnacipran up to 200 mg/day (up to 100 mg BID) Milnacipran up to 200 mg /day (up to 200 mg QD)	1:1.5 (BID):1.5 (QD)	1 - 4	2	4[a]	8
Phase 3 pivotal studies	FMS031	Randomised, double-blind, placebo-controlled, parallel, fixed-dose	Pivotal safety and efficacy	Placebo Milnacipran 200 mg/day (100 mg BID) Milnacipran 100 mg /day (50 mg BID)	1:2:1	1 - 4	2	3	24
	MLN-MD-02				1:1:1	1 - 4	2	3	12-26[b]
	GE 3 02[c]	Randomised, double-blind, placebo-controlled, parallel, fixed-dose	Pivotal safety and efficacy	Placebo Milnacipran 200 mg/day (100 mg BID)	1:1	1 - 4	2	4	12
Phase 3 extension studies	FMS034	Randomised, double-blind, parallel, fixed-dose	Long-term safety and persistence of efficacy	Milnacipran 200 mg/day (100 mg BID) Milnacipran 100 mg/day (50 mg BID)	4:1[d]	-	-	2[e]	26
	MLN-MD-04				4:1[d]	-	-	2[e]	Up to 37

Objectives

The primary objective of the pivotal studies was to evaluate the efficacy of milnacipran administered at doses of 200 mg/day (BID) and also of 100 mg/day (BID) in the US studies, compared to placebo for the whole complex of the fibromyalgia syndrome, including pain, physical and emotional outcomes.

Outcomes/endpoints

Primary endpoints: All studies comprised pain reduction using a self-reported 0-100 unit VAS scale as primary efficacy endpoint, accompanied by the Patient Global Impression of change (PGIC) and in the US studies (studies FMS031 and MLN-MD-02) by the Physical Component Summary (SF-36-PCS) as co-primary endpoints. The original protocol for study FMS031 used the Fibromyalgia Impact Questionaire (FIQ-PF) as functional endpoint; in the European study GE 302, the FIQ total score was used as a secondary endpoint, following scientific advice from the EMEA.

Besides pain FMS is characterized by additional severe physical and emotional function impairment. Therefore, the FIQ total score as the only adequately validated instrument in FMS is regarded as the most relevant secondary endpoint.

The definition of response was based on responder analyses incorporating pain, patient global status and physical function into a composite assessment. Responder Analyses were conducted as below described, as well as on all three domains:

Study GE 302: The primary efficacy assessment was a composite responder rate based on analysis of two assessments: pain (≥ 30% reduction in pain from baseline in the 24-hour recall pain score recorded in the daily morning report) and PGIC (rating of 1 "very much improved" or 2 "improved"). FIQ total was considered to be a key secondary criterion and was included in the primary efficacy analysis.

Study FMS031: The primary efficacy assessments were composite responder rates. The responder rate for **pain of fibromyalgia** was based on the assessment of pain (≥ 30% reduction in pain from baseline in the 24-hour recall pain score recorded in the daily morning report) and PGIC at the 3-month and 6-month Landmark Visits. The responder rate for **FMS** also included assessment of physical function (≥ 30% improvement from baseline in FIQ-PF subscale score).

Study MLN-MD-02: The primary efficacy assessments were composite responder rates. The responder rate for **pain** of fibromyalgia was based on the assessment of pain (≥ 30% reduction in pain from baseline in the 24-hour recall pain score recorded in the daily morning report) and PGIC (rating of 1 "very much improved" or 2 "improved"). The responder rate for **FMS** also included assessment of physical function using SF-36-PCS (improvement from baseline of at least 6 points).

Criteria for Evaluation (Study GE 302): Regarding the primary analysis of efficacy, patients were classified as responders for the composite primary criterion if they reached the Week 4 visit (end of Dose Escalation) and satisfied the following criteria at Week 16 or premature withdrawal (PW): ≥ 30% reduction from baseline in the PED 24-hour recall pain VAS score during the endpoint period, no

forbidden medications having a potential significant impact on FMS taken for possible FMS reasons during the 2 weeks prior to and including V 8/PW, at least seven available 24-hour recall pain VAS score data during the endpoint period, PGIC rated as "very much improved" or "much improved" (i.e., scored 1 or 2 on the 7 point scale) at the Week 16 visit or PW visit.
The End-of-Fixed-Dose Period was defined: For patients withdrawn after V5: as the 14 days immediately prior to and including V8/PW, limited to seven days before V5. If there were less than seven available daily data, this period was backward extended until seven daily data were available (limited to seven days before V5). If, after the backward extension, there were still less than seven daily data, the pain value was set to missing. For patients withdrawn before or at V5: as the seven days immediately prior and including V8/PW, limited to the day after V3. If there were less than seven daily data, this period was backward extended until seven daily data were available (limited to the day after V3). If, after the backward extension, there were still less than seven daily data, the pain value was considered missing.

In the pivotal studies, patients were classified as responders if they reached a predefined week-visit and satisfied further predefined criteria. However, exclusion of patients who did not reach that point of time resulted in a selected study population and could have influenced results of the studies. Therefore, the applicant was asked to provide supplementary responder analyses for all main trials in which all patients who discontinued prematurely were regarded as non-responders.

Several methodical inconsistencies between the 3 pivotal studies were seen. For example, the studies differed in their mean duration of fibromyalgia symptoms (if they had been evaluated) and in their predefined included BDI baseline scores, resulting in a more depressed study population in the US studies compared to the European population.
In the US studies, patients who had exacerbations of fibromyalgia pain severe enough to require additional analgesic therapy were allowed to use hydrocodone. In the EU study GE 302, short-acting benzodiazepines (e.g. alprazolam and bromazepam) were allowed in cases of severe exacerbation of anxiety.

Baseline data

Inclusion criteria relating to baseline efficacy variables:

Study	Pain		FIQ-PF at baseline (raw score)	BDI
	Scale and timing of assessment	Score		
FMS021	Gracely pain intensity scale recording (weekly recall) at the end of the baseline period (0-20 VAS)	≥ 10	-	-
FM031	Average self reported pain intensity scale recording at the end of the baseline period (0-100 VAS)	≥ 50	-	-
MLN-MD 02		≥ 40	≥ 4	≤ 25 at randomisation visit[a]
GE 3 02		40 - 90 (both inclusive)	≥ 3	≤ 25 at end of wash-out period and randomisation visit

Outcomes and estimation:
The following tables and graphs show the most statistically and clinically relevant results for the three pivotal phase III studies:

Study GE 302
Percentage of responders on PED 24 h-recall pain VAS and PGIC at V8-Week 16, FAS population, LOCF analysis:

	Placebo (N=446)	Milnacipran (N=430)
Responders at Week 16 visit	65 (14.6%)	104 (24.2%)
Model Composite Response = Baseline Pain + Treatment		
OR		1.90
[OR 95% CI]		[1.34 ; 2.68]
Test for treatment effect		p=0.0003

FIQ-Total: Change from Baseline (V3-Day 1) to V8-Week 16 (LOCF) [FAS]:

	Placebo n=446	Milnacipran n=430
Missing	11	17
Baseline		
Mean (SD)	57.14 (11.76)	56.62 (11.80)
[Mean 95%CI]	[56.03 ; 58.25]	[55.48 ; 57.76]
Min/Max	19.48 / 83.48	24.10 / 86.82
Median	56.62	56.98
Value		
Mean (SD)	46.66 (18.71)	43.42 (19.96)
[Mean 95%CI]	[44.90 ; 48.42]	[41.49 ; 45.35]
Min/Max	0.50 / 98.20	1.10 / 89.91
Median	47.52	43.49
Change		
Mean (SD)	-10.48 (18.76)	-13.20 (19.47)
[Mean 95%CI]	[-12.25 ; -8.71]	[-15.08 ; -11.32]
Min/Max	-67.73 / 31.01	-77.75 / 36.03
Median	-7.65	-10.56
Adjusted change, model Change=Baseline+Country+Treatment		
LSMeans (SE)	-11.18 (0.99)	-14.18 (1.03)
Adjusted change difference between treatment groups		
F Test for treatment effect, p=0.015		
[LSM 95% CI] : [-5.42; -0.58]		
LSMeans (SE) = -3.00 (1.23)		

PED 24 h-Recall Pain VAS: Change from Baseline to V8-Week 16 (LOCF) [FAS]:

	Placebo n=446	Milnacipran n=430
Missing	2	4
Baseline		
Mean (SD)	65.05 (12.68)	65.41 (12.85)
[Mean 95%CI]	[63.87 ; 66.24]	[64.18 ; 66.63]
Min/Max	21.21 / 96.23	31.43 / 95.86
Median	65.58	65.07
Value		
Mean (SD)	54.12 (22.74)	49.85 (23.72)
[Mean 95%CI]	[52.00 ; 56.24]	[47.59 ; 52.11]
Min/Max	0.00 / 99.57	0.00 / 100.00
Median	57.00	51.76
Change		
Mean (SD)	-10.93 (20.79)	-15.56 (21.81)
[Mean 95%CI]	[-12.87 ; -8.99]	[-17.63 ; -13.48]
Min/Max	-86.14 / 40.17	-82.07 / 37.17
Median	-7.40	-12.70
Adjusted change, model Change=Baseline+Country+Treatment		
LSMeans (SE)	-11.97 (1.14)	-16.50 (1.18)
Adjusted change difference between treatment groups		
F Test for treatment effect, p=0.001		
[LSM 95% CI] : [-7.29; -1.76]		
LSMeans (SE) = -4.52 (1.41)		

Distribution of patients according to the seven classes of PGIC (ranged between "very much improved=1" and "very much worse=7") at Week 16/PW and the corresponding numeric descriptive summary statistics (LOCF) [FAS]:

	Placebo n=446	Milnacipran n=430
PGIC at V8-Week 16 (LOCF)		
Missing	9	17
Very much improved	15 (3.4 %)	40 (9.7 %)
Much improved	77 (17.6 %)	103 (24.9 %)
Minimally improved	136 (31.1 %)	124 (30.0 %)
No change	142 (32.5 %)	94 (22.8 %)
Minimally worse	36 (8.2 %)	19 (4.6 %)
Much worse	27 (6.2 %)	25 (6.1 %)
Very much worse	4 (0.9 %)	8 (1.9 %)
PGIC at V8-Week 16 (LOCF)		
Missing	9	17
Mean (SD)	3.5 (1.2)	3.1 (1.4)
[Mean 95%CI]	[3.4 ; 3.6]	[3.0 ; 3.3]
Min/Median/Max	1 / 3.0 / 7	1 / 3.0 / 7
Cochran Mantel-Haenszel Test		
p<0.0001		

Study FMS031

Summary of Composite responder Rates at 3 and 6 months:

Summary of Composite Responder Rates at 3 and 6 Months—Pain Claim						
	Composite Response at 3 Months (Indication End Point)			*Composite Response at 6 Months (Extended Treatment)*		
	Placebo (N = 223)	*Milnacipran*		Placebo (N = 223)	*Milnacipran*	
		100 mg/d (N = 224)	200 mg/d (N = 441)		100 mg/d (N = 224)	200 mg/d (N = 441)
Protocol Specified Analysis (LOCF)[a]	27.8%	33.5%	34.9%	25.1%	30.8%	32.2%
		p = 0.187	p = 0.058		p = 0.197	p = 0.053
Protocol Specified Analysis (BOCF)[a]	25.1%	32.1%	32.4%	20.6%	26.8%	27.0%
		p = 0.094	p = 0.048		p = 0.167	p = 0.067
Uniform Program Analysis (BOCF/LOCF)[b]	19.3%	27.2%	26.8%	18.4%	25.9%	25.6%
		p = 0.056	p = 0.032		p = 0.072	p = 0.034
Observed Cases Analysis[c]	27.2%	45.2%	45.4%	27.9%	43.8%	45.2%
		p = 0.003	p < 0.001		p = 0.021	p = 0.001

a Original protocol specified analysis for pain (score of 1, 2, or 3 on the PGIC).
b Uniform program analysis for pain (score of 1 or 2 on the PGIC); BOCF for first 3 months and LOCF for 3-6 months.
c Completers of landmark endpoint with observed values for responder assessment, using the uniform program analysis.

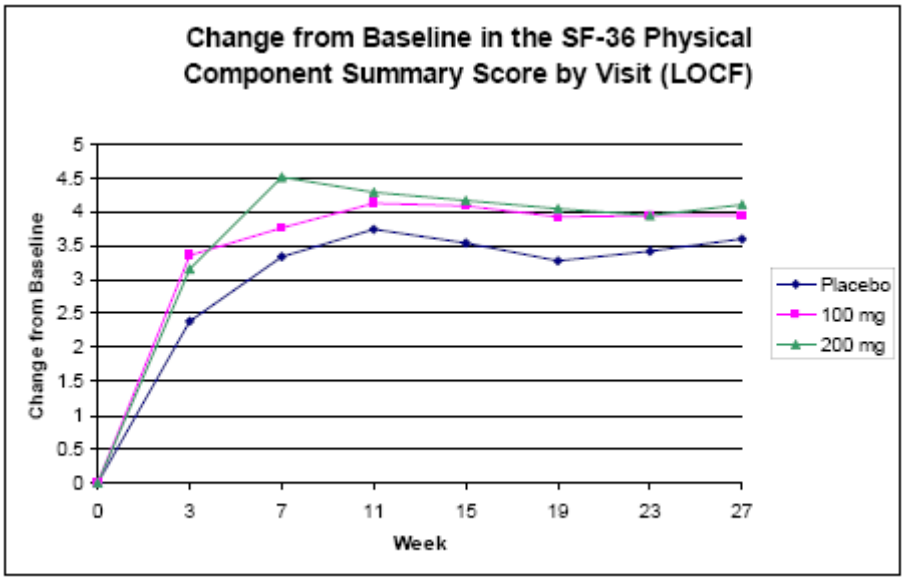
BOCF/LOCF = baseline observation carried forward/last observation carried forward; PGIC = Patient Global Impression of Change.

Summary of Composite Responder Rates at 3 and 6 Months—Syndrome Claim						
	Composite Response at 3 Months (Indication End Point)			*Composite Response at 6 Months (Extended Treatment)*		
	Placebo (N = 223)	*Milnacipran*		Placebo (N = 223)	*Milnacipran*	
		100 mg/d (N = 224)	200 mg/d (N = 441)		100 mg/d (N = 224)	200 mg/d (N = 441)
Protocol Specified Analysis (LOCF)[a]	20.2%	19.6%	23.6%	18.8%	19.6%	22.0%
		p = 0.865	p = 0.328		p = 0.937	p = 0.348
Protocol Specified Analysis (BOCF)[a]	17.5%	18.8%	22.2%	15.3%	17.0%	18.4%
		p = 0.721	p = 0.164		p = 0.819	p = 0.324
Uniform Program Analysis (BOCF/LOCF)[b]	12.1%	19.6%	19.3%	13.0%	18.3%	18.1%
		p = 0.028	p = 0.017		p = 0.245	p = 0.105
Observed Cases Analysis[c]	17.3%	32.8%	32.8%	19.4%	33.3%	31.9%
		p = 0.003	p < 0.001		p = 0.056	p = 0.017

a Original protocol specified analysis for syndrome (score of 1, 2, or 3 on the PGIC and use of the FIQ-PF score for determination of physical function)
b Uniform program analysis for syndrome (score of 1 or 2 on the PGIC and use of the SF-36-PCS score for determination of physical function); BOCF for first 3 months and LOCF for 3-6 months
c Completers of landmark endpoint with observed values for responder assessment, using uniform program analysis.

BOCF/LOCF = baseline observation carried forward/last observation carried forward; FIQ-PF =Fibromyalgia Impact Questionnaire Physical Function Subscore; PIGC = Patient Global Impression of Change; SF-36-PCS = Short Form-36 Health Survey–Physical Component Summary.

Change from Baseline in the Short Form-36 Health Survey–Physical Component Summary Score by Visit (LOCF):



LOCF = last observation carried forward.

Study MLN-MD-02

Summary of Composite Responder Rates:

Primary Efficacy Assessments						
Composite Responder Rates for Milnacipran Versus Placebo at the 3-Month Landmark Visit						
Efficacy Claim	*BOCF Analysis*			*OC Analysis*		
	Placebo (N=401)	*100 mg/d (N=399)*	*200 mg/d (N=396)*	*Placebo (N=262)*	*100 mg/d (N=236)*	*200 mg/d (N=215)*
Pain	16.5%	22.8%	24.8%	25.2%	38.6%	45.6%
		P=.025	P=.004		P=.001	P<.001
Syndrome	8.7%	14.5%	13.9%	13.4%	24.6%	25.6%
		P=.011	P=.015		P=.002	P<.001
BOCF = baseline observation carried forward (all patients who did not have an adequate observation for the evaluation of composite responder status at the 3-month landmark visit were defined as nonresponders); OC = observed case.						

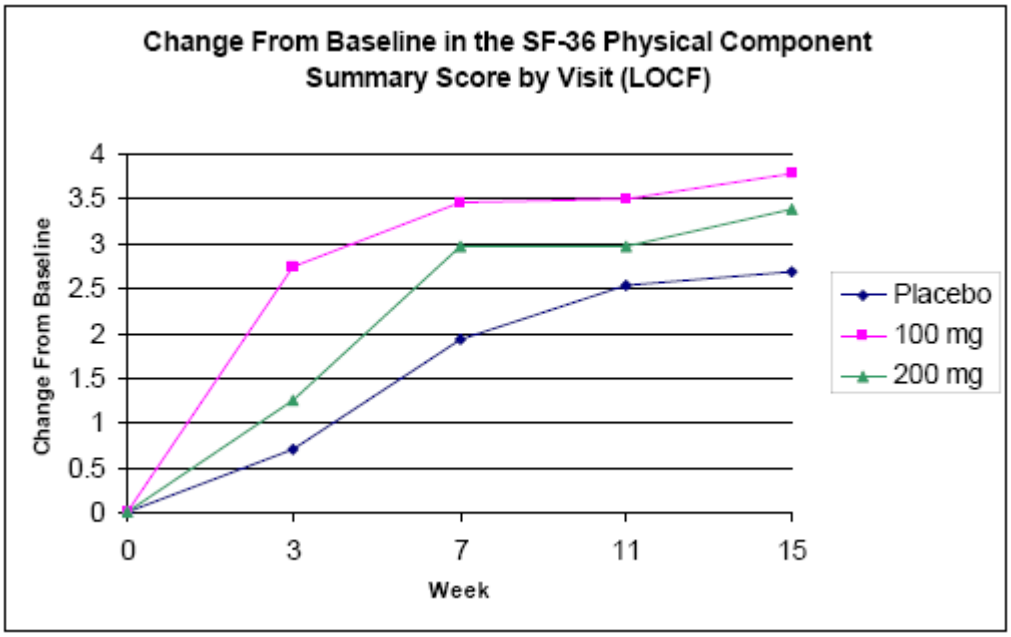
Responder Analysis for the Pain Component of the Composite Responder Criteria at the 3-Month Landmark: ITT Population:

	Placebo (N=401)	*Milnacipran*			
		100 mg/d (N=399)	*200 mg/d (N=396)*		
	% responders	% responders	% responders	OR (95% CI)	P-value
Placebo vs 100 mg/d					
BOCF	25.2	31.1	---	1.33 (0.98, 1.82)	.069
LOCF	28.7	37.3	---	1.49 (1.10, 2.00)	.009
OC[a]	38.4	52.3	---	1.76 (1.23, 2.51)	.002
Placebo vs 200 mg/d					
BOCF	25.2	---	30.1	1.28 (0.93, 1.75)	.125
LOCF	28.7	---	39.9	1.66 (1.23, 2.23)	<.001
OC[a]	38.4	---	54.8	1.95 (1.35, 2.81)	<.001

Change from Baseline in the Weekly Average of PED-Reported Morning 24-Hour Recall Pain Scores for the 3-month Treatment Period (LOCF) Intent-to-Treat Population:

Treatment Group	N	Mean change (week 15)	LS Mean change (SE)*	p-Value*
Placebo	**401**	**-13.00**	**-13.62 (1.359)**	
Milnacipran 100 mg	**399**	**-15.70**	**-15.44 (1.326)**	**0.034**
Milnacipran 200 mg	**396**	**-17.41**	**-18.27 (1.402)**	**0.002**

Change from Baseline in the SF-36 Physical Component Summary Score by Visit (LOCF):



Responder Analysis for the Physical Function Component of the Composite Responder Criteria at the 3-Month Landmark: ITT Population:

	Placebo (N=401)	*Milnacipran*			
		100 mg/d (N=399)	*200 mg/d (N=396)*		
	% responders	**% responders**	**% responders**	**OR (95% CI)**	**P-value**
Placebo vs 100 mg/d					
BOCF	21.5	27.1	---	1.38 (0.98, 1.92)	.063
LOCF	25.4	32.3	---	1.43 (1.04, 1.98)	.029
OC[a]	29.7	41.1	---	1.69 (1.16, 2.44)	.006
Placebo vs 200 mg/d					
BOCF	21.5	---	22.5	1.10 (0.78, 1.55)	.586
LOCF	25.4	---	27.5	1.17 (0.84, 1.62)	.348
OC[a]	29.7	---	34.9	1.35 (0.93, 1.95)	.118

Change from Baseline in FIQ Total Score and Physical Function Score at the 3-Month Landmark Visit (LOCF):

Domain	*Placebo (N=401)*	*Milnacipran 100 mg/d (N=399)*			*Milnacipran 200 mg/d (N=396)*		
	Mean (SE)	*Mean (SE)*	*LSMD[a] (95% CI)*	*P-value*	*Mean (SE)*	*LSMD[a] (95% CI)*	*P-value*
Total score	−12.04 (1.04)	−16.59 (1.02)	−4.92 (−7.64, −2.21)	<.001	−15.44 (1.01)	−3.70 (−6.45, −0.96)	.008
Physical function score	−0.33 (0.03)	−0.34 (0.03)	−0.04 (−0.13, 0.04)	.314	−0.30 (0.03)	0.00 (−0.09, 0.08)	.931

With regard to the primary assessment, study FMS031 initially failed to demonstrate a statistically significant effect for the claim of treatment of pain in fibromyalgia and treatment of fibromyalgia syndrome for either dose. Borderline statistical significance was seen for a post hoc analysis suggested by the FDA for 200 mg/day of milnacipran for an effect on pain at 3 months ($p = 0.032$) and on the treatment of fibromyalgia syndrome ($p = 0.017$). The decision to change the definition of improvement in the physical function from FIQ-PF to SF-36-PCS was a post-hoc decision that the applicant made after the study was unblended, after consultation with the FDA. In this case the results should be evaluated using both definitions of improvement in physical function. Numerous secondary endpoints were also evaluated in this study. There were no significant differences between active treatment and placebo for most of the secondary endpoints with the exception of the MASQ total score and the BDI at three month landmark for patients who received 200 mg milnacipran per day.
The revised analysis exhibited 3 changes to the predefined analysis. The revised analysis carried forward baseline values (BOCF) for any missing value in the first 3 months and using Last Observation Carried Forward (LOCF) for any missing value between 3-6 months. It also used a revised definition of a responder for the PGIC score (responder if a patient has a score of 1 or 2). Finally, the revised analysis uses the SF-36-PCS to define physical function instead of FIQ-PF. The revised analyses as suggested by the FDA for handling of missing data and the definition of a responder for the PGIC endpoint appear sensible. However, since the primary efficacy results lied either side of the 5% significance level it was obvious that this study did not provide robust evidence of efficacy. The proposal to use a different endpoint to measure physical function is more of a concern. In summary, this study was not considered supportive for the benefit of this product.

With regard to the primary analyses of the three pivotal studies (study FMS031: post hoc analysis), statistically significant improvement was shown in the primary composite criterion for milnacipran 200 mg/day treatment and in part also for 100 mg/day treatment at 3-months landmark.

However, regarding the primary efficacy endpoints and additional responder analyses only a small effect of doubtful relevance was shown, which on the other hand had not been consistently demonstrated. For instance, responder rates for active treatment versus placebo differ between 7 and 12%, using LOCF and BOCF approaches. Sensitivity analyses handling missing data in various ways do not consistently confirm the robustness of primary analyses; particularly using the BOCF approach handling of PW and missing data in responder analyses, although this was the preferred approach, chosen in agreement with the FDA for study FMS031.

With respect to the PED 24 h-Recall Pain VAS in study GE 302, the only study in which a European population was included, and the mean difference in change from baseline was 4.63 on a 0-100 unit pain-scale for milnacipran 200 mg compared to placebo. Regarding the PGIC, a total of 21% of the patients improved “much” or “very much” in the placebo group and 34.6% in the active-treatment group. Most of the milnacipran treatment patients only showed “minimally” improvement. For the FIQ total score, response to placebo treatment was substantial (mean change from baseline of 10.48

compared to mean change from baseline of 13.20 in the milnacipran group). The improvement for milnacipran relative to placebo represents a difference in decrease about 3 (LSMeans). The applicant was requested to discuss the clinical relevance. However the provided explanation, which was again considered insufficient, confirms the previous Rapporteurs` opinion that the presented results only demonstrate an unconvincing clinical effect. The provided additional analyses failed to demonstrate robustness of the effects.

Most analyses of the secondary efficacy variables demonstrate a trend towards a better effect. However, there is a lack of consistent statistical significance and clinical relevance of the mean differences. The total FIQ, considered to be the most relevant secondary endpoint, did not reach statistical significance in one pivotal study (study FMS031), neither for 100 mg nor for 200 mg milnacipran.

Concerning efficacy, the recommended dose in the SPC is 100 mg daily. The applicant states, that some patients would benefit from a dose of 200 mg daily. However, up to now, the recommended dose (100 mg) was derived only from trials conducted in the US population (one study failed in it`s primary endpoint). Efficacy of the recommended 100 mg dose has not been demonstrated in an EU clinical setting; no data are available that allow for a conclusion whether the recommended dose might have an effect in the target population, the European population, as it is still uncertain, whether regional differences in medical and social culture influence the effect. Study GE 302 only evaluated the efficacy of MLN 200 against placebo, whereas study GE 304 was a long-term uncontrolled study, designed to assess long-term safety as primary objective; the secondary objective was to assess long-term efficacy.
No dose dependent increase of the therapeutic effect was shown for milnacipran in the higher dose (200 mg/d); consequently study-results for the lower treatment dose (100 mg/d) are of questionable relevance. The applicant was asked to discuss the proposed posology in the claimed indication with respect to the presented efficacy results.
No statistically significant and clinically relevant effect was shown for the male population.

In the FAS population of the three pivotal studies, there was a higher and dose dependent incidence of early discontinuations due to adverse events in the 100 mg/d (19.2%) and the 200 mg/day (23.9%) milnacipran treatment groups when compared to placebo (9.6%). Discontinuation due to lack of efficacy was clearly higher in the US population when compared to the European population, which leads to difficulties in adopting results from one region to another. The fact that only one study (study GE 302) took place in Europe further questions the generalisability of the efficacy results.

Maintenance of effect:
The 2 US phase III extension studies do not investigate whether long-term treatment is appropriate. For patients who have completed 3 months treatment with 200 mg/day of milnacipran it remains possible that a reduced dose of 100 mg/day or less would be equally effective. It also remains possible that long term treatment is not necessary at all. Discontinuation in the long-term extension studies, was high, which questions the evidence of long-term efficacy.

With the answer to the day 180 LoOI, the applicant provided Study GE 304, a long-term uncontrolled study, designed to assess the long-term safety of milnacipran in the treatment of FM over 12 months of exposure at the target doses of 100, 150 and 200 mg/day. Long-term efficacy (including the durability of efficacy) of these milnacipran doses in terms of pain relief, improvement in patients' global ratings of change and alleviation of the associated symptoms of FM was studied as a secondary objective. The study was performed in a dose-blinded manner. The number of withdrawn patients was high, especially due to adverse events, therapeutic failure and patient`s decision. Overall, a modest effect of milnacipran in patients with fibromyalgia can be seen from the data presented. There was a tendency of a better effect at endpoint for the 200 mg dose. However, with respect to the lack of a placebo control group, the clinical relevance of the estimated effects is not clearly comprehensible; analyses to assess statistical significance are missing. The Last Observation Carried Forward (LOCF) approach to deal with missing data has been used in these analyses.
Due to the fact that the primary objective was the evaluation of long-term safety and a placebo control is lacking, study GE 304 only has supportive value for the assessment of efficacy of milnacipran in the

treatment of fibromyalgia. These data can be considered supportive for understanding maintenance of efficacy, but not confirmative as efficacy was only a secondary outcome variable. Long-term placebo-controlled data are furthermore needed.

Subgroup analyses:
Subgroup analyses based on gender, age, BMI and BDI were performed with the pooled database. Although the patient numbers were limited for patients ≥ 65 and males (≤ 65) and the mean weight of patients in the EU study was approximately 10 kg less than in all treatment groups in the US studies, the effect of milnacipran seems to be similar in patients regardless of age and BMI.

BDI
Patients were divided into 3 subgroups according to BDI score (0-9, 10-18 and ≥ 19). All three pivotal studies excluded patients if they were suffering from a current major depressive episode. Although all studies should exclude patients with a baseline BDI score >25, the applicant admitted that there are differences in means at baseline for BDI score between US and Europe. For example, study MLN-MD-02 included 40 patients with a BDI at baseline > 25 in every treatment group.
From the presented data, it cannot be adequately concluded, that more depressive patients (baseline BDI > 25) in the US studies do not limit the external validity of the studies. Furthermore, no conclusions can be drawn, whether an improvement of depressive mood state has influenced the direct analgetic effect. Study FMS031 and study MLN-MD-02 demonstrated statistically significant changes in the BDI score at 3-month landmark for milnacipran 200 mg, resulting from a modest antidepressive effect of milnacipran hydrochloride. Whether the treatment effect in fibromyalgia is independent of improvements in depressive symptoms has not been sufficiently answered. It rather seems that there is a link between drug effect and mood.

- Analysis performed across trials (pooled analyses and meta-analysis)

Pooling of the pivotal study-results is considered not acceptable due to several inconsistencies between the studies, which were not adequately answered by the applicant until now. Concerning baseline disease status, no conclusions can be drawn from the provided data: History duration of diagnosis was presented for study FMS-031 whereas history duration of symptoms was evaluated for study MLN-MD-02. However, it should be kept in mind, that despite a trend of efficacy one of the three studies failed in its primary analyses and there were no consistent effects in both, primary and secondary endpoints. The pivotal studies showed positive results but not consistently supported by results from relevant secondary endpoints. This aspect should be considered when assessing the value of the pooled analyses provided by the Applicant.
As no conclusions can be drawn about the mean duration of fibromyalgia symptoms between the pivotal studies and more depressive patients were included in the US studies in comparison to the European study the generalisability of the effects remains questioned.

- Supportive study

Supportive study: Study FMS-021
A phase II, multicenter, double-blind, randomized, placebo-controlled study of Milnacipran compared two dosing regimens of milnacipran (200 mg QD and 100 mg BID) with placebo in patients with FMS. The primary outcome measure in this trial was based on patients' self-reported pain scores (anchored visual analog scale [VAS] using Gracely units) recorded on the PED. Statistically significant results were only received for the weekly recall pain. However, the difference between mean changes from baseline for BID to QD of 0.6 on a 0-20 VAS scale is of questionable clinical relevance. Given the choice of dose regimen namely 200 mg milnacipran once a day versus 100 mg twice a day the study contained an insufficient number of test dose schedules to provide sufficient evidence of a dose related effect. More patients discontinued in the QD group due to adverse events. Therefore, this study indicates, that taking milnacipran 200 mg/day (BID) is better tolerated.

Furthermore, the applicant presented an abbreviated study report of the recently completed US study MLN-MD-03, a Phase III US and Canadian pivotal, multicenter, double-blind, randomized, placebo-controlled monotherapy study of milnacipran for the treatment of fibromyalgia. The primary objective

of this study was to demonstrate the safety and efficacy of milnacipran in the treatment of FMS or the pain associated with fibromyalgia. The primary outcome measure was a composite responder status assessing response rates when patients were dosed with 100 mg/day (50 mg BID) of milnacipran as compared to placebo, after twelve weeks of stable dose treatment. However, due to the provided abbreviated study report, no definite conclusion can be drawn with respect to study design and efficacy results.

- Other studies submitted during the evaluation.

Two tudies, MLN-MD-03 and GE 3 04, were not completed for the initial submission in 2008.
The final report for GE 304 was provided upon CHMP request with the "Clinical written responses to the CHMP D180 List of Outstanding Issues".
Study MLN-MD-03 was finalized at the end of the procedure. Only a short summary was submitted and assessed at Day 180 Assessment Report. The final report for MLN-MD-MD03 was attached to the reexamination submission.

Both studies are discussed in the re-examination section.

Clinical safety

- Patient exposure

The milnacipran safety data in FMS were classified into three different analysis sets based on study design and duration: Group A: Five princeps studies (FMS021, GE 2 04, FMS031, MLN-MD-02, and GE 3 02), Group B: Two extension studies (FMS034 and MLN-MD-04) and Group C: Patients exposed to milnacipran for at least one year (this was a subgroup of group B). A total of 3445 patients have been included in clinical studies with milnacipran. Overall, 1144 patients with FMS received placebo, 684 patients received milnacipran 100 mg/day, and 1819 patients received milnacipran 200 mg/day. The mean duration of exposure was 126.1 days for placebo, 145.3 days for milnacipran 100 mg/day, and 154.1 days for milnacipran 200 mg/day.

Extensive safety information on milnacipran in Major Depressive Disorder (MDD) was also reviewed including clinical study data as well as spontaneous post-marketing experience data. 47 studies were conducted in 6803 adult patients and 2 studies in 150 young patients. A total of 4544 patients were treated with milnacipran alone. Post-marketing exposure in MDD is estimated to involve 18.5 million patient-months.

- Adverse events

The most commonly reported adverse reactions in FMS patients trials were nausea, headache, constipation, hyperhidrosis and hot flush, these were reported in more than 10% of patients. There is a relatively high rate of hyperhidrosis reported in the European study (23.1%) versus the US studies (8.0-9.2%). The analysis of concomitant treatment showed that US patients are more frequently treated by psycholeptics (42.1 % vs. 22.9%), antihistaminics (31.9 % vs. 8.8 %) and hormone therapy (33.61 % vs. 20.12 %) than the EU patients (numbers for MLN 200 mg). This could be one explanation for the difference in reporting hyperhidrosis in Europe versus US. The hypothesis that the US population could be less bothered by this symptom than the EU patients might be another explanation contributing to this difference. Both explanations however suggest that US and EU populations are different as far as concomitant treatment and perception of symptoms are concerned which might lead to differences in the perception of the disease as well.
The overall safety profile does not appear very different for fibromyalgia patients than for patients treated with milnacipran for MDD except for psychiatric and somatic events in the non-FM group, and musculoskeletal events in the FM group, as expected from the difference in indications and underlying pathologies.
The percentage of patients who discontinued prematurely ranged from 15.4% in the placebo group in the EU study, to 40.0% in the US milnacipran 200 mg/day group. In all treatment groups, AEs were the most common reason for premature discontinuation.

The fibromyalgia patients tended to have higher frequencies of adverse events than non FMS patients, following both milnacipran and placebo administration, suggesting a population-specific rather than drug-specific phenomenon In spite of the low numbers in male (only 4.3 % of study population) and older patients (<6%), there does not appear to be a signal of an increased risk in these two subgroups of patients different from the current known safety profile registered during FM clinical studies and in non FM studies.

No clear relationship between the dose and the incidence of TEAEs and SAEs was observed.

- Serious adverse event/deaths/other significant events

Three deaths were reported in the fibromyalgia studies and were considered by the investigator as not treatment related.

- Laboratory findings

Milnacipran has not shown evidence of clinically important hepatotoxicity in clinical studies. Reports of hepatitis in the post-marketing experience have been uncommon and of uncertain relationship to milnacipran, and any European and Japanese regulatory concerns have been addressed with mild precautionary labelling statements. While milnacipran has caused mild elevations of aminotransferases in some patients participating in clinical studies, these elevations have not been associated with concomitant elevations of bilirubin.

The number of patients with ALAT elevation in non FMS was 0.2% for placebo, 0.4% for milnacipran 100 mg and 0.1% for milnacipran 200 mg . The increases in FMS patients were substantially higher (1.6% placebo, 2.3% milnacipran 100 mg and 4.2% milnacipran 200 mg) and dose dependent. There was a slight gender difference in both FM and non-FM patients, with males having a higher incidence of elevated ALAT and ASAT on both placebo and milnacipran. Females have lower incidences. This is not consistent with the scientific literature stating that females are predisposed more than males to develop transaminase increase. The sample size of male FM patients was rather small so that the data are difficult to interpret. Nevertheless, the difference is small and the majority of cases had only slightly elevated liver enzymes (> 1 or > 1.5 x ULN for ALAT and ASAT).

- Safety in special populations

The cardiovascular effects of NA and 5-HT are well-known and changes in HR and BP during treatment with milnacipran are not unexpected. Cardiovascular effects of milnacipran include a slight to moderate increase in both SBP and DPP, a moderate increase in heart rate in non-hypertensive and in patients with controlled and uncontrolled hypertension. Patients with a history of cardiovascular disorder or concomitant cardiac medication might have a higher incidence of cardiovascular adverse events (e.g. hypertension, hypotension, postural hypotension, tachycardia and palpitations). Consequently, it is recommended to increase the clinical monitoring in FMS patients with hypertension or cardiac disease.

- Discontinuation due to adverse events

Discontinuations due to AEs was significantly more frequent in the milnacipran patient groups (24.6%) compared with the placebo group (11.2%, $p<0.001$). The proposed up-titration scheme in the SmPC, with low initial dose (25 mg QD), slow dose escalation (increased by 50 mg increments of 1 week each) with possibility of stepping down to the previous dose, or step prolongation, and the use of rescue and/or corrective treatment, is considered the best scheme to limit patient's discontinuation and supported by data from study 302. After up-titration, the dose will be accommodated between 100 mg/day and 200 mg/day, with a 150 mg/day step, according to individual data on efficacy/safety profile as is the case for the management of all chronic diseases.
The incidence of nausea leading to discontinuation was dose dependent. A dose relationship was also observed for headache, hyperhidrosis, insomnia, heart rate increased, vomiting, constipation,

abdominal pain leading to discontinuation. No clear relationship however was seen in the extension studies.

The Applicant has provided data for the evaluation of QT interval prolongation from two sources:

- The first is the full report of study MLN-PK-10, a thorough QT study sponsored by Forest Research Institute (NJ, USA) in 2005.
- The second is the "Report for Additional Pooled Analysis of Safety - Regression-based calculation of the corrected QT interval"

The uncorrected QT interval was increased in patients who received milnacipran. Depending on whether Bazett's or Fredica's correction is applied the number of patients in whom QT prolongation is observed changes. In the pooled analysis four of the fibromyalgia studies were available for the analysis of the QT interval based on regression method.
Regardless of the correction used there were more potentially clinically significant prolongations in QT interval (>=60ms) observed in patient who received milnacipran compared to placebo.
Half of the cases of cardiac arrhythmias were excluded on the bases that adverse events such as irregular heart rate, unspecified arrhythmia, or unspecified extrasystoles could not be characterized as supraventricular or ventricular arrhythmia due to lack of diagnosis by the investigator and were considered as unspecified. The remaining cardiac arrhythmias were four cases of QTc prolongation in the milnacipran and 32 coded as arrhythmia in 28 patients.

In milnacipran 3 out of 4 cases of QT/QTc interval prolongation were considered as serious (atrial fibrillation / atrial flutter, premature ventricular contraction / atypical chest pain / palpitations, and syncopal episode / irregular heart beat) and required hospitalization, compared to 1 in the placebo group. The events led to milnacipran discontinuation in ten patients (including the 3 serious adverse events). For the QTc prolongation the Applicant stated that they were moderate and possible confounding factors were observed.
These confounding factors were also proposed as the cause of arrhythmia and these are the presence of cardiovascular diseases such as mitral valve prolaps, previous atrial fibrillation, hypertensive cardiopathy, supraventricular arrhythmia, cardiac ablation and ventricular extrasystoles. Apart from that there were 13 patients concomitantly treated with medications which could induce arrhythmia or tachycardia such as anti asthma agents (salmeterol, salbutamol), antihistamine agents (desloratadine, loratadine, fexofenadine), lisinopril, levothyroxine, cyclobenzaprine, pseudoephedrine, ketoconazole and tramadol.
In addition to the above arrhythmia cases there were nine cases of syncope, presyncope or loss of consciousness, 4 cases were considered as serious (feeling syncopal / intermittent chest pain / intermittent rapid heart beat, acute transient ischemic attack, near syncope, and presyncope / hypertension) and 3 of these led to milnacipran discontinuation. In the placebo group, 2 non-serious syncopes in two patients were reported.

In conclusion:

- Milnacipran works through the modulation of noradrenergic neurotransmission and therefore can result in changes in blood pressure and heart rate and predispose to cardiovascular adverse effects.
- High incidence of raised systolic and diastolic BP and high incidence of raised heart rate are well documented with milnacipran.
- If the reported cases of arrhythmias/QTc are stated as caused by (half of the arrhythmias as suggested by the Applicant) the confounding factors then for this reason a warning is needed.

This is supported by an US epidemiological study that evaluated patient profile, treatment patterns, and cardiovascular disease risk for patients with fibromyalgia syndrome in the United States presented by the applicant in the day 180 response to LoQ. The reported data provide some evidence that fibromyalgia is independently associated with an increased risk of CVD events. Underlying hypertension and fibromyalgia treatment seemed to increase this risk.

Therefore a contraindication in patients with severe cardiac function impairment or with an identified very high risk of a serious cardiac arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV), uncontrolled hypertension, severe or unstable coronary heart disease was implemented as these underlying conditions may be worsened by increases in blood pressure or heart rate. Furthermore these should be part of the risk management plan.

The urinary adverse reactions (eg dysuria) mainly occurred in male patients. Therefore, the use of milnacipran in patients with urinary problems (eg prostatic hypertrophy) should be initiated with close monitoring of urinary symptoms. However it would appear that male patients with normal urinary flow are equally at risk to urinary symptoms.

In the Day 180 response to LoQ document the applicant provided new safety data from the following studies: Study MLN-MD-O3: A Phase III US and Canadian Pivotal, multicenter, double-blind, randomized, placebo-controlled monotherapy study of milnacipran for the treatment of fibromyalgia and
Study F02207 GE 3 04: A European Phase III, multicenter, double-blind, randomised, monotherapy, 12 month study of milnacipran for the treatment of the fibromyalgia syndrome.

As far as assessment of data in abbreviated report of Study MLN-MD-O3 was possible, the adverse event profile in this 12-week study did not differ from previously reported short term data. No urinary adverse reactions were reported in this study. No unexpected safety aspects were discovered. The safety profile seen in the long-term European study F02207 GE 3 04 was satisfactory and no unexpected adverse reactions and/or safety findings were observed with long term administration of milnacipran for the treatment of FM. The data did not support a long-term dose-dependence for adverse events.
The drop out rate however, is considered to be high (39.5%). 28.6 % of patients experienced AEs which led to discontinuation.

Overall, the size of the safety database was considered adequate and the exposure to milnacipran in FMS studies had been adequately summarized by the applicant. Given the pharmacological properties of milnacipran there is nothing unexpected in the AE profile.

However, this has to be viewed in light of the overall benefit/risk profile, which was considered to be negative. The CHMP considered that, given the modest clinical effect size observed, the significantly higher discontinuations due to adverse events in the milnacipran patients group weighed against a positive risk/benefit balance.

Pharmacovigilance System
The Applicant has provided documents that set out a detailed description of the system of pharmacovigilance (Version 8 dated May 2009). A statement signed by the Applicant and the qualified person for pharmacovigilance, indicating that the Applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The Applicant has committed to submitting together with the first PSUR a revised DDPS answering the former questions 15-17 and adhering to the structure specified in Volume 9A. Provided that the commitment is fulfilled as stated, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The Applicant must ensure that the system of Pharmacovigilance is in place and functioning before the product is placed on the market.

2.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted an appropriate risk management plan.

The CHMP, having considered the data submitted in the application is of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

Information on development, manufacture, and control of the active substance milnacipran hydrochloride and the medicinal product Impulsor 25 mg, 50 mg and 100 mg hard capsules have been presented in a satisfactory manner. Results carried out indicated adequate manufacture, and stability of the medicinal product.

Non-clinical pharmacology and toxicology

Acute oral toxicity testing has demonstrated that milnacipran is moderately toxic. LD50 values were 240 mg/kg, p.o., and 36 mg/kg, i.v., in mice and 228 mg/kg, p.o., and 51.2 mg/kg, i.v., in rats. Major clinical signs included convulsions, hypoactivity and prostration.
In subchronic studies, the major organ affected was the liver. Slight to moderate increases in liver weights and/or centrilobular hepatocellular hypertrophy were observed. These changes did not involve adverse biochemical or major histologic modifications. At doses greater than the NOAEL, mainly hepatocyte hypertrophy with vacuolation was observed, predominately in the centrilobular area, sometimes with a slight lipidic accumulation, but without significant effects on hepatic enzymes.

Milnacipran did not demonstrate carcinogenic, genotoxic, embryotoxic, teratogenic, phototoxic, or immunotoxic potential in preclinical studies.
Toxicokinetic studies demonstrate that milnacipran is readily absorbed and does not show major accumulation.

Efficacy

The efficacy of milnacipran in fibromyalgia syndrome (FMS) has been evaluated in eight clinical efficacy studies: 1 double-blind, placebo-controlled Phase II study, 4 double-blind, placebo-controlled Phase III pivotal studies and 3 double-blind, Phase III long-term extension studies.

The primary objective of the pivotal studies was to evaluate the efficacy of milnacipran administered at doses of 200 mg/day (BID) and (also of 100 mg/day (BID) in the US studies), compared to placebo for the whole complex of the fibromyalgia syndrome, including pain, physical and emotional outcomes.

With regard to the primary analyses of the three pivotal studies (study FMS031: post hoc analyses), statistically significant improvement could be shown in the primary composite criterion for milnacipran 200 mg/day treatment and in parts also for 100 mg/day treatment after 3-months landmark. However, regarding the primary efficacy endpoints and further responder analyses the clinical effect was modest, inconsistent and of doubtful relevance. Study FMS031 initially failed to demonstrate a statistically significant effect for the claim of treatment of pain in fibromyalgia and

treatment of fibromyalgia syndrome for either dose. Although statistical significance was seen for a post hoc analysis suggested by the FDA after development of 3 changes to the predefined analysis, this study does not provide robust evidence of efficacy. Sensitivity analyses did not consistently confirm the robustness of improvements. Additional analyses of the primary endpoints as well as analyses of further secondary efficacy variables demonstrated a trend towards a better effect for treatment with milnacipran, without stringent consistency with the primary outcome parameters.

The presented analyses and further explanations given by the applicant are not considered acceptable to demonstrate a consistent and clinically relevant benefit for patients in pain and functional improvement. This related to milnacipran-treatment in doses of 100 mg/day but especially for doses of 200 mg/day. As there was no convincing effect with the higher dose (200 mg/d), study-results for the lower treatment dose (100 mg/d) are of questionable relevance. The studies submitted do not provide the answer to whether once or twice daily dosing is the best approach. Hence the dose response has not been fully defined and the optimal dose has not been established.
Provided additional analyses, stratified for male and female patients did not show significant and clinically relevant effects for the male population.

Only one study to show short-term efficacy was performed in the European population. Several methodical inconsistencies between this study and the 2 pivotal US studies were given. No adequate explanation was given by the applicant to justify these indifferences sufficiently. On the basis of these discrepancies, the pooled data are considered to be doubtful to demonstrate efficacy. It should be kept in mind that despite a trend of effect one of the three studies failed in it`s primary analyses. This should be considered when assessing the value of the pooled analyses provided by the Applicant.

As the tested drug has antidepressant properties it should be clear that the effect size observed can not be attributed to an improved mood. Whether the treatment effect in fibromyalgia is independent of improvements in depressive symptoms cannot be assessed so far from the submitted data. However, it seems that there is a link between drug effect and mood.

Long-term efficacy of milnacipran has not convincingly been demonstrated in the US population. The discussion regarding maintenance of effect has been based on studies that were carried out exclusively in the US. The external validity of this, still questionable, evidence for the EU population is uncertain as obviously differences in attitudes towards fibromyalgia, the treatment and the perception of the disease and perception of efficacy exist. This makes it necessary to obtain maintenance of efficacy from the EU population.
With the answer to the day 180 LoOI, the applicant provided Study GE 304, a long-term uncontrolled study, designed to assess the long-term safety of milnacipran in the treatment of FM over 12 months of exposure at the target doses of 100, 150 and 200 mg/day. Long-term efficacy (including the durability of efficacy) of these milnacipran doses in terms of pain relief, improvement in patients' global ratings of change and alleviation of the associated symptoms of FM was studied as a secondary objective. The study was performed in a dose-blinded manner. The number of withdrawn patients was high, especially due to adverse events, therapeutic failure and patient`s decision. Overall, a modest effect of milnacipran in patients with fibromyalgia can be seen from the data presented. There was a tendency of a better effect at endpoint for the 200 mg dose. However, with respect to the lack of a placebo control group, the clinical relevance of the estimated effects is not clearly comprehensible. Due to the fact that the primary objective was the evaluation of long-term safety and a placebo control is lacking, study GE 304 only has supportive value for the assessment of efficacy of milnacipran in the treatment of fibromyalgia. Long-term data from the European population are still considered necessary.

Safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Given the pharmacological properties of milnacipran as serotonin and noradrenalin reuptake inhibitor there is nothing unexpected in the AE profile. Class effects include blood pressure and heart rate

elevations, potential interactions with MAOIs, serotonine syndrome and elevation of aminotransferases.
The most commonly reported adverse reactions in FMS patients' trials were nausea, headache, constipation, hyperhidrosis and hot flush and the typology does not appear very different in comparison to the adverse event profile in patients treated with milnacipran for MDD.
There were significantly higher discontinuations due to adverse events in the milnacipran patients group versus placebo with a clear dose dependence for nausea, headache, hyperhidrosis, insomnia, heart rate increased, vomiting, constipation and abdominal pain. The adverse event profile in the 12-week study MLN-MD-O3 submitted as abbreviated report with the answer to the day 180 LoOI did not differ from previously reported short term data. No urinary adverse reactions were reported in this study.
The safety profile seen in the long-term European study F02207 GE 3 04 submitted with the answer to the day 180 LoOI was satisfactory and no unexpected adverse reactions and/or safety findings were observed with long term administration of milnacipran for the treatment of FM. The data did not support a long-term dose-dependence for adverse events.
The drop out rate however, is considered to be high (39.5%). 28.6 % of patients experienced AEs which led to discontinuation.

Milnacipran works through the modulation of noradrenergic neurotransmission and therefore can result in changes in blood pressure and heart rate and predispose to cardiovascular adverse effects.
High incidence of raised systolic and diastolic BP and high incidence of raised heart rate are well documented with milnacipran.
There is some evidence that fibromyalgia is independently associated with an increased risk of CVD events. Underlying hypertension and fibromyalgia treatment increase this risk.

Therefore a contraindication in patients with severe cardiac function impairment or with an identified very high risk of a serious cardiac arrhythmia (e.g. those with a significant left ventricular dysfunction, NYHA Class III/IV), uncontrolled hypertension, severe or unstable coronary heart disease was implemented as these underlying conditions may be worsened by increases in blood pressure or heart rate. Furthermore these should be part of the risk management plan.

- User consultation

A package leaflet user testing report conducted by LNA Ltd, London EC1V 4PY, UK and dated December 2008 has been provided. The provided PL is considered easy to read and appropriately usable for patients or caregivers.

Risk-benefit assessment

A robust and clinical relevant effect in the treatment of fibromyalgia syndrome in a patient population that corresponds to the EU setting has not convincingly been demonstrated, neither for 200 mg/day nor for 100 mg/day. It is not clear whether the effect size observed can be attributed to an improved mood state. It is questioned given the doubt on the clinical relevance of the effect size observed, whether the significantly higher discontinuations due to adverse events in the milnacipran patients group with a clear dose dependence for some adverse events justifies approval.

The benefit/risk balance of milnacipran in the treatment of fibromyalgia syndrome remains negative.
In light of the modest and inconsistent clinical effect the given safety profile is not acceptable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Impulsor in the treatment of fibromyalgia syndrome was unfavourable and therefore did not recommend the granting of the marketing authorisation.

Grounds for refusal

1. There is a lack of robust evidence of efficacy in the short term, especially for the recommended dose of 100 mg/day. Furthermore the effect seen has not been convincingly shown to be clinically meaningful.

2. There is an insufficient demonstration of maintenance of effect in appropriately designed studies of relevance to the EU population.

3. The results from the US studies cannot be extrapolated to the EU population, taking into account the differences in procedures.

4. The safety profile, whilst well characterised, is not considered to be outweighed by the benefits, given the lack of robust evidence of efficacy.

5. Due to the aforementioned concerns, a satisfactory summary of product characteristics cannot be agreed at this stage.

3. RE-EXAMINATION OF THE CHMP OPINION of 23 July 2009

Following the CHMP conclusion that the risk-benefit balance of Impulsor in the treatment of fibromyalgia syndrome was unfavourable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

The CHMP asked the CNS –SAG (Scientific Advisory Group) to answer the following questions proposed by the re-examination Rapporteurs:

1. Are the statistically significant improvements of the primary and secondary endpoints seen in the presented clinical studies of a clinical relevance for the fibromyalgia patients?

2. Do the long-term data sufficiently demonstrate the long-term efficacy of milnacipran in the treatment of fibromyalgia?

3. Are there substantial differences between the EU and US population, both in the presented clinical studies and real-life situation, which would preclude extrapolating the results obtained in the US to the European population?

4. Could the treatment effect of milnacipran in FMS be considered independent of the improvement in mood?

The SAG meeting took place the 5th of November 2009 and discussed the questions, providing their answer to CHMP.

During the CHMP meeting on 16 - 19 November 2009, the grounds for refusal were addressed by the applicant during an oral explanation before the CHMP.

The following assessment presents the arguments submitted by the applicant to address each ground for refusal, and the CHMP position on each of the grounds.

CHMP ground for refusal 1:

"There is a lack of robust evidence of efficacy in the short term, especially for the recommended dose of 100 mg/day. Furthermore the effect seen has not been convincingly shown to be clinically meaningful."

Summary of Applicant's position:

Argument 1: The clinical package provides adequate demonstration of efficacy in a large population relevant to the indication and the target European population

The clinical development programme performed with milnacipran is comprehensive and featured both mechanistic studies (pre-clinical and clinical) and a complete efficacy/safety programme including eight clinical studies (1 double-blind, placebo-controlled phase 2 study, 4 double-blind, placebo-controlled phase 3 pivotal studies and 3 double-blind, phase 3 long-term extension studies), in a total of 4110 FM patients. The Applicant therefore argued that the composition and the size of this programme are sufficient to provide adequate demonstration of efficacy and safety.

The key features of the clinical efficacy/safety studies in FM are summarized below.

Summary of clinical efficacy/safety study designs

	Study	Study design	Objective	Treatment groups	Randomisation ratio placebo: active group(s) (200:100 mg/day)	Patients analysed	Duration (weeks)			
							Washout	Baseline	Dose escalation	Fixed dose
Phase 2 study	FMS021	Randomised, double-blind, placebo-controlled, parallel, flexible-dose	Initial safety, efficacy and tolerability	Placebo Milnacipran up to 200 mg/day (up to 100 mg BID) Milnacipran up to 200 mg /day (up to 200 mg QD)	1:1.5 (BID):1.5 (QD)	28 51 46	1 - 4	2	4[a]	8
Phase 3 pivotal studies	FMS031	Randomised, double-blind, placebo-controlled, parallel, fixed-dose	Pivotal safety and efficacy	Placebo Milnacipran 200 mg/day (100 mg BID) Milnacipran 100 mg/day (50 mg BID)	1:2:1	223 441 224	1 - 4	2	3	24
	MLN-MD-02				1:1:1	401 396 399	1 - 4	2	3	12-26[b]
	GE 3 02[c]	Randomised, double-blind, placebo-controlled, parallel, fixed-dose	Pivotal safety and efficacy	Placebo Milnacipran 200 mg/day (100 mg BID)	1:1	446 430	1 - 4	2	4	12
	MLN-MD-03[d,e]	Randomised, double-blind, placebo-controlled, parallel, fixed-dose	Pivotal safety and efficacy	Placebo Milnacipran 100 mg/day (50 mg BID)	1:1	509 516	1 - 4	2	4-6	12

	FMS034	Randomised, double-blind, parallel, fixed-dose	Long-term safety and persistence of efficacy	Milnacipran 200 mg/day (100 mg BID) Milnacipran 100 mg/day (50 mg BID)	4:1 [f]	401 48	-	Randomisation visit	2[g]	26
	MLN-MD-04				4:1 [f]	330 54	-	Randomisation visit	2[g]	Up to 37
Phase 3 extension studies	GE 3 04[c,e]	Randomised, double-blind, parallel, fixed-dose	Long-term safety and persistence of efficacy	Milnacipran 200 mg/day (100 mg BID) Milnacipran 150 mg/day (75 mg BID) Milnacipran 100 mg/day (50 mg BID)	1:1:1 [h]	285 92 91	1	Randomisation visit	4	48

Source: Study reports FMS021, FMS031, MLN-MD-02, GE 3 02, MLN-MD-03, FMS034, MLN-MD-04 and GE 3 04
BID = twice daily, QD = once daily
a dose escalation phase may be shorter. If dose limiting side effects were encountered during this phase the patient stepped down to the previous week's dose and maintained that lower dose for the remainder of the study.
b the pivotal efficacy evaluation was performed at 15-weeks following discussions with the FDA and a protocol amendment reducing study duration from 6 to 3 months.
c studies GE 3 02 and GE 3 04 also had a 9-day down-titration phase after the fixed dose phase followed by a 2-week follow-up phase without treatment.
d In the study MLN-MD-03, the fixed dose phase was followed by a two-week discontinuation phase where 50% of milnacipran-treated patients having completed the 12 weeks of stable dose medication were to be removed from active treatment and given placebo for the final two week of the study
e MLN-MD-03 and GE 3 04 studies were not completed for the initial submission in June 2008. The final report for GE 304 was provided upon CHMP request with the "Clinical written responses to the CHMP D180" document. The final report for MLN-MD-MD03 was attached to the reexamination submission.
f patients entering the study having previously received placebo or milnacipran 100 mg/day were randomised to receive either milnacipran 100 mg/day or 200 mg/day at a ratio of 1:4. Patients who had previously received 200 mg/day continued on this dose
g patients continuing on the same dose as they received in the previous study underwent sham dose escalation.
h patients entering the study having previously received placebo were randomised to receive either milnacipran 100 mg/day, 150 mg/day or 200 mg/day at a ratio of 1:1:1. Patients who had previously received 200 mg/day continued on this dose

In its initial assessment the CHMP stated that the "presented results for study MLN-MD-03 cannot be properly evaluated due to the fact that only an abbreviated study report was provided". This point was addressed during the re-examination by the transmission of the full and final study report for this study.

Study MLN-MD-03:
This study was finalized at the end of the procedure. A short summary was then submitted and assessed at Day 180 Assessment Report. The Applicant provided the final study report with the main body of re-examination documentation. The design of this US study was similar to those of all other pivotal phase 3 studies; inclusion criteria, and therefore, in the view of the Applicant, population baseline characteristics were very similar to those of the European pivotal phase 3 study.

The study MLN-MD-03 was a phase 3, multicenter, randomised, double-blind, placebo-controlled, two-arm parallel-group study to investigate the safety and efficacy of milnacipran 100 mg/day in patients with FM. After a washout period from disallowed medications, patients entered a 2-week baseline period. Eligible patients were then randomised to treatment with milnacipran 100 mg/day (50 mg BID) or placebo (1:1). After a 4-6-week dose escalation phase, patients entered a 12-week stable dose treatment period, which was followed by a 2-week re-randomised double-blind, placebo-controlled discontinuation phase where 50% of milnacipran-treated patients were abruptly discontinued from milnacipran therapy, other patients continuing their initial assigned therapy. Patients who completed the study had therefore a total of 16 to 20 weeks of treatment exposure. Response to the same composite criterion defined for other pivotal phase 3 studies (requiring ≥ 30% reduction in pain from baseline and a PGIC rating of 1 "very much improved" or 2 "improved"), reflecting the overall effect of the product on FM was used in the primary analysis.

As for other pivotal phase 3 studies, the MLN-MD-03 study was performed in outpatients with FM classified according to the 1990 ACR criteria, patients were aged 18-70 years, both male and females were eligible for inclusion, moderate to severe pain was required at baseline and patients suffering from a current major depressive episode were excluded in order to avoid any confounding effect due to a potential antidepressant effect of the product. As for the European study, the assessment of depressive disorders was performed at both screening and randomization using the Mini-International Neuropsychiatric Interview (MINI) and the BDI (BDI ≤ 25 being required for inclusion) and patients with a minimum average baseline VAS pain score between 40 and 90 were eligible.

Similar results to those of other pivotal phase 3 studies were observed.

Out of 1025 randomised patients, 516 patients received milnacipran 100 mg/day and 509 patients received placebo. The study was completed by 716 (69.9%) patients: 357 (69.2%) in the 100 mg/day milnacipran group and 359 (70.5%) in the placebo group. When applying similar inclusion and non inclusion criteria, baseline characteristics between studies are very similar, as evidenced by the comparison of the specific European GE 302 study.

Demographic and baseline efficacy criteria characteristics for the MLN-MD-03 study and the European GE 3 02 study:

	GE 3 02 n=876	MLN-MD-03 n=1025
Age in Years Mean (SD)	48.8 (9.8)	48.9 (10.7)
Sex Female % Male %	94.3 5.7	95.3 4.7
FM Duration (symptoms) Mean (SD)	9.5 (8.6)	10.8 (8.0)
PED 24-hour Recall Pain Score Mean (SD)	65.2 (12.8)	63.7 (12.6)
Mean (SD)	56.9 (11.8)	57.3 (13.4)
MFI Total Score Mean (SD)	66.6 (13.4)	67.5 (13.2)
BDI2 Total Score Mean (SD)	10.6 (6.7)	8.9 (6.4)
SF36-PCS Score Mean (SD)	33.6 (6.8)	32.9 (7.7)
SF36-MCS Score Mean (SD)	46.7 (9.8)	46.7 (11.1)
MASQ Total Score Mean (SD)	86.6 (25.1)	90.1 (20.5)

Sources: Responses to Clinical Questions Document Day 180, tables 20 and 21 and Clinical Study Report of the MLN-MD-03 study, tables 14.2.1A and 14.2.5A
SD = Standard Deviation, FM = Fibromyalgia, PED = Patient Electronic Diary, FIQ = Fibromyalgia Impact Questionnaire, MFI = Multidimensional Fatigue Inventory, BDI = Beck Depression Index, SF-36-PCS = Short Form 36-Physical Component subscale, SF-36-MCS = Short form 36-Mental health Component subscale, MASQ = Multiple Ability Self-Report Questionnaire

At the end of the stable dose period, milnacipran showed a significantly greater improvement in the primary composite criterion (pain + PGIC) compared with placebo ($p<0.001$). The responder/non-responder ratio for patients meeting criteria for composite response was significantly greater with milnacipran than placebo (odds ratio [OR] 1.9). These results were further supported by results from sensitivity analyses.

Composite (Pain + PGIC) Responder Rates for Milnacipran Versus Placebo at the end of the stable dose period – ITT Population (Primary and Sensitivity Analyses)

	Placebo (N = 509)	***Milnacipran 100 mg/d (N = 516)***		
Analysis/Imputation Method	*Composite (Pain + PGIC) Responder Rates %*		*OR (95% CI)*	*p-value*
Primary analysis[a] (BOCF)	17.7	28.5	1.86 (1.38, 2.51)	< 0.001
Sensitivity analysis 1[b] (LOCF)	19.1	32.9	2.09 (1.57, 2.79)	< 0.001
Sensitivity analysis 2[c] (modified BOCF)	17.7	28.9	1.90 (1.41, 2.56)	< 0.001
Sensitivity analysis 3[d] (OC)	25.6	41.8	2.10 (1.53, 2.90)	< 0.001
Sensitivity analysis 4[e] (GLMM)	18.9	38.2	2.65 (1.63, 4.30)	< 0.001

Source: Clinical Study Report of the MLN-MD-03 study, table 11.4.1-1
a Primary Analysis used the BOCF approach at Visit TX12 to impute missing postbaseline values (all patients who did not have an adequate observation for the evaluation of composite responder status at Visit TX12 were defined as nonresponders).
b Sensitivity Analysis 1 imputed data using the LOCF approach for all patients who lacked primary efficacy data at Visit TX12.
c Sensitivity Analysis 2 used the BOCF approach for patients who were noncompleters at Visit TX12, but used the LOCF approach for patients who completed Visit TX12 but who lacked primary efficacy data at this time point (Modified BOCF)
d Sensitivity Analysis 3 used observed cases only (ie, patients who completed Visit TX12 with an adequate observation for the evaluation of composite responder status).
e Sensitivity Analysis 4 used the GLMM approach for patients at Visit TX12 (The proportions are model based estimations and evaluated at median value of corresponding baseline value).
BOCF = baseline observation carried forward; GLMM = generalized linear mixed model; LOCF = last observation carried forward; MLN = milnacipran; OC = observed cases, CI = confidence interval; OR = odds ratio.

Secondary analyses found that milnacipran led to statistically significant improvements on multiple domains as compared to placebo (in particular on SF-36 (both component summary scores and all 8 domains of the SF-36), MFI, FIQ and MASQ). Randomised withdrawal data show the absence of any rebound phenomenon after treatment cessation.

In conclusion, according to the Applicant, the MLN-MD-03 study confirms, on all relevant parameters, that milnacipran at the dose of 100 mg/d is an effective treatment for the multidimensional symptoms of FM. Similarity of design, inclusion criteria, baseline characteristics and results with the European GE 302 study justify the use of the US study results to support the present application.

Standardized and validated efficacy assessment methods were used in all studies, providing consistent and comparable data

In all studies, the clinical outcomes assessed the different symptoms of FM, used validated patient-reported-outcomes, and included the Patient Global Impression of Change (PGIC), pain Visual Analog Scales (VAS) (recorded daily on a patient electronic diary in all phase 3 studies), the Fibromyalgia Impact Questionnaire (FIQ), the Multidimensional Fatigue Inventory (MFI), the Short Form-36 Health Survey Mental and Physical Component Summary (SF-36-MCS and SF-36-PCS), the Multiple Ability Self-report Questionnaire (MASQ) and the Medical Outcomes Study-Sleep Index (MOS-Sleep). The efficacy of milnacipran is therefore assessed in a very comprehensive and appropriate manner, using validated assessment tools in all studies.

The efficacy of milnacipran is demonstrated statistically in three pivotal placebo controlled studies; this efficacy is clinically relevant

Four specific phase 3 pivotal placebo-controlled studies were performed. The results of the first phase 3 study conducted in the US were in favour of the efficacy of milnacipran, but reached statistical significance only for post-hoc analyses performed in agreement with the FDA; this study is therefore considered by the CHMP as negative. However, in all three following pivotal studies, including the specific European study, the efficacy of milnacipran was demonstrated both from a statistical and from a clinical point of view.

The absence of contradictory results, and the remarkable convergence of all results in the phase 3 studies is a strong argument for the robustness of the effects. This is further confirmed by the consistency of results when using various statistical approaches within each study and between studies.

The primary composite response criterion used in the clinical programme corresponds, by definition, to individually meaningful changes, with both a reduction in pain score of at least 30% and a PGIC rated as "very much" or "much improved". Both components of this composite endpoint have been validated in various indications and do correspond, separately, to clinically meaningful improvements. The combination of both improvements to qualify a patient as responder represents therefore a very stringent criterion. Therefore a statistically significant difference versus placebo is based on a clinically relevant parameter. This criterion was defined a priori and validated by the CHMP in the 2005 Scientific Advice.

The results of the European phase 3 pivotal study show a responder rate of 24.2% on milnacipran, statistically higher than the 14.6% response rate observed on placebo (primary analysis); the chances to be responder to the primary criterion with milnacipran (odds ratio) are substantial compared with placebo: odds ratio estimates vary from 1.9 to 2.4 depending on the analyses; these results are coherent with those observed in the US studies.

Out of all statistical approaches, analyses in completers should be considered with attention, since they do reflect the effect of the product in conditions that mimic clinical practice, in patients who stay on treatment. In these analyses, the placebo-corrected response rate on milnacipran for the primary criterion reaches for the 100 mg dose 13.4% and 16.2% for studies MLN-MD-02 and MLN-MD-03 respectively, and for the 200 mg dose 20.4% and 15.6% for studies MLN-MD-02 and GE 302 respectively.

When considering the overall effect observed with a product, one should obviously take into account the placebo-corrected effect in order to ensure that the efficacy brought by the product is real and consistent. This effect was statistically significant. However, an additional approach may be considered in order to quantify the effect that is most likely to be observed in daily practice, by assessing the overall drug effect. The overall effect observed in patients receiving milnacipran is comprised, depending on the studies, between 24% and 33% of responders to the primary criterion (LOCF approach), which means that, in daily practice, at least one in four FM patients will be significantly improved by the treatment.

Moreover, most analyses of the change from baseline in the intensity or the score of the secondary efficacy criteria demonstrate a favourable effect of milnacipran, especially for fatigue, which is acknowledged as a key secondary symptom in FM.

In addition, improvements on key secondary criteria (FIQ, stiffness, fatigue, restorative sleep) are highly correlated with response measured by the composite criterion, for example the minimum mean change in FIQ total score is 34 in milnacipran composite responders over studies.

Therefore, the response to the composite primary criterion in patients treated with milnacipran reflects a major improvement of the syndrome, with a high overall satisfaction of patients (as measured by PGIC) and significant benefit on the different symptoms of the syndrome.

It is argued that the efficacy of milnacipran as demonstrated using the primary composite criterion is also observed on criteria that are very relevant to the disease, excluding any artificial finding. The effects of milnacipran are therefore observed on various dimensions that both characterize the disease and are relevant targets for therapeutic intervention.

In the absence of any product approved for the treatment of FM and of any guideline setting a minimally acceptable effect size, it is argued that the effect demonstrated with milnacipran is real, clinically relevant, and represents an adequate response for a significant proportion of patients with no current therapeutic alternative.

The dose regimen recommended in the SmPC is in line with the composition of the dossier and the key efficacy results

The clinical development programme focused on the doses of 100 mg/d and 200 mg/d which were investigated in the pivotal placebo-controlled phase 3 studies. The European study evaluated only the higher dose further to the 2005 Scientific Advice. Results observed in studies assessing the both dose of 100 and 200 mg/d showed that the 100 mg/d dose was almost as efficient as the 200 mg/d dose on most efficacy criteria but was better tolerated. The proposed recommended dose is, therefore, 100 mg/d.

In the short-term phase 3 studies, the 200 mg/d dose appeared to provide some additional benefit in pain and overall global patient's satisfaction. In the US extension studies FMS034 and MLN-MD-04, an additional mean improvement in both pain and physical functioning was observed in the group of patients who switched from milnacipran 100 mg/d in the lead-in studies to 200 mg/d in the extension studies. Last, in the European extension GE 3 04 study, there was a tendency for a greater effect at endpoint for the 200 mg/d dose compared to the 100 and 150 mg/d doses.

Therefore, in the instance of a patient who tolerates the 100 mg/day dose well and does not achieve adequate efficacy, it would be reasonable to propose the 200 mg/day dose on an individual basis. For many patients, 100 mg/day is expected to be adequate. The criteria to decide to increase the dosage to 200 mg/day would always be based on the clinical judgment of the treating physician in consultation with the patient. When the drug is well-tolerated and the patient and the physician mutually decide that adequate symptomatic relief has not been obtained with the initial dosage, then an increase to a dose of 200 mg/day may be considered.

In summary, as the benefit/risk ratio is slightly better with milnacipran 100 mg/day, the recommended dose for milnacipran in the treatment of FM is 100 mg/day. Some patients may benefit from the dose of 200 mg/day on an individual basis.

CHMP position on the first ground for refusal

The original dossier of milnacipran for the treatment of fibromyalgia syndrome included 1 double-blind, placebo-controlled phase 2 study, 3 double-blind, placebo-controlled phase 3 pivotal studies and 2 double-blind, phase 3 long-term extension studies. A total of 3445 patients formed the initial safety database. During the evaluation procedure (at day 180) the Applicant submitted the results of two additional studies: one placebo-controlled short-term phase 3 study (study MLN-MD-03) and a long-term extension study (study GE 3 04).

Two doses, 100 mg and 200 mg have been tested in the short-term (12 wk) studies. In these studies the efficacy of milnacipran was based on two main aspects:

- the effect on pain, measured by the VAS score and the Patient Global Impression of Change score in a composite outcome ;
- the global effect over the syndrome including the VAS score, the Patient Global Impression of Change and a physical function endpoint (SF-36 PF or FIQ- Physical Function subscore) also measured as a composite outcome.

Efficacy was ultimately expressed as response rates in order to capture a clinically meaningful effect for the patients.

With respect to pain, and based on the primary analyses conducted in each pivotal study, the following results were observed:

Response rates for the Pain criterion (Pain+PGIC) at 3 months

Study number	Treatment groups Daily dose (BID regimen)	Number of patients	Response rates (%)	Differences vs placebo in % Responders
FMS031	MLN 200 mg/day	441	32.4%	7.3 (p = .048)
(BOCF analysis)*	MLN 100 mg/day	224	32.1%	7.0 (p = .094)
	Placebo	223	25.1%	
MLN-MD-02	MLN 200 mg/day	396	24.8%	8.3 (p =.004)
(BOCF analysis)	MLN 100 mg/day	399	22.8%	6.3 (p=.025)
	Placebo	401	16.5%	
F2207 GE 302	MLN 200 mg/day	430	24.2%	9.6 (p<.0001)
(LOCF analysis)	Placebo	446	14.6%	
MLN-MD-03	MLN 100 mg/day	516	28.5%	10.8 (p<.001)
(BOCF analysis)	Placebo	509	17.7%	

*Post-hoc analysis suggested by FDA.

The CHMP commented as follows on these results:

a) As pain reliever, milnacipran appears to have a small effect in fibromyalgic patients with moderate pain. A gain (in terms of responders) over placebo of 6.3% - 10.8% for the 100 mg dose and 7.3% to 9.6% for the 200 mg dose was observed. Although some effect is detected with a consistent trend across clinical trials, it still has to be determined whether a less than 10 percent improvement in the responder rate can be considered clinically relevant. It means that approx. one in 10 to one in 7 FM patients will be improved > 30% by this treatment when compared to the placebo treated patients. The Applicant has submitted throughout the procedure and at the oral explanation several analyses in order to qualify the clinical relevance of these modest figures, but this crucial point has not convincingly solved yet in the view of the CHMP, who considered that the absolute magnitude of the effect shown was low.

It would be helpful whether according to the sought indication “Treatment of fibromyalgia syndrome”, this effect could be translated into a global benefit of the condition (e.g. syndrome composite endpoint, FIQ Total Score).
If the Syndrome criterion (a composite endpoint involving pain, global effect, physical function) is examined, an even more reduced effect is shown (see below).

Response rates for the Syndrome criterion (Pain+PGIC+SF-36-PCS /FIQ-PF) at 3 months

Study number	Treatment groups Daily dose (BID regimen)	Number of patients	Response rates (%)	Differences vs placebo in % Responders
FMS031	MLN 200 mg/day	441	22.2%	4.7% (p = 0.164)
(BOCF analysis)*	MLN 100 mg/day	224	18.8%	1.3% (p = 0.721)
	Placebo	223	17.5%	
MLN-MD-02	MLN 200 mg/day	396	13.9%	5.2% (p=.015)
(BOCF analysis)	MLN 100 mg/day	399	14.5%	5.8% (p=.011)
	Placebo	401	8.7%	
F2207 GE 302**	MLN 200 mg/day	430	-11.18	-3.0 (p= .015)
FIQ-Total score	Placebo	446	-14.18	
(LOCF analysis)				
MLN-MD-03	MLN 100 mg/day	516	20.0%	9.0% (p<.001)
(BOCF analysis)	Placebo	509	11.0%	

* Post-hoc analysis suggested by FDA ** In the EU study GE 302, the FIQ total score (and not the composite score) was used as a functional endpoint

b) This pattern is also reflected in the pain and physical functional secondary endpoints, in which the superiority of milnacipran over placebo appears to be strictly numerical.

When the effect was evaluated through some of the relevant clinical features of the disease such as sleep disturbances, fatigue, psychological or neurocognitive disturbances, milnacipran does not appear to improve the treatment of the condition in a meaningful way.
This concern is also raised when the patients judged their status: patients receiving milnacipran either 100 mg or 200 mg doses defined their change as minimally improved (100 mg: ranged from 2.9 to 3.07 and 200 mg: ranged from 3.02 to 3.1 depending on the study). These changes represent less than 0.5 points of benefit over placebo.
The relevance of this finding is doubtful.

b) Some doubts have been raised with respect to the true effectiveness of the 100 mg dose and the proposed posology in general.
The main proof of efficacy for this dose has been provided with the US study MLN-MD-03, whose final report was submitted during the re-examination. In this study, patients treated with milnacipran 100 mg for 12 weeks showed significantly greater responder rates (both in pain and syndrome outcomes) than those treated with placebo. In spite of this, the efficacy of the recommended 100 mg dose has not been adequately demonstrated in an EU clinical setting (see also the discussion below concerning acceptability of US vs. EU data).

The CHMP considered that no significant benefit seems to be obtained from increasing the milnacipran dose from 100 mg to 200 mg.

c) From the analysis of published studies, which used the FIQ, it was apparent that the course of the disease is very sensitive to various treatments and interventions.
The overall absolute improvement on the 0-100 unit scale obtained with milnacipran is even smaller than the impact of e.g. physical exercise, cognitive behavioural therapy or the use of various antidepressants (Bennet 2005).

Author	Ref.	Intervention	FIQ pre	FIQ post	Pvalue
Gowans (2004)	25	Exercise	58.6 ± 49	49.3 ± 50.5	< 0.002
Redondo	26	CBT	52.0 ± 11.4	40.8 ± 13.7	< 0.01
Rooks	27	Exercise	44.3 ± 9.0	31.8 ± 13.5	< 0.002
Geel (2000)	28	Exercise	53.1 ± 18.6	28.3 ± 15.0	< 0.0005
Bennett	29	Group therapy	50.4 ± 12.9	37.7 ± 15.8	< 0.00001
Bailey	30	Exercise	67.0 ± 17.0	56.0 ± 22	< 0.001
Arnold	31	Fluoxetine	42.0 ± 14.0	33.4 ± 14.5	< 0.002
Astin	32	Qigong	57.8 ± 10.8	46.4 ± 19.5	< 0.05
Bennett	12	Tramadol/APAP	54.0 ± 11.0	44.7 ± 17.0	< 0.008
Creamer	33	Educational/CBT	51.0 ± 10.8	42.1 ± 13.8	< 0.001
Valim	14	Exercise	53.0 ± 15.0	30.4 ± 19.2	< 0.05
Cedraschi	34	Education/Pool	55.0 ± 13.0	49.0 ± 14.0	< 0.001
Goldenberg	35	Fluoxetine + Amitryptiline	57.3 ± 17.6	38.0 ± 21.2	< 0.006
Arnold	11	Duloxetine	48.7 ± 14.7	35.1 ± 18.2	< 0.027
Bennett	36	Growth hormone	50.0 ± 13.1	36.2 ± 16.6	< 0.0025
Gowans (2001)	37	Exercise	56.6 ± 12.9	48.6 ± 16.2	< 0.05
Burckhardt	38	Education + PT	67.1	57.8	< 0.001

The issue of clinical relevance of the observed results was the principal objection during the marketing authorization procedure, and is particularly relevant for fybromyalgia where a number of interventions appear to have some effect, but response to any single treatment modality seems to be poor.

This point is still considered not resolved in view of the CHMP

CHMP ground for refusal 2: There is an insufficient demonstration of maintenance of effect in appropriately designed studies of relevance to the EU population.

Summary of Applicant's position:

The maintenance of effect has been investigated in line with existing guidelines and 2005 scientific advice; it provides ample information that the effect of milnacipran is sustained in patients receiving the drug for up to 12 months.

The composition of the clinical dossier regarding the maintenance of effect was specifically discussed with the CHMP during the 2005 Scientific Advice. On this occasion, it was stated that an open label extension was adequate for such an objective.

In the view of the Applicant, the requirement for placebo controlled data is unexpected and in contradiction with the position expressed by the CHMP during the consultation process. It is also in contradiction with existing guidelines published by the CHMP for treatments in other chronic pain conditions (see for instance Guideline CPMP/EWP/252/03Rev.1 "Guideline on clinical medicinal products intended for the treatment of neuropathic pain") which recommend open label extension studies, without placebo, during 6 to 12 months.

The requirement by the CHMP for a placebo group in the extension study is therefore not appropriate; it may be furthermore ethically discussable in a chronic pain condition.

Beyond this contradiction, it is argued that:

- The design of the European extension study, with a 12-month extension in patients re-randomised blindly to 3 different doses of milnacipran (100, 150 and 200 mg/d), is more stringent than what was required at the 2005 Scientific Advice.
- Extension studies, both in the US (MLN-MD-04) and in the European (GE 3 04) have shown on a total of 852 patients that the continuation of treatment is accompanied by a stability of efficacy parameters over 12 months.

However, in order to reach a mutually acceptable position, the applicant proposed that the SmPC be adjusted as follows:

The indication section (§4.1) may read:
"Short term management of fibromyalgia syndrome in adults.
Long term maintenance of effect has not been investigated versus placebo".

CHMP position on the second ground for refusal

The short-term effect of milnacipran over placebo is still of uncertain relevance to be considered as a truly established benefit.
When it comes to long-term data, efficacy of milnacipran in fibromyalgia is insufficiently supported by uncontrolled data from studies primarily aimed to assess the safety of milnacipran up to 1 year of treatment.

In this respect, when milnacipran was given for 6-month period time under controlled circumstances (Study FMS031) a lower response than that achieved at 3 months both in pain and syndrome scores was reported. Differences versus placebo in pain responder rates were 7.1% for 200 mg dose and 5.7% for 100 mg. The figures for syndrome responder rates were 1.2% (200 mg) and 0.8% (100 mg). This suggests a potential weaning effect of milnacipran and in any case it casts doubts on the persistence of the effect.

The applicant proposed during the reexamination to restrict the indication to a short-term treatment. A modest short-term effect mainly focused on pain is not deemed enough to grant an indication in a chronic condition without being supported by robust, long-term data.

During the Oral explanation, the applicant suggested that the product information could be amended to continue treatment only in patients responding after 3 months of treatment. However the CHMP remained concerned with regards to the demonstration of maintenance of effect, particularly in light of the high discontinuation rate (40%) in the maintenance phase of study GE 304.

The CHMP considered this point not solved.

CHMP ground for refusal 3: "The results from the US studies cannot be extrapolated to the EU population, taking into account the differences in procedures."

Summary of Applicant's position:

<u>US study designs, populations and results are coherent with the European studies; the overall clinical package is adequate and relevant for the target European population</u>

The clinical studies were conducted either in the US or in Europe; all methodological precautions were taken in order to ensure adequate characterization of FM patients in each study, and comparability of populations between studies, as described below. US data are considered as relevant as European data since there is no significant restriction which would limit extrapolation of results from the US studies to the European population.

Both in the US and in the European studies, inclusion criteria were defined in order to include patients' representative of the established FM patient profile and to ensure homogeneity between study populations:

- in all studies, patients were classified according to the ACR criteria published in 1990;
- special efforts were made to exclude co-morbidities such as major depression in order to avoid any major confounding factors in the assessment of efficacy;

- similarly, systemic autoimmune diseases, systemic infections or unstable endocrine diseases constitued also exclusion criteria because of the potential overlap of the symptomatology with FM and to ensure that patients included were actually suffering from FM;
- in line with the well documented epidemiology of FM, the majority of patients are middle-aged female in all studies;
- associated symptoms and complaints collected in all studies are similar and reflect the profile of symptoms widely acknowledged in the FM population (muscle pain, fatigue, trouble falling asleep, morning stiffness, inability to concentrate…);
- baseline mean scores of efficacy criteria are similar between studies (VAS pain, FIQ, MFI, SF36-PCS, SF36-MCS and MOS-Sleep baseline scores).

The baseline differences between regions are limited and only concern the body mass index (BMI), the FM duration and the baseline Beck Depression Inventory (BDI) score. These differences do not induce significant bias for efficacy assessment:

- Differences in BMI are in line with established differences between the US and European overall populations and have been assessed by the CHMP to be negligible as regards the impact on efficacy assessment.
- FM duration was collected differently in the pivotal studies (duration of symptoms and/or duration since FM diagnosis). When the comparisons of similar criteria are performed, FM duration is actually only marginally longer in the US studies than in the European study: the mean duration since diagnosis was of 5.9 and 4.1 years, respectively in the US FMS031 and European GE 3 02 studies and the mean duration of FM symptomatology was of 10.0, 10.8 and 9.5 years, respectively in the US MLN-MD-02 , US MLN-MD-03 and European GE 3 02 studies. The absence of impact of FM duration on the assessment of efficacy is furthermore confirmed by the absence of any significant FM "duration x treatment" interaction in all studies.
- Differences in baseline BDI between studies are limited:
    - These differences do not reflect actual differences in source populations but result from the evolution of exclusion criteria during the course of development: to ensure that any positive efficacy results was not attributable to the antidepressant effect of milnacipran, exclusion criteria comprised major depressive episode from the very start of development and became more strict during the development with the introduction of a baseline BDI cut-off (mean baseline BDI score is about 14 in the first US studies, 11 in the European GE 3 02 study and 9 in the recently completed US MLN-MD-03 study).
    - These differences do not hinder comparison of results between studies: subgroup analyses did not show any clear impact of baseline BDI score on response to the study treatment.
    - Therefore, for these two reasons, BDI baseline differences do not restrict extrapolation of results from the US studies to the European population.

<u>Robustness of the results: similar results were observed in all studies, irrespective of the regions</u>

All clinical studies provide results that are qualitatively and quantitatively similar, irrespective of the regions (US or Europe) where the studies were performed. Especially the results of the 3 positive phase 3 studies are coherent, as summarized below.

Response rates for the primary criterion (Pain+PGIC) (OC)

Study number	Treatment groups Daily dose (BID regimen)	Response rates (%)	Differences vs placebo in % Responders
MLN-MD-02	MLN 200 mg/day	45.6	20.4 (p<.001)
	MLN 100 mg/day	38.6	13.4 (p=.001)
	Placebo	25.2	
F2207 GE 302	MLN 200 mg/day	31.3	15.6 (p<.0001)
	Placebo	15.7	
MLN-MD-03	MLN 100 mg/day	41.8	16.2 (p<.001)
	Placebo	25.6	

Source: Study reports MLN-MD-02, GE 3 02 and MLN-MD-03

Response Rates for the primary criterion (Pain+PGIC) (LOCF)

Study number	Treatment groups Daily dose (BID regimen)	Response rates (%)	Differences vs placebo in % Responders
MLN-MD-02	MLN 200 mg/day	29.6	11.4 (p<.001)
	MLN 100 mg/day	25.8	7.6 (p=.010)
	Placebo	18.2	
F2207 GE 302	MLN 200 mg/day	24.2	9.6 (p<.001)
	Placebo	14.6	
MLN-MD-03	MLN 100 mg/day	32.9	13.8 (p<.001)
	Placebo	19.1	

Source: Study reports MLN-MD-02, GE 3 02 and MLN-MD-03

In summary:
Study populations and results are appropriate and justify the use of both European and US study results for the present submission:

- The composition of the dossier is in line with the 2005 Scientific Advice
- The characteristics of the population included in the clinical programme are in line with the general FM patient profile
- Generalisability of results between regions is allowed, since :
    - study populations are globally similar;
    - differences with respect to baseline characteristics (BMI and BDI), drop out rates and concomitant medications use are limited and do not induce any significant bias for efficacy assessment;
    - analyses testing for a global region effect (corresponding to the aggregation of all observed differences between regions) did not show any statistically significant region x treatment interaction;
    - out of the 3 positive pivotal studies one study was exclusively conducted in Europe and provided positive results with no element in favour of a lesser effect of milnacipran in European patients.

CHMP position on the third ground for refusal

The MAH provided justification about the similarities in demographic characteristics of patients and the efficacy results of the studies conducted in both regions (US and EU). This is acknowledged.

However, the CHMP considered that fibromyalgia syndrome possesses singular features in which local conditions, perceptions and access to additional healthcare interventions take special relevance. Therefore, in this context robust EU efficacy (and safety) data are required, considering results from other regions (i.e. US data) as supportive. In this dossier only the 200 mg dose has been tested for efficacy purpose in EU pivotal trial, the proof of efficacy of the main 100 mg dose relying on US patients.

CHMP ground for refusal 4: The safety profile, whilst well characterised, is not considered to be outweighed by the benefits, given the lack of robust evidence of efficacy.

Summary of Applicant's position:

The safety of milnacipran has been extensively evaluated in all the safety and efficacy phase 2 and phase 3 studies summarized above, in a total of 2,503 FM patients on both a short term basis and a long term basis. Extensive safety information on milnacipran in patients with Major Depressive Disorder was also reviewed on the basis of both clinical study data and post-marketing experience over more than 10 years in an estimated 18.5 million patient x months.

The safety profile of milnacipran is predictable, in agreement with class effects of serotonin and noradrenalin reuptake inhibitor. No unexpected safety signal has been identified.

The combined review of all these safety data collected in FM and in MDD provides very coherent information: the typology of Adverse Events is very similar between populations. No new and /or unexpected findings were observed in the FM population.

The majority of the most frequent adverse reactions occurred mainly in the first four weeks of therapy and were mild to moderate in severity.

The most commonly reported adverse events drug reactions in fibromyalgia patients treated with milnacipran in clinical trials were nausea, headache, constipation, hyperhidrosis and hot flush.

Increases in blood pressure and in heart rate have been observed with milnacipran, as with other drugs pertaining to the same class. The extensive post marketing exposure experience provides reassuring data on the long-term cardio-vascular safety of milnacipran. Nevertheless, the applicant also took significant measures to ensure the optimal reduction of potential safety risks: the SmPC has been modified accordingly (the Contra-indication section mentions severe cardiac function impairment, uncontrolled hypertension, sever or unstable coronary heart disease), and a risk management plan has been provided with an extensive survey plan along with a commitment to implement a specific observational study.

CHMP position on the fourth ground for refusal

The long term safety profile of milnacipran is reasonably known and the main risks are currently reasonably identified. This does not entail the absence of risk for those patients who are treated with the drug. Therefore only an unequivocally positive efficacy assessment could outweigh the potential risks of a non trivial long term treatment.

The CHMP considered this point not solved

CHMP ground for refusal 5: Due to the aforementioned concerns, a satisfactory summary of product characteristics cannot be agreed at this stage.

A revised indication has been suggested by the applicant:

The indication section (§4.1) may read:
"Short term management of fibromyalgia syndrome in adults.

Long term maintenance of effect has not been investigated versus placebo".

CHMP position on the fifth ground for refusal

The applicant proposed a restriction of the indication to a short-term treatment, and further amendments concerning the maintenance treatment during the oral explanation. A modest short-term effect mainly focused on pain is not deemed sufficient to get an indication on a chronic condition without being supported by robust, long-term data.
At present, the benefit-risk assessment of milnacipran is still negative.

The CHMP considered this point not solved.

Overall conclusions on grounds for reexamination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the SAG.

With the grounds for re-examination the applicant has reiterated its position regarding the deficiencies identified in the CHMP assessment and provided further discussion of the points forming the ground of refusal by the CHMP. The applicant proposed a restricted indication to the short term management of fibromyalgia syndrome in adults.
However, the CHMP maintained that the estimation of the effect size is not reassuring. This applies not only to pain, but also to functional evaluations.
Therefore the CHMP concluded that even for this restricted indication the benefit-risk assessment of milnacipran remains negative as the effect size is considered modest and of doubtful clinical relevance. This reduced short-term effect is not deemed enough to get an indication on a chronic condition without being supported by robust, long-term data.

Therefore the CHMP considered the initial grounds for refusal still maintained.

GROUNDS FOR REFUSAL

Whereas the CHMP considered:

- There is a lack of robust evidence of efficacy in the short term, especially for the recommended dose of 100 mg/day. Furthermore the effect seen has not been convincingly shown to be clinically meaningful.

- There is an insufficient demonstration of maintenance of effect in appropriately designed studies of relevance to the EU population.

- The results from the US studies cannot be extrapolated to the EU population, taking into account the differences in procedures.

- The safety profile, whilst well characterised, is not considered to be outweighed by the benefits, given the lack of robust evidence of efficacy.

- Due to the aforementioned concerns, a satisfactory summary of product characteristics cannot be agreed at this stage.

The CHMP has recommended the refusal of the granting of the Marketing Authorisation for Impulsor.