Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Levomilnacipran (as hydrochloride)

Proprietary Product Name: Fetzima

Sponsor: Pierre Fabre Australia Pty Ltd

December 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
%Dose	% of compound excreted in urine relative to administered dose
(1S,2R)-F2782	*p*-hydroxy levomilnacipran
(1S,2R)-F2782 glucuronide	*p*-hydroxy levomilnacipran glucuronide
5HT	serotonin
5-HT	5-hydroxytryptamine (serotonin)
AAG	α1-acid-glycoprotein
Ae	cumulative amount of unchanged compound excreted into the urine from time zero to time t
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASEX	Arizona Sexual Experiences
AST	alanine aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0-\infty}$	area under the plasma concentration versus time curve from time 0 to infinity
AUC_{0-inf}	area under the plasma concentration versus time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration versus time curve from time zero to time t
$AUC_{0-\tau}$	area under the plasma concentration versus time curve from time 0 to the end of the dosing interval, τ
$AUC_{0-\tau,ss}$	area under the plasma concentration versus time curve during the dosing interval, τ, at steady-state
$AUMC_{0-inf}$	area under the first moment of the plasma concentration versus time curve from time zero to infinity
$AUMC_{0-t}$	area under the first moment of the plasma concentration versus

Abbreviation	Meaning
	time curve from time zero to time t
b.i.d.	twice daily
BA	bioavailability
BE	bioequivalence
BMI	body mass index
BP	blood pressure
BSA	body surface area
C_{12h}	observed plasma concentration 12h after drug administration
C_{24h}	observed plasma concentration 24h after drug administration
$C_{av,ss}$	average plasma drug concentration at steady-state
CFB	change from baseline
CGI-I	Clinical Global Impressions–Improvement
CGI-S	Clinical Global Impressions–Severity
CI	confidence interval
CL/F	apparent clearance
C_{last}	last measurable plasma drug concentration
CLcr	creatinine clearance
CLr	renal clearance of the drug from plasma
Cmax	maximum plasma drug concentration
Cmax,ss	maximum steady-state plasma drug concentration
$C_{min,ss}$	minimum plasma drug concentration during a dosing interval at steady-state
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P-450 enzyme
D	day

Abbreviation	Meaning
DBP	diastolic blood pressure
DBP	diastolic blood pressure
ECG	electrocardiogram
ECT	electroconvulsive therapy
F	bioavailability
F17400	N-desethyl levomilnacipran
F2695	levomilnacipran
F2696	the opposite enantiomer to levomilnacipran
FETZIMA	levomilnacipran hydrochloride/F2695
GG	γ-globulins
h	hour/s
HAMD-17	17-item Hamilton Rating Scale for Depression
HAS	human serum albumin
HBcAb	hepatitis B core antibody
HBs	hepatitis B antigen
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HSA	human serum albumin
IBW	ideal body weight
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	immediate-release
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety

Abbreviation	Meaning
ITT	intention to treat
IUD	intrauterine
IVRS	interactive voice response system
IWRS	interactive web response system
Ka	absorption rate constant
LB	lower bound
LC/MS-MS	liquid chromatography with tandem mass spectrometry
LLOQ	lower limit of quantification
LOQ	limit of quantification
LS	least squares
LVM	levomilnacipran
MADRS	Montgomery-Åsberg Depression Rating Scale
MADRS-CR	Montgomery-Åsberg Depression Rating Scale, Clinician Rated
MDD	major depressive disorder
MEI-SF	Motivation and Energy Inventory –Short Form
Min	minute/s
MR	modified-release
ms	millisecond
NADPH – β	nicotinamide adenine dinucleotide phosphate, reduced
NE	norepinephrine
NEAE	newly emergent adverse event
PCS	potentially clinically significant
PD	pharmacodynamics
PK	pharmacokinetics
PMM	pattern mixture model
PopPK	population pharmacokinetic analysis

Abbreviation	Meaning
PW	premature withdrawal
QD	once daily
QTc	QT interval corrected for heart rate
QTcB	QT intervals using Bazett's correction
QTcB	QT interval corrected for heart rate using the Bazett formula (QTcB = QT/(RR)^{½})
QTcF	QT intervals using Fridericia's correction
QTcF	QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)^{⅓})
QTcNi	QT intervals using individual correction
QTcNi	QT interval corrected for heart rate using an individual correction
R^2	coefficient of determination
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SDS	Sheehan Disability Scale
SNRI	serotonin-norepinephrine reuptake inhibitor
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
SVES	supraventricular extrasystoles
T_0	time of drug administration
$t_{½}$	terminal elimination half-life
TBM	to-be-marketed
TCA	tricyclic antidepressant
TEAE	treatment-emergent adverse event
T_{lag}	lag time (time delay between drug administration and first observed concentration above LOQ in plasma)

Abbreviation	Meaning
T_{max}	time of maximum plasma drug concentration
UB	upper bound
ULN	upper limit of normal
Vc/F	apparent volume of the central compartment
Vd/F	apparent volume of distribution based on the terminal phase after oral administration
WOCBP	women of child bearing potential
WT	body weight

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Initial decision:	Rejected
Final decision:	Rejected
Date of initial decision:	16 February 2016
Date of final decision:	6 July 2016
AAT outcome*	Appeal was withdrawn[1]
Date of entry onto ARTG:	Not applicable
Active ingredient(s):	Levomilnacipran (as hydrochloride)
Product name(s):	Fetzima
Sponsor's name and address:	Pierre Fabre Australia Pty Ltd 504 Pacific Highway St Leonards NSW 2065
Dose form(s):	Extended release capsules
Strength(s):	20 mg, 40 mg, 80 mg and 120 mg
Container(s):	A unit-dose blister consisting of a polyvinylchloride (PVC) 250 µm/ polychlorotrifluoroethylene (ACLAR) 51 µm sheet sealed with an aluminium foil 20 µm A unit-dose blister consisting of a polyamide 25 µm/aluminium 45 µm/ polyvinylchloride (PVC) 60 µm sheet sealed with an aluminium foil 20 µm.
Pack size(s):	Pack sizes of 30 capsules in addition to a titration pack containing 2 x 20 mg and 28 x 40 mg capsules.
Approved therapeutic use:	Not applicable
Route(s) of administration:	Oral (PO)
Dosage:	Not applicable
ARTG number (s):	No applicable

*AAT= Administrative Appeals Tribunal

[1] The sponsor appealed to the AAT for a review of the TGA's decision not to register Fetzima.

Product background

This AusPAR describes the application by the sponsor Pierre Fabre Australia Pty Ltd to register the new chemical entity levomilnacipran as Fetzima for the *Treatment of major depressive disorder*. The proposed dosing regimen involves oral administration of 40 to 120 mg once daily for several months duration.

Levomilnacipran is a selective serotonin and noradrenaline reuptake inhibitor (SNRI) and an enantiomer of the racemate milnacipran. It has an approximately 2 fold greater potency at inhibiting noradrenaline relative to serotonin reuptake.
Milnacipran was registered in 2011 under the tradename Joncia for the treatment of fibromyalgia. The sponsor stated that milnacipran is approved for the treatment of depression in 49 countries. While not approved in the European Union (EU), USA or Australia milnacipran has been used as an antidepressant at least since 1996. Unlike milnacipran which requires twice daily dosing, this enantiomer has been formulated in an extended release capsule and is proposed for once daily dosing.
In the USA the sponsor has committed to performing another relapse prevention study to evaluate the longer-term (maintenance) efficacy of levomilnacipran in the treatment of adults with major depressive disorder. This trial must be placebo-controlled, utilise a randomised withdrawal design, and include an adequate period of stabilisation with open-label treatment of levomilnacipran prior to double-blind randomisation. The final report of that study is due to be submitted to the FDA by 25 March 2019.

Current SNRI treatments for major depressive disorder (MDD) registered in Australia are: desvenlafaxine, venlafaxine and duloxetine. Additionally mirtazapine, while not an SNRI, acts to increase both adrenergic and serotonergic transmission but not via reuptake inhibition. Another antidepressant, reboxetine is primarily a noradrenaline reuptake inhibitor with little effect on serotonin reuptake.

Regulatory status

This is an application to register a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved for levomilnacipran in the *Treatment of major depressive disorder* in the USA (25 July 2013) and Canada (8 May 2015). No submission has been made to the European Medicines Agency (EMA).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

Levomilnacipran (as hydrochloride) is a new chemical entity (see structure below in Figure 1) released by Pierre Fabre Medicament Production (France).

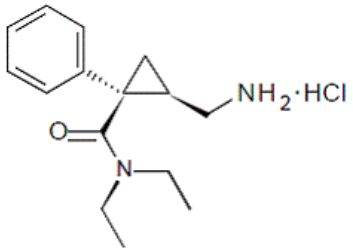
In the present submission, the sponsor seeks to register extended release capsules containing levomilnacipran (as hydrochloride) 20 mg, 40 mg, 80 mg and 120 mg under the trade name Fetzima, to be administered with or without food at a recommended

maximum daily dose of 120 mg. It is also recommended that the drug product be taken at approximately the same time each day.

Drug substance (active ingredient)

Levomilnacipran is the more active enantiomer of the racemate milnacipran and exists as the 1S, 2R isomer.

Figure 1: Chemical structure



The drug substance is a crystalline powder, with no known polymorphs. It has a pKa of 9.65 and is freely soluble (approx. 70% weight/volume (w/v)) in both water and 0.1 M hydrochloride (HCl), freely soluble in ethanol and practically insoluble in acetonitrile.

A particle size study was performed by laser diffraction in accordance to the compendial requirements of European Pharmacopoeia (monograph 2.9.31). The results obtained from eight industrial batches were presented.

The three Identification tests adequately control the presence of chlorides (as per the US Pharmacopeia <191>), the stereo-specificity of the product by the Specific Optical Rotation test and Identification by its infrared spectrum.

The enantiomer F2696 is limited at 1.0 % which is above the qualification threshold of 0.15%. F2696 is however qualified by the racemate milnacipran hydrochloride used in a medicinal product that has been registered and marketed in Europe and the United States for at least 6 years.

The proposed Specification limit for ethanolamine is ≤ 0.1 % (w/w). This equates to a maximum of 138 µg/day based on a maximum daily dose of 138 mg (120 mg of levomilnacipran free base). This is equivalent to > 90 times the TTC of 1.5 µg/day.

An assessment was made by a TGA nonclinical evaluator on the potential genotoxicity and carcinogenicity of ethanolamine in other prescription medicine products that have been approved for registration in Australia. Based on the average dietary intake and endogenous level of ethanolamine and the overall risk-benefit assessment of available genotoxicity and carcinogenicity studies, it was concluded that there appeared to be no imminent risk associated with ethanolamine in the clinical use of these products which allowed for up to 20.7 mg per day PO.

The two identified specified impurities (F16154 and phthalimido amide F2695) are limited to 0.15 % corresponding to the qualification limit.[2] The limit for each unspecified impurity is set at 0.10 % in accordance with Note for Guidance ICHQ3A.[3]

There are outstanding issues relating to the quality control of the levomilnacipran HCl drug substance that were raised with Pierre Fabre Australia Pty Ltd which are expected to be resolved in due course.

[2] ICH Topic Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
3 ICH Topic Q 3 A (R2) Impurities in new Drug Substances

Drug product

The proposed levomilnacipran HCl 20, 40, 80 and 120 mg extended release capsules are described as follows:

- Size 4 capsule with yellow cap and white body imprinted in black ink with 'PF' on the cap and '20' on the body.
- Size 3 yellow opaque capsule imprinted in black ink with 'PF' on the cap and '40' on the body
- Size 2 capsule with pink cap and white body imprinted in black ink with 'PF' on the cap and '80' on the body
- Size 1 pink opaque capsule imprinted in black ink with 'PF' on the cap and '120' on the body.

During the early Phase III clinical development, Pierre Fabre Medicament entered into an agreement with Forest Laboratories to develop, manufacture and market levomilnacipran HCl extended release capsules in the United States. With this agreement, Forest Laboratories continued the development of the levomilnacipran HCl extended release capsule formulation which included formulation optimisation.

The formulation composition of batches used in Phase III clinical studies and batches manufactured for stability studies are qualitatively similar, however there were small differences in drug loading and excipient levels. The capsules contain the following ingredients F2695, sugar spheres, povidone K-30, talc, eythylcellulose and triethyl citrate.

A clinical study (Study number LVM-PK-14) was conducted to evaluate the bioequivalence of levomilnacipran HCl sustained release capsules at the highest dose (120 mg) of the proposed commercial formulation and the earlier Phase III clinical formulation. The study was conducted using healthy subjects under fasted conditions. The 90% confidence intervals (CIs) of the geometric mean ratios of peak plasma concentration (C_{max}), area under the plasma concentration versus time curve from time 0 to time t (AUC_{0-t}), and AUC from 0 to infinity ($AUC_{0-\infty}$) were all within the range of 80% to 125%.

The drug product Specification includes a limit for the known degradation product F16154 which meets the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) qualification threshold limit of 0.2%. The dissolution test method conditions are consistent with those recommended by the US FDA Office of Generic Drugs[4] for Levomilnacipran HCl extended release capsules. An outstanding issue remains with regard to the Residual ethanol Specification limit, which is expected to be resolved in due course.

The stability data presented showed that under long term conditions (25°C/60%RH) and accelerated conditions (40°C/75%RH) the product was stable with no significant trends observed in the testing parameters.

A shelf life at the proposed 36 months for levomilnacipran HCl extended release capsules packaged in blister pack PVC 250 µm/Aclar 51 µm/Alu 20 µm when stored below 25°C was not approvable however, due to an outstanding issue relating to forced degradation studies. This issue is expected to be resolved in due course.

Biopharmaceutics

Seven bioavailability/bioequivalence studies were submitted in support of this application. Summaries of the most relevant studies (LVM-PK-12 (2012), USA F02695 LP 1-01 (2006) and USA LVM-PK-16 (2012) are presented below.

[4] US FDA Office of Generic Drugs; *Dissolution Methods Database* at http://www.fda.gov/cder/ogd/index.htm

Study LVM-PK-12 (2012)

The study was a single-centre, randomised, open-label, crossover, single-dose study evaluating the bioequivalence of the levomilnacipran to-be-marketed formulation and the clinical formulation and the effect of food on oral bioavailability of the to-be-marketed formulation in healthy subjects.

Out of the 50 subjects entering the study, 50 subjects were dosed with 46 subjects completing all periods and their data included in the final pharmacokinetic and statistical analyses.

No subjects discontinued due to adverse events. Two subjects discontinued because of schedule conflicts and 2 subjects due to withdrawal of consent to participate in the study.

Due to zero plasma concentration in Subject A [after receiving treatment C (1 x 120 mg extended release capsule under fed conditions] and a very low plasma concentration (Cmax = 6.85 ng/mL) in Subject B [after receiving treatment A (1 x 120 mg extended release capsule under fasted conditions], statistical analyses were also performed by the company excluding these 2 subjects.

The clinical evaluator commented that based on the information provided by the sponsor, the omission of Subjects A and B from the PK analysis appeared to be justified.

The key results are summarised below.

Table 1: Key results from Study LVM-PK-12 (2012)

Pharmacokinetic Analysis Population							
PK Parameter	Trt A Fasted N = 36	Trt B Fasted N = 31	Trt C Fed N = 35	Statistical Comparison			
				Geometric Means Ratio, %		90% CI	
				Trt A/B	Trt C/A[a]	Trt A/B	Trt C/A[a]
C_{max}, ng/mL	226.4 ± 63.9	222.6 ± 48.6	232.8 ± 64.8	89.6	90.7	68.12 - 117.85	69.84-117.86
AUC_{0-t}, ng•h/mL	4928.2 ± 1209.2	5064.5 ± 966.6	5032.2 ± 1264.2	86.0	90.5	65.04 - 113.71	69.34-118.19
$AUC_{0-\infty}$, ng•h/mL	5134.0 ± 1310.1	5224.0 ± 1043.2	5345.0 ± 1009.8	87.8	89.3	66.72 - 115.66	68.65-116.06
T_{max}, h[b]	6.0 (4.0, 8.0)	6.5 (5.0, 16.0)	8.0 (5.0, 12.0)	—	—	0.0812[c]	< 0.0001 c
$T_{½}$, h	13.8 ± 3.7	12.7 ± 2.9	13.0 ± 2.9	—	—	—	—

Pharmacokinetic Analysis Population							
Pharmacokinetic Analysis Population Excluding Subjects A and B[d]							
C_{max}, ng/mL	234.6 ± 51.9	226.7 ± 47.3	239.6 ± 51.3	100.5	102.3	95.04 - 106.21	97.13-107.79
AUC_{0-t}, ng•h/mL	5084.4 ± 900.8	5154.0 ± 918.3	5180.2 ± 925.5	97.5	101.7	94.49 - 100.7	98.74-104.82
$AUC_{0-\infty}$, ng•h/mL	5298.7 ± 1013.0	5317.9 ± 998.6	5345.0 ± 1009.8	98.7	100.8	95.52 - 101.97	97.74-103.92
T_{max}, h[b]	6.0 (4.0, 8.0)	6.5 (5.0, 16.0)	8.0 (5.0, 12.0)	—	—	0.0990[c]	< 0.0001 c
T½, h	13.9 ± 3.8	12.7 ± 2.9	13.0 ± 2.9	—	—	—	—

Treatment A To-Be-Marketed SR 1 x 120 mg Fasted. Treatment B Clinical SR 3 x 40 mg Fasted. Treatment C To-Be-Marketed SR 1 x 120 mg Fed.

a. In order to allow logarithmic transformation of C_{max} and AUC parameters for Subject A who had no detectable level of levomilnacipran (LLOQ = 1 ng/mL) in all plasma samples after receiving Treatment C in the statistical comparison, C_{max} was assigned to be 0.5 ng/mL; and AUC_{0-t} and $AUC_{0-\infty}$ to be 12 ng•h/mL (0.5 ng/mL x 24 h = 12 ng x h/mL).
b. Median (minimum, maximum).
c. p-Value is based on Signed Rank Test.
d. Subject [information redacted] had undetectable level of levomilnacipran (< LLOQ of 1 ng/mL) in all plasma samples after receiving Treatment C (120 mg Levomilnacipran SR under fed conditions); Subject [information redacted] had plasma C_{max} of levomilnacipran 6.85 ng/mL after receiving Treatment A (120 mg Levomilnacipran SR under fasted conditions). Subject 0040 withdrew consent after completing Treatment A and Treatment B.

Conclusions

Evaluation of bioequivalence between to-be-marketed formulation (Treatment A) and clinical formulation (Treatment B) under fasted conditions

When Subject A and B were excluded from the statistical comparison analysis, the geometric means ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 97% to 101%, and the 90% confidence intervals were all within the range of 80% to 125%, suggesting that the proposed extended release capsule was bioequivalent to the clinical extended release capsule.

Evaluation of the effect of food on the bioavailability of the to-be-marketed SR formulation

When Subjects A and B were excluded from the statistical comparison analysis, the geometric means ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 101% - 103% and the 90% confidence intervals were all within the range of 80% to 125%, suggesting that food has no effect on the bioavailability of the to-be-marketed extended release capsule.

Mean half-life ($t_{½}$) values of the extended release formulation under both fasted and fed conditions were similar (13.0 ± 2.9 h observed under the fed conditions relative to 13.8 ±

3.7 h observed under the fasted conditions). Median time to C_{max} (T_{max}) was delayed about 2.0 h, from 6.0 h when the extended release formulation was administered under the fasted conditions to 8.0 h when given under the fed conditions

Study F02695 LP 1-01 (2006)

The study was a single centre, open label, single dose, 4-period design, testing first the IV formulation (20 mg, one-hour infusion) and after, according to a cross-over randomised design, three sustained release formulations (50 mg capsule) in healthy male volunteers. The primary objectives were to:

- evaluate whether a level A correlation[5] existed for extended release formulations of levomilnacipran between the fraction dissolved in vitro and the fraction absorbed in vivo and if such a correlation was demonstrated, to validate the corresponding model.
- develop a multiple level C correlation, in order to evaluate the dissolution limits for one of the three sustained release formulations (SR2 formulation) to fulfil the bioequivalence criteria.

The absolute bioavailabilities of the sustained release formulations were close to 100% with a limited variability: SR1 ranging from [96% - 113%], SR2 from [82% - 114%] and SR3 from [73% - 100%].

The prediction errors between observed and predicted C_{max} and AUC_{∞} were lower than 10% which indicated that the level A correlation for the levomilnacipran HCl sustained release formulations can predict in vivo performance accurately and consistently.

A multiple level C correlation was also developed and validated between C_{max} ratios (using SR2 as reference) and in vitro dissolution percentages. From this level C correlation, in vitro dissolution limits were determined: 0 – 18% at T+1h, 9 - 43% at T+2h, 39 - 67% at T+4h and 83 - 99% at T+16h.

The proposed in vitro dissolution limits were checked for bioequivalence using the level A correlation. According to the FDA Guidance for Industry (*Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations, September 1997*), the batches for which the dissolution profiles are in the predefined limits, were considered to be bioequivalent.

Study LVM-PK-16.

This was a comparative pharmacokinetic study with levomilnacipran extended release capsules and levomilnacipran oral solution to compare the PKs of levomilnacipran extended-release formulation and levomilnacipran oral solution formulation after single and multiple dose administration.

The following table summarises the PK parameters from the study after the single oral dose.

[5] Level A correlation - a point-to-point relationship between in vitro dissolution and in vivo absorption and is also viewed as a predictive model for the relationship between the entire in vitro release time course and entire in vivo response time course.

Table 2: PK parameters (mean ± SD) for levomilnacipran in healthy male and female subjects after oral single dose administration of levomilnacipran oral solution an SR capsule formulations PK Analysis Population

PK Parameter	*Levomilnacipran Oral Solution, 40 mg (Treatment A) (N = 11)*	*Levomilnacipran SR Capsule, 120 mg (Treatment B) (N = 15)*	*Treatment B/Treatment A*
			Ratio of Geometric Means (90 % CI)[a], %
C_{max}, ng/mL	125.3 ± 27.4	213.3 ± 70.4	59.6 (52.7-67.4)
AUC_{0-t}, ng•h/mL	1759.9 ± 369.4	4802.0 ± 1266.3	91.0 (86.6-95.6)
$AUC_{0-\infty}$, ng•h/mL	1794.9 ± 372.9	4978.8 ± 1309.8	92.5 (89.0-96.1)
T_{max}, h[b]	4.0 (1.0, 5.0)	6.0 (5.0, 12.0)	p < 0.01[c]
$T_{½}$, h	10.6 ± 3.3	13.7 ± 2.6	NA

a Based on dose normalized parameter values
b Median (minimum, maximum).
c Wilcoxon signed rank test (N = 8, only subjects who had values for both treatments were included.)
$AUC_{0-\infty}$ = area under the plasma concentration versus time curve from time zero to infinity; AUC_{0-t} = area under the plasma concentration versus time curve from time zero to time t; CI = confidence interval; C_{max} = maximum plasma drug concentration; NA = not available; PK = pharmacokinetic; SR = sustained release; T½ = terminal elimination half-life; T_{max} = time of maximum plasma drug concentration.

The following table summarises the PK parameters from the study after multiple oral doses.

Table 3: PK parameters (mean ± SD) for levomilnacipran in healthy male and female subjects after oral multiple dose administration of levomilnacipran oral solution an SR capsule formulations PK Analysis Population

PK Parameter	*Levomilnacipran Oral Solution, 40 mg (Treatment A) (N = 19)*	*Levomilnacipran SR Capsule, 120 mg (Treatment B) (N = 22)*	*Treatment B/Treatment A*
			Ratio of Geometric Means (90% CI)[a], %
$C_{max,ss}$, ng/mL	185.0 ± 32.6	384.6 ± 66.1	69.7 (65.9-73.8)
$AUC_{0-\tau}$, ng•h/mL	2097.5 ± 220.7	5752.0 ± 871.2	91.2 (86.9-95.7)
$C_{min,ss}$, ng/mL	31.5 ± 7.2	144.9 ± 25.1	155.2 (143.3-168.0)
$T_{max,ss}$, h[b]	2.0 (1.0, 5.0)	5.0 (4.0, 6.0)	p < 0.01[c]
$C_{av,ss}$, ng/mL	87.4 ± 9.2	239.7 ± 36.3	NA
$T_{½}$, h	12.0 ± 2.7	13.5 ± 3.3	
Fluctuation, %	175.5 ± 34.6	100.0 ± 19.7	
Swing, %	525.1 ± 207.7	170.6 ± 54.0	

a Based on dose normalized parameter values
b Median (minimum, maximum).
c Wilcoxon signed rank test (N = 19, only subjects who had values for both treatments were included).
$AUC_{0-\tau}$ = area under the plasma concentration versus time curve from time zero to dose-interval time τ; $C_{av,ss}$ = average plasma drug concentration at steady state; $C_{max,ss}$ = maximum plasma drug concentration at steady state; $C_{min,ss}$ = minimum plasma drug concentration during a dosing interval at steady state; CI = confidence interval; NA = not available; PK = pharmacokinetic; SR = sustained release; T½ = terminal elimination half life; $T_{max,ss}$ = time of maximum plasma drug concentration at steady state.

Summary and Conclusions

- Compared with the levomilnacipran extended release capsule formulation, dose-normalised C_{max} was significantly higher for the levomilnacipran oral solution both following single and multiple-dose administration by 40.4% and 30.3%, respectively.
- T_{max} and $t_{½}$ were shorter with the levomilnacipran oral solution compared to the extended release capsule formulation.
- AUC was slightly lower for the levomilnacipran extended release capsule compared with the oral solution but the difference was not statistically significant, regardless of dosing regimen.
- In this study, while a higher incidence of adverse events (AEs) was observed when 40 mg oral solution of levomilnacipran was administered as a single dose and 120 mg levomilnacipran extended release capsule in multiple doses, both of the formulation safety profiles were generally comparable and well tolerated otherwise.

Quality summary and conclusions

There are no objections in respect of biopharmaceutics to registration of these products. However, there are some minor matters relating to the quality control of the drug substance and the finished product requiring resolution before approval can be recommended from a quality perspective.

III. Nonclinical findings

Introduction

The main body of this evaluation report was largely based on the US FDA assessment report for levomilnacipran, which is available from the public domain.

General comments

The nonclinical submission comprised sufficient data to be assessed as a stand-alone new chemical entity (NCE); the alternate approach for developing a single enantiomer of a registered racemate of providing bridging studies was not used. The submitted nonclinical part of the dossier was compliant with the relevant ICH guidelines, and all pivotal safety studies were conducted under Good Laboratory Practice (GLP) conditions.

Pharmacology

Primary pharmacology

Levomilnacipran is a selective inhibitor of the noradrenaline transporter (NET) and serotonin (5-HT) transporter (SERT). Levomilnacipran showed higher affinity for recombinant human (rh) and rat brain SERT compared to NET. However, the levomilnacipran 50% inhibitory concentration (IC_{50}) values for uptake inhibition for NET were generally lower than those for SERT (IC_{50} 11 nM for rhNET and 16-19 nM for rhSERT). In rat brain homogenates or synaptosomes the IC_{50} values ranged from 15-62 for NET and 46-103 nM for SERT. In vivo, a single administration of levomilnacipran inhibited reuptake of noradrenaline and serotonin, thereby increasing extracellular levels of these neurotransmitters, and also dopamine, within the brain. Administration of 20 mg/kg PO led to a greater increase in extracellular noradrenaline (59-86%) compared to serotonin (36%) in the prefrontal cortex, which is consistent with the in vitro data for reuptake inhibition. Extracellular dopamine levels were also increased by 55 to 67% in the prefrontal cortex. However, these effects were attenuated following repeated dosing of 40 mg/kg/day PO, with an increase in extracellular noradrenaline (42%), but not serotonin, observed in the prefrontal cortex.

Levomilnacipran showed anti-depressant like activity in two of three models of depression in rodents. Levomilnacipran dose-dependently reduced the duration of immobility in the forced swim test in mice. The effective dose varied between studies, with doses of ≥ 3 mg/kg IP and 32 mg/kg PO significantly reducing immobility time. Similarly, levomilnacipran significantly reduced immobility duration in the tail suspension test at doses of 10 and 20 mg/kg IP and 64 mg/kg PO. In contrast, ≤ 40 mg/kg PO levomilnacipran did not improve escape performance in the learned helplessness test. The weight of evidence from these studies indicates that levomilnacipran shows anti-depressant activity in rodents.

The anti-anxiolytic effects of levomilnacipran were investigated in a variety of tests. Levomilnacipran dose-dependently (0.6-10 mg/kg intraperitoneally (IP)) decreased

stress-induced ultrasonic vocalisations, with a 50% effective dose (ED_{50}) of approximately 4 mg/kg. In contrast, acute (≤ 30 mg/kg) and chronic (≤ 1 mg/kg/day) dosing of levomilnacipran did not induce anti-anxiolytic effects in four other animal models of anxiety (Vogel conflict, elevated plus-maze, four plates and marble burying tests). It should be noted that the chronic doses used in these studies were relatively low, and this may have contributed to the null findings.

Levomilnacipran had catecholaminergic activity, which is expected due to the increased extracellular noradrenaline and dopamine levels. Levomilnacipran attenuated tetrabenazine-induced ptosis and potentiated yohimbine toxicity with ED_{50} values of 0.8 and 1.7 mg/kg PO, respectively. Levomilnacipran generally attenuated the effects of reserpine, but at the highest dose (64 mg/kg PO) tested there was an exacerbation of reserpine-induced hypothermia.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic pharmacology studies demonstrated that levomilnacipran did not significantly inhibit serotonin, adrenergic, dopamine, muscarinic or histamine receptors, or the dopamine transporter (IC50 >10 μM). Levomilnacipran had low binding affinity for the phencyclidine (PCP) binding site (Ki = 1.7 μM). In addition, levomilnacipran inhibited N-methyl-D-aspartate (NMDA) and/or glutamate-induced whole cell currents with IC_{50} values of 28 μM for NR1/NR2A glutamate receptor[6] and 5-24 μM for the NR1/NR2B glutamate receptor. As the plasma C_{max} is 1.6 μM at the maximum recommended human dose (MRHD) of 120 mg, and distribution to the brain is low, levomilnacipran is unlikely to inhibit these receptors under clinical usage conditions.

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular and respiratory systems. Adverse CNS effects, including altered gait and posture, hypothermia, hypoactivity, decreased arousal, mydriasis and ptosis were observed in NMRI[7] mice and Sprague Dawley (SD) rats that received ≥ 90 mg/kg PO levomilnacipran. Hypothermia and/or mydriasis were also observed at lower doses (≥ 30 mg/kg PO). Mortality and/or convulsions also occurred in mice at doses ≥ 256 mg/kg PO, consistent with observations in acute toxicity studies (relative exposure ≥ 10 times based on mg/m^2).

In vitro studies demonstrated modest hERG[8] inhibition (about 30%) at 10 μM levomilnacipran (6.4 x clinical C_{max}), and increased action potential duration in isolated dog Purkinje fibres with ≥ 1 μM levomilnacipran (<clinical C_{max}) following slow stimulation (0.33 Hz). In conscious dogs, 10 mg/kg/day PO levomilnacipran increased QTc interval, but not QT interval.[9] QT and QTc intervals were increased in cynomolgus monkeys at a dose of 45 mg/kg PO (relative exposure 19 times based on C_{max}). QT and QTc were unaffected by 15 mg/kg/day (relative exposure 4 times C_{max}). Prolongation of QT and QTc intervals was not observed in the pivotal repeat dose toxicity study in monkeys after a single dose of ≤ 45 mg/kg PO or following repeated dosing of ≤ 90 mg/kg/day PO (relative exposures ≤ 40 times based on C_{max}). While the electrocardiogram (ECGs) was conducted prior to T_{max} (4 h), calculation of the C_{max} exposure ratios at 1 and 2 h post-dose indicates

[6] The NMDA receptor forms a heterotetramer between two GluN1 and two GluN2 subunits (the subunits were previously denoted as NR1 and NR2), two obligatory NR1 subunits and two regionally localized NR2 subunits.
[7] Naval Medical Research Institute
[8] hERG (the human Ether-à-go-go-Related Gene) is a gene (KCNH2) that codes for a protein known as Kv11.1, the alpha subunit of a potassium ion channel.
[9] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. Like the R-R interval, the QT interval is dependent on the heart rate in an obvious way (the faster the heart rate the shorter the R-R Interval and QT interval) and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia. There are a number of different correction formulas e.e Bazett's and Fridericia's.

an adequate safety margin (20 times and 29 times, respectively). Similar effects were reported for milnacipran but QT prolongation was not observed in a clinical trial using supratherapeutic doses.[10] The weight of evidence indicates that while levomilnacipran has the potential to cause QT prolongation, this effect is unlikely to occur clinically. Clinical studies of the effects of levomilnacipran on QT interval were also conducted, and are reviewed in the clinical evaluation.

Levomilnacipran increased blood pressure in monkeys that received ≥ 5 mg/kg PO, but the magnitude of effect was not dose-dependent. Studies in dogs produced conflicting results, with blood pressure and heart rate decreased in anesthetised dogs that received 10 mg/kg IV but increased in conscious dogs that received the same dose PO. Blood pressure also increased in anesthetised dogs that received lower IV doses of levomilnacipran (0.01–3 mg/kg) but heart rate was decreased in dogs that received 0.1–3 mg/kg. Increased blood pressure and heart rate have been reported clinically and are consistent with the pharmacological effects of levomilnacipran.

Respiration was depressed by 200 mg/kg PO levomilnacipran in rats, associated with increased respiratory rate, decreased tidal and minute volumes, peak inspiratory flow and expiration time and increased airway resistance. The No observable adverse effect level (NOAEL) for adverse respiratory effects was 63 mg/kg PO which was associated with a relative exposure of 11 times based on C_{max}.

Pharmacokinetics

Absorption

Levomilnacipran was rapidly absorbed in rodents (T_{max} ≤ 1 h), with slower absorption in cynomolgus monkeys and humans (T_{max} 2–6 h). Bioavailability was high in monkeys and humans (>90%) and moderate in rats (about 70%), consistent with levomilnacipran having both high permeability and solubility. Mean plasma half-life ranged from approximately 2–6 h in rats, monkeys and humans, and was generally similar between monkeys and humans but shorter in rats. In humans, exposure to levomilnacipran was dose-proportional. In contrast, exposure was greater than dose-proportional in rats (AUC) and monkeys (C_{max} and AUC). Following repeated dosing, exposure to levomilnacipran increased in rats and humans, but not monkeys.

Distribution

Plasma protein binding was low in human plasma (22%) and was not investigated in animals. Studies of milnacipran reported low plasma protein binding in humans (15%) and animals (19% in rats, 26% in dogs and 14% in monkeys). The volume of distribution was high in rats and monkeys, which is consistent with the extensive tissue distribution observed in rats (levomilnacipran) and monkeys (milnacipran). Highest levels of radioactivity were observed in the gastrointestinal tract, liver and kidneys. There was low distribution of levomilnacipran to the brain (≤ 0.1 times plasma concentration), with the highest levels in the brain observed in the thalamus (0.6 to 1.4 times plasma concentration). Melanin binding was evident in pigmented rats. There was moderate distribution of levomilnacipran to reproductive tissues in rats.

[10] AusPAR for milnacipran (accessed 13th May 2015).

Metabolism

Levomilnacipran was metabolised to six identified metabolites formed by dealkylation, hydroxylation and/or glucuronide conjugation. In plasma, levomilnacipran was the dominant circulating species, with *N*-desethyl levomilnacipran (F17400) being the major metabolite in rats, monkeys and humans. F17400, also coded as F2800, is not pharmacologically active. Metabolism of levomilnacipran by cytochrome P450 (CYP) enzymes was slow, with CYP3A4/5 likely being the predominant CYP enzyme responsible for formation of F17400.

Excretion

Levomilnacipran was excreted predominantly unchanged in the urine in rodents, monkeys and humans.

Conclusion

Levomilnacipran had very similar pharmacokinetic profiles in monkeys and humans, and a similar profile in rats, making these animals models suitable for assessing the toxicity profile of levomilnacipran.

Pharmacokinetic drug interactions

Levomilnacipran and F17400 modestly inhibited CYP3A4 but only at concentrations higher than that anticipated clinically. Similarly, levomilnacipran modestly inhibited CYP2C9 in the presence of Nicotinamide adenine dinucleotide phosphate (NADPH) but only at high concentrations. No other effects on CYP enzymes (induction or inhibition) were observed in vitro. Levomilnacipran was not a substrate for P-glycoprotein and did not inhibit it at clinically relevant concentrations. Similarly, while some inhibition of transport proteins was observed (organic anion-transporting 3 (OAT3) and organic anion-transporting polypeptide B3 (OATP1B3) and organic cation transporter 2 (OCT2)), these observations are not clinically relevant. Levomilnacipran was not a substrate for, or inhibitor of, BCRP.

F17400 was not a substrate for, or inhibitor of, P-glycoprotein. Similarly, F17400 did not inhibit OAT1, OAT3 or OCT2 in vitro at concentrations exceeding that anticipated clinically.

Together, these data indicate levomilnacipran and its major metabolite are unlikely to cause clinically relevant drug-drug interactions.

Toxicology

Acute toxicity

Acute oral toxicity of levomilnacipran was assessed in SD rats and Swiss mice. Mortality was observed at all dose levels (≥ 140 mg/kg in mice and ≥ 215 mg/kg in rats). Acute toxicity was associated with convulsions, tremors, prostration and hypomotricity. The 50% lethal dose (LD_{50}) was 270 mg/kg in mice and 238 mg/kg in rats. A maximum tolerated dose was not established in these studies. In a separate study[11], the plasma concentration 1 h after a single dose of 200 mg/kg PO in SD rats was 8429 ng/mL, which is approximately 22 times the clinical C_{max} at the MRHD. The relative exposure based on body surface area for the LD_{50} was 11 times in mice and 20 times in rats, and at the lowest

[11] Study CEPC 08-0443

dose tested were 6 times in mice and 18 times in rats. However, as mortality occurred in 20 to 30% of rodents at the lowest dose, the minimum lethal dose may be lower. These data indicate a high order of acute toxicity for levomilnacipran (see also *Secondary pharmacodynamics and safety pharmacology* and *Major toxicities* for other CNS-related effects).

Repeat-dose toxicity

The effects of repeated daily oral dosing of levomilnacipran was assessed in SD rats (≤ 6 months) and cynomolgus monkeys (≤1 year), with the reversibility of effects assessed in both species. The study design and conduct was consistent with EMA guideline on repeated dose toxicity studies[12].

Relative exposure

Exposure ratios were calculated based on animal: human plasma AUC_{0-24h}.[13] Toxicokinetic data from the latest available time-point from animals, with male and female values averaged, were used. Human reference values are from Clinical Study LVM-PK-16. Low to moderate exposure ratios were achieved in both species.

Table 4: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration	Dose (mg/kg/day)	AUC_{0-24h}^ (ng·h/mL)	Exposure ratio#
Mouse$ (Tg.rasH2)	26 weeks [carcinogenicity; Study AC32RU. 7G8R.BTL]	15	4450	0.8
		50	15,750	2.7
		150	56,100	9.8
Rat (SD)	6 months [Study 1712-005]	10	3265	0.6
		30	13,350	2.3
		100/120	74,800	13
	2 years [carcinogenicity; Study 1712-001]	10	3750	0.7
		30	13,100	2.3
		70 (♂)*	33,500	5.8
		90 (♀)	75,500	13
Monkey (Cynomolgus)	1 year [Study 1712-006]	5→10	7205	1.3
		15→30	41,350	7.2
		45→70→90	161,000	28
Human (healthy	steady state	120 mg	5752	–

[12] CPMP/SWP/1042/99 Rev 1 Corr*
[13] In the absence of animal plasma protein binding data, total drug rather than free (unbound) drug AUC values were used.

Species	Study duration	Dose (mg/kg/day)	AUC_{0-24h}^ (ng·h/mL)	Exposure ratio#
volunteers) [Study LVM-PK-16]				

= animal: human plasma AUC_{0-24h} ; ^male and female values combined; *Male HD was reduced from 90 to 70 mg/kg/day in week 45; $data from wild-type littermates.

Major toxicities

The major target organ for levomilnacipran was the liver, with adverse clinical signs and effects on the gastrointestinal, central nervous and renal systems also observed.

The main adverse findings were decreased body weight and/or body weight gain in rats and monkeys that received ≥ 90 mg/kg/day PO levomilnacipran. Reduced weight gain was associated with reduced food intake. Increased frequency of emesis was also observed in the high dose monkeys.

Adverse clinical signs, consistent with the CNS effects of levomilnacipran, were observed in rats (≥35 mg/kg/day, relative exposure 2 times) and monkeys (≥ 30 mg/kg/day, relative exposure 7 times). The CNS effects included decreased activity, salivation, mydriasis, ptosis, hunched posture and tremors. At higher doses convulsions were also observed in monkeys. In acute toxicity, mortality was associated with similar CNS observations, including convulsions. In monkeys, the no effect level for CNS related clinical signs was 10 mg/kg/day, which is associated with plasma levomilnacipran exposure similar to anticipated clinical AUC, and approximately 2 times higher than expected clinical C_{max}. While adverse CNS-effects are possible clinically, the safety margin associated with the more serious adverse effects of convulsions and tremors in monkeys were greater (≥ 28 times based on AUC and ≥ 36 times based on C_{max}).

Increased liver weights, minimal to mild hepatocellular hypertrophy and hepatocyte vacuolation was observed in both rats and monkeys that received ≥ 90 mg/kg/day PO levomilnacipran for ≥ 6 months (relative exposure 13 times in rats and 28 times in monkeys). Consistent with these effects in liver, modest clinical chemistry changes were observed in male monkeys (increased alanine aminotransferase (ALT), decreased bilirubin, cholesterol and albumin). The effects of levomilnacipran on liver weight and histopathology were reversible after a 4 week recovery period. Similar effects on liver were observed with milnacipran. The no effect level for liver effects in monkeys was 30 mg/kg/day which is associated with levomilnacipran exposures approximately 7 times that expected clinically. Together with the mild or minimal severity of the hepatic effects, adverse liver events are not expected clinically.

In rats there was an increase in urinary volume in rats that received ≥ 30 mg/kg/day PO levomilnacipran, with decreased specific gravity observed in males (relative exposure 2 times). Increased urinary volume was also reported following repeated dosing of milnacipran in rats. In clinical trials, urinary hesitation and retained urinary volume have been reported (PI).

Together, the nonclinical data do not indicate serious adverse events for the proposed dose of levomilnacipran. Mild effects on the CNS and the renal system may be expected clinically.

Genotoxicity

The genotoxic potential of levomilnacipran was assessed in a standard battery[14] which included in vitro assays of bacterial mutagenesis and the mouse lymphoma *Tk* gene mutation, and an in vivo micronucleus test in SD rats. All of these tests were negative, indicating a low genotoxic potential for levomilnacipran. This is consistent with previous assessment of the genotoxicity of the racemate milnacipran.

Carcinogenicity

A two year carcinogenicity study was conducted in SD rats, with an additional study conducted in Tg.rasH2 mice for 6 months. A maximum tolerated dose was achieved in the high dose groups of the rat study as indicated by a reduction in weight gain in males and reduced survival in females. In the transgenic mouse study the high dose was well tolerated but higher dose levels would likely have been associated with increased mortality. Overall, the design and conduct of both studies was consistent with the relevant ICH guidelines.[15]

There were no treatment-related neoplasms or pre-neoplastic lesions in rats that received ≤ 90 mg/kg/day PO levomilnacipran for ≥ 87 weeks (relative exposure 6 times in males and 13 times in females). There was a numerical increase in the incidence of hemangiosarcoma in the spleen of male and female Tg.rasH2 mice that received 150 mg/kg/day PO levomilnacipran, but this effect was not significant (relative exposure 10 times). The incidence in females was within the facilities historical control range, and in males was only marginally higher (5/25 compared to expected range of 0-4/25). Splenic hemangiosarcomas are a common spontaneous tumour in this transgenic mouse strain, with spontaneous incidences of ≤ 20% reported.[16,17,18] Together, the weight of evidence indicates a low carcinogenic potential for levomilnacipran.

Reproductive toxicity

The studies conducted to assess the reproductive toxicity of levomilnacipran were consistent with ICH guideline.[19] Fertility, embryofetal development and pre-/postnatal studies were conducted in Wistar rats, with an embryofetal development study also conducted in NZW rabbits. Pilot studies were also conducted to determine dosage levels. For all studies, the timing and duration of dosing was appropriate to assess the different types of reproductive toxicity. Maternal toxicity was observed at the high dose level in all studies.

Relative exposure

Exposure ratios in pregnant animals were presented as AUC_{last} values. In rats, these values represented AUC_{0-24h}, except for the low dose (LD) group on gestation day (GD) 6 in which levomilnacipran levels were below the lowest limit of quantification (LLoQ) at 24 h. Exposure ratios were similar between GD6 and GD17, with the GD17 values presented in Table 5. In rabbits, the AUC values were AUC_{0-4h} in the LD groups, AUC_{0-8h} in the mid dose

[14] The genotoxicity studies were conducted in compliance with ICH guideline S2(R1): *Genotoxicity testing and data interpretation for pharmaceuticals intended for human use*.
[15] ICH S1B: Note for guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals and ICH S1C(R2): Note for guidance on dose selection for carcinogenicity studies of pharmaceuticals.
[16] Nambiar PR et al. Spontaneous Tumor Incidence in RasH2 Mice: Review of Internal Data and Published Literature. Toxicol Pathol 2012; 40: 614-623
[17] Paranjpe MG et al. Historical Control Data of Spontaneous Tumors in Transgenic CByB6F1-Tg(HRAS)2Jic (Tg.rasH2) Mice. International Journal of Toxicology 2013; 32: 48
[18] Takaoka M et al. Interlaboratory comparison of short-term carcinogenicity studies using CB6F1-rasH2 transgenic mice. Toxicologic Pathology 2003; 31: 191-199.
[19] Detection of toxicity to reproduction for medicinal products & toxicity to male fertility S5(R2)

(MD) group and AUC_{0-24h} in the high dose (HD) group. Toxicokinetic data were not measured in the fertility study therefore the relative exposure was calculated using doses based on body surface area.

Only limited toxicokinetic data were collected in the pre-/postnatal study in rats which used dose levels of 7, 20 and 60 mg/kg/day. Plasma levomilnacipran levels were measured at 0.5 and 6 h on GD6 and GD17 and in pups 2 h post-maternal dose on lactation day (LD) 4. Based on data in the embryofetal development study in Wistar rats, the concentrations at 0.5 h are likely indicative of C_{max}. The 0.5 h values were approximately dose-proportional compared to C_{max} in the embryofetal development study (doses were 60-70% and 0.5 h plasma concentration was about 60-70% compared to that in Study AA78122). Extrapolating from this, the relative exposures in the pre-/postnatal study are estimated to be 0.3 times, 1.2 times and 4.8 times at the doses of 7, 20 and 60 mg/kg/day PO, respectively. These estimated exposure ratios are broadly consistent with those derived from body surface area calculations (0.5 times, 1.5 times and 4.6 times).

In rats, low to moderate levomilnacipran exposures were achieved in comparison to anticipated human exposure at the MRHD. Relative exposures in rabbits were below anticipated clinical exposure, except on GD19 in the high dose group. The time-course of levomilnacipran accumulation is unclear, and therefore the relative exposure calculated using exposure values at the end of treatment as an estimate of exposure throughout organogenesis should be interpreted with caution.

The placental transfer of levomilnacipran was not studied. In studies of the racemate, milnacipran, limited placental transfer and subsequent elimination was observed (see SN PM-2010-02780-3-1).[20] Levomilnacipran, F17400 and low levels of other metabolites were excreted into milk in lactating rats, with the concentration in milk approximately 4 times higher than that in maternal plasma.

Table 5: Relative exposures in pregnant rats and rabbits

Species	Study	Dose mg/kg/day PO		AUC_{0-24h} ng·h/mL	Exposure ratio#	
					AUC	BSA
Rat (Wistar)	Fertility [AA78124]	10		–	–	0.8
		30		–	–	2.3
		100		–	–	7.6
	Embryofetal development Study AA78122	10	GD17	2593^	0.5	–
		30	GD17	10,061	1.7	–
		100	GD17	45,738	8.0	–
	Pre-/postnatal development AA78125	7		–	0.3*	0.5
		20		–	1.2*	1.5
		60		–	4.8*	4.6
Rabbit	Embryofetal	10	GD6	70^	0.01	–

[20] AusPAR for milnacipran, January 2012 (accessed 11 May 2015).

Species	Study	Dose mg/kg/day PO		$AUC_{0-24\,h}$ ng.h/mL	Exposure ratio#	
(NZW)	development Study AA78128		GD19	121^	0.02	–
		30	GD6	469^	0.1	–
			GD19	1101^	0.2	–
		100	GD6	4427	0.8	–
			GD19	21,715	3.8	–
Human healthy volunteers	steady state Study LVM-PK-16	120 mg		5752	–	–

= animal:human plasma $AUC_{0-24\,h}$; ^AUC value represent AUC_{last}, with the last value <24h (see accompanying text); *Toxicokinetic data were limited to plasma concentration at 0.5 & 6h post-dose, with the 0.5h time-point considered to represent T_{max}. Plasma concentrations at 0.5h were proportional to C_{max} values in Study AA78122 following dose-normalisation. Therefore, extrapolation of AUC from the measured AUC in Study AA78122 was performed by multiplying the AUC values by the respective doses in the pre-/postnatal study over the embryofetal study (for example, AUC for 7 mg/kg/day group calculated as: 2593 × 7/10). For exposure ratios based on body surface area (BSA) dose, the MRHD value was 79.2 mg/m^2 (120 mg in a 50 kg person).

There was no effect of levomilnacipran on male or female fertility or reproductive performance when dosed daily at up to 100 mg/kg/day PO. This corresponds to an estimated relative exposure of approximately 8 times based on body surface area.

There was no evidence of teratogenicity in either rats or rabbits that received up to 100 mg/kg/day PO levomilnacipran. Daily dosing of 100 mg/kg/day PO levomilnacipran during the period of organogenesis induced maternotoxicity in pregnant Wistar rats and NZW rabbits, characterised by reduced food intake and body weight gain in both species and, in rabbits, maternal mortality (3/22) as well as weight loss. In rats, fetal weight was significantly reduced in the offspring of dams that received 100 mg/kg/day (-11%). These pups also had an increased incidence of skeletal variations in the sternebrae (bipartite ossification, asymmetry, incomplete ossification or unossified sternebrae). These variations are indicative of delayed ossification which is commonly observed with reduced fetal weight and is consistent with the observed maternotoxicity. In rats the NOAEL for both maternal and embryofetal developmental toxicity was 30 mg/kg/day PO levomilnacipran, which was associated with a relative exposure of 1.7 times. In rabbits, similar skeletal findings were observed in the absence of effects of fetal weight. Delayed ossification, primarily in the phalanges, was observed in the fetuses of dams that received 100 mg/kg/day PO levomilnacipran, but this was not considered an adverse effect. No other treatment-related effects were observed in fetal rabbits. The NOAEL for maternal toxicity in rabbits was 30 mg/kg/day PO (relative exposure ≤ 0.2 times), with the NOAEL for embryofetal development being 100 mg/kg/day PO (relative exposure ≤ 3.8 times).

The effects of levomilnacipran on pre-/postnatal development were assessed in Wistar rats that received 7, 20 or 60 mg/kg/day PO levomilnacipran from the beginning of organogenesis until the end of lactation. In addition, doses up to 100 mg/kg/day PO were assessed in a pilot study in which Wistar rats were treated until postnatal day (PND) 7. In the pilot study there was a marked increase in the incidence of stillborn pups at the high dose, which was not observed at the lower doses used in the main study (estimated

relative exposure 8 times).[21]. In dams that received ≥ 20 mg/kg there was a significant reduction in weight gain during gestation and lactation, associated with decreased food intake. Levomilnacipran at doses up to 60 mg/kg/day did not affect gestation index, delivery index, live birth index or gestation length (estimated relative exposure approximately 5 times). However, increased postnatal mortality (pups were cannibalized) was observed on PND1 in the HD (60 mg/kg/day) group (7% compared to 0.4% in control group). A trend for higher mortality was also observed in the offspring of dams that received 20 mg/kg/day (1.7%).

In the pre-/postnatal study, pup weight and pup weight gain during lactation was significantly decreased in the offspring of dams receiving ≥ 20 mg/kg/day PO levomilnacipran. Body weight remained lower in these animals throughout the study. Physical development was also delayed in F_1[22] pups, with incisor eruption delayed in the offspring of dams that received ≥ 20 mg/kg/day and pinna unfolding delayed in the HD offspring only. Exposure to levomilnacipran during gestation and lactation did not affect behavioural indices in the F_1 pups. Reduced body weight persisted throughout gestation in the F_1 from dams that received 60 mg/kg/day, but did not affect reproductive indices. The NOAEL for both maternal and developmental toxicity in the pre-/postnatal study was 7 mg/kg/day, which was associated with a low estimated relative exposure (≤ 0.5 times).

In the levomilnacipran studies, it was unclear whether increased stillbirths and postnatal mortality were related to maternal toxicity or direct toxicity in the pups. Increased stillbirths, reduced postnatal survival and decreased weight have been reported for other SSRI and SNRI drugs[23] including milnacipran. In studies of milnacipran, the live birth index was decreased at doses ≥ 20 mg/kg/day PO from GD17 through to the end of lactation. The viability index (pups surviving to PND4) was also markedly reduced in the high dose group (80 mg/kg/day; 21% compared to 84% in controls). Reduced postnatal survival was associated with under-developed nipples and impaired nursing in 6/24 dams. In addition, total litter loss also occurred in another 5 HD dams. Together, these data suggest direct effects of (levo) milnacipran on post-implantation loss and postnatal survival.

Placental transfer of milnacipran, and presumably levomilnacipran, was low. However, distribution to the brain in the fetus and/or neonate may be enhanced compared to adults due to immaturity of the blood brain barrier. Therefore, it is possible that fetuses and/or neonates are more sensitive to the pharmacological effects of levomilnacipran.

Adverse events have also been reported in human neonates immediately after delivery following maternal treatment with SSRIs or SNRIs late in the third trimester. These effects include respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These effects are thought to be associated with direct toxicity, withdrawal syndrome and/or serotonin syndrome.

In summary, levomilnacipran did not affect fertility at doses up to 100 mg/kg/day in Wistar rats. Embryofetal development was adversely affected at high doses (decreased body weight and/or delayed ossification), likely due to maternal toxicity. High doses of levomilnacipran were associated with stillbirths and post-natal mortality. Reduced body weight at birth persisted through to adulthood.

[21] Relative exposure value for pilot study estimated from embryofetal development study which was conducted in the same rat strain using the same dose levels.
[22] An F1 hybrid (or filial 1 hybrid) is the first filial generation of offspring.
[23] Statements regarding increased stillbirths, postnatal mortality and/or reduced growth in rats are included in the Product Information statement for the following SSRI and SNRI medicines: escitalopram, fluvoxamine, citalopram, duloxetine and sertraline.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3[24], which is supported by the findings in animals and is consistent with the Pregnancy Category of milnacipran. However, this Category appears inconsistent with the reported effects in human neonates, and with class effects of serotonin reuptake inhibitors. Therefore, Pregnancy Category C[25] is recommended, as the reported adverse effects in human neonates are consistent with the pharmacological effects of levomilnacipran. However, as this recommendation is based on statements relating to clinical data it requires consideration by the clinical evaluator.

Paediatric use

Levomilnacipran is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- The nonclinical dossier was of high quality and adequately addressed the relevant ICH guidelines. All pivotal safety studies were conducted under GLP conditions.
- Levomilnacipran is a selective inhibitor of the noradrenaline (NET) and serotonin (SERT) transporters, with greater affinity for SERT compared to NET (K_i 11 nM compared to 91 nM, human recombinant transporters), but slightly more potent inhibition of NET compared to SERT (IC_{50} of 11 nM compared to 16-19 nM, respectively). Oral administration of levomilnacipran increased extracellular noradrenaline and serotonin concentration by inhibiting their reuptake, with increased dopamine also observed after a single dose. The expected catecholaminergic effects were also observed. In vivo studies supported an antidepressant, but not anxiolytic, effect in rodents.
- Levomilnacipran did not show inhibition or binding to other receptors or transporters at clinically relevant concentrations. Safety pharmacology studies in rodents showed expected effects in the CNS at low to moderate doses, including hypothermia, mydriasis, decreased activity and arousal, altered gait and posture, and ptosis. At higher doses convulsions were associated with mortality (relative exposure 10 times based on body surface area). Adverse effects on respiration occurred with high oral doses in rats, but based on a relative exposure of 11 times C_{max} at the no-effect level, this is unlikely to occur clinically.
- Adverse effects were observed on the cardiovascular system, including increased blood pressure and/or heart rate and QT interval prolongation in beagle dogs (10 mg/kg/day for 5 days) and cynomolgus monkeys (45 mg/kg, relative exposure 19 times based on C_{max}). In vitro studies supported the potential for levomilnacipran to prolong QT intervals, with inhibition of hERG channels and increased action potential duration. However, QT and QTc were unaffected following repeated dosing with up to 90 mg/kg/day in cynomolgus monkeys for 1 year (relative exposure ≥ 20 times human C_{max} when ECGs were performed). While QT interval prolongation is possible, it is not expected clinically based on the exposure ratios achieved in the repeat-dose monkey

[24] Category B3: 'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.'

[25] Category C: 'Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.'

study. Clinical studies have assessed the effects of both milnacipran and levomilnacipran on QT interval and found no adverse effects.

- Oral bioavailability was moderate in rats and high in monkeys and humans. Plasma protein binding was low in humans (22%), but not measured in animals. Low plasma protein binding has been reported in humans and animals for milnacipran. Tissue distribution was extensive, with melanin binding in rats. Low levels of levomilnacipran and/or its metabolites were observed in the brain. Levomilnacipran was metabolised to 6 metabolites, with *N*-desethyl levomilnacipran (F17400) being the major metabolite in all species. Excretion was predominantly in the urine, with high levels of unchanged drug excreted. The pharmacokinetics of levomilnacipran was very similar between monkeys and humans, and was sufficiently similar in rodents, making these animals suitable for profiling the toxicity of levomilnacipran.
- In vitro and in vivo studies indicated levomilnacipran and its major metabolite, F17400, were unlikely to cause clinically relevant drug-drug interactions through effects on either CYP enzymes or transport proteins, including p-glycoprotein. At high concentrations levomilnacipran and/or F17400 modestly inhibited CYP3A4/5 and CYP2C9.
- Acute toxicity was associated with adverse CNS effects, including tremors and convulsions, and death. The LD_{50} in mice and rats was associated with estimated relative exposures of 11 times and 20 times based on body surface area, respectively.
- Repeat dose toxicity studies were conducted in SD rats (up to 6 months) and cynomolgus monkeys (up to 1 year). Adverse clinical signs indicative of CNS toxicity, reduced weight gain and food intake, and emesis were observed in high dose groups. The main target organ for toxicity was the liver, with increased liver weight associated with hepatocellular hypertrophy and/or vacuolation observed in rats and monkeys. The no-effect level was associated with relative exposures of 2 times and 7 times based on AUC in rats and monkeys, respectively. Increased urinary volume was also observed in rats (relative exposure ≥ 2 times). Similar liver and renal effects were observed with milnacipran.
- Levomilnacipran was not mutagenic in bacterial or mammalian cells in vitro, and was not clastogenic in an in vivo micronucleus test in rats, indicating a low genotoxic potential. The carcinogenicity of levomilnacipran was assessed in a long term study (SD rats) and in a short-term (6 month) study (transgenic Tg.rasH2 mice). Levomilnacipran was not carcinogenic in either study, associated with relative AUC exposures up to 6 to 13 times in rats and 10 times in mice.
- Levomilnacipran did not impair male or female fertility in Wistar rats at estimated relative exposures of ≤ 8 times based on body surface area. Levomilnacipran was not teratogenic in rats or NZW rabbits at doses which produced maternal toxicity characterised by reduced body weight gain and food intake (relative exposure 8 times in rats and 0.8 to 3.8 times in rabbits, based on AUC). Maternal toxicity was associated with reduced pup weight and/or delayed ossification of the sternebrae (rats) or phalanges (rabbits). Administration of levomilnacipran from GD6 and throughout lactation in rats led to increased stillbirths (100 mg/kg/day, estimated relative exposure of 8 times) and postnatal death on PND1 (≥ 60 mg/kg/day, estimated relative exposure of 5 times). Similar outcomes were observed for milnacipran at doses that also induced maternal toxicity, with similar findings also reported for other SSRIs and SNRIs. In addition, pup growth and physical development were delayed in the offspring of dams that received ≥ 20 mg/kg/day PO levomilnacipran. The no-effect level for decreased pup weight, and delayed growth and development was 7 mg/kg/day, which was associated with an estimated relative exposure of ≤ 0.5 times.

Nonclinical conclusions and recommendation

- The nonclinical data was of high quality and addressed the relevant ICH guidelines.
- The primary pharmacology studies supported the proposed mechanism of action and provided evidence of antidepressant effects in vivo.
- In vitro studies indicated the potential for QT interval prolongation, but results from in vivo studies were mixed. QT and/or QTc interval were not increased following repeated administration of levomilnacipran at exposures ≥ 20 times clinical C_{max}. The weight of evidence indicates QT interval prolongation is unlikely to occur at the MRHD of 120 mg/day.
- The toxicity profile was similar to that for the racemate, milnacipran. The effects observed in liver were mild and reversible, and are unlikely to occur clinically based on the anticipated exposures. CNS and renal effects, related to the pharmacology of levomilnacipran, may occur clinically.
- The nonclinical data indicate a low genotoxic and carcinogenic potential for levomilnacipran.
- Levomilnacipran was not teratogenic. Adverse effects on fetal and postnatal growth and development may have been secondary to maternotoxicity. Pre- and postnatal death also occurred which may be a direct effect of levomilnacipran. Pregnancy Category C is considered to better reflect the nonclinical and clinical data than the proposed Category of B3.
- There are no nonclinical objections to the registration of levomilnacipran as proposed by the sponsor.
- Amendments to the draft Product Information document were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Current treatments of MDD include tricyclic antidepressants (TCAs, such as amitriptyline), selective serotonin reuptake inhibitors (SSRIs, such as fluoxetine), selective serotonin and norepinephrine reuptake inhibitors (SNRIs, such as duloxetine) and some other agents. As there are still patients who have an insufficient response to current antidepressants, there is a clinical need for further therapies.

With respect to the SNRIs, the sponsor's rationale for the NE and 5-HT activity is that *targeting both systems may produce improvements in components of MDD that are associated with both noradrenergic (e.g. alertness, energy, pain, attention) and serotonergic (e.g. mood, anxiety, obsessive-compulsive behaviors) neurotransmission* (sponsor's Clinical Overview). The sponsor states that as levomilnacipran has a greater potency at inhibiting NE compared to 5-HT. This is in contrast to other SNRIs which have a greater effect on 5-HT than NE reuptake. Levomilnacipran was therefore *developed to provide MDD patients with a safe and effective alternative to the current drug treatment options* (sponsor's Introduction and Clinical Overview).

All studies were conducted in the US and Canada and sponsored by Forest Research Institute Inc apart from Study F02695 LP2 02 which was sponsored by Pierre Fabre Medicament. It was stated that the two companies partnered for the clinical development of levomilnacipran.

Levomilnacipran has the drug code of F2695. There are 3 other SNRIs approved for treatment of MDD in Australia: duloxetine, venlafaxine and desvenlafaxine.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- Nineteen clinical pharmacology studies, including 19 that provided pharmacokinetic data and 1 that provided pharmacodynamic data
- One population pharmacokinetic analysis
- One population pharmacokinetic/pharmacodynamics study
- Four short term (8 week double-blind treatment, doses 40-120 mg/day) placebo-controlled studies in adult patients with MDD (LVM-MD-01, LVM-MD-02, LVM-MD-03, LVM-MD-10).
- One short term (10 week double-blind treatment, doses 75-100 mg/day) placebo-controlled study (F02695 LP 2 02).
- One relapse prevention study (LVM-MD-05).
- One open-label 48 week extension study (LVM-MD-04).
- Two studies in other indications (fatigue associated with MDD, generalised anxiety disorder).
- Five periodic adverse drug experience reports (October 2013 to July 2014), literature references, table for the *Integrated Summary of Efficacy*, an *Integrated Summary of Safety*, and a Cardiovascular Analyses Report.

Paediatric data

The submission did not include paediatric data. The sponsor stated that in the US there is a waiver for paediatric studies in the 0 to 6 year age group and a deferral for ages 7 to 17 in the treatment of MDD until 2018.

Comment: The sponsor has been asked to outline the paediatric clinical development plan.

Good clinical practice

The sponsor stated in their Clinical Overview that all studies were conducted in accordance with ICH Good Clinical Practice (GCP) and the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 6 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 6: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK	**F02695 GE 1 01**	PKs following single and repeated oral administrations of an IR form
		F02695 GE 1 02	PKs of 3 SR versus the IR formulation
		F02695 LP 1 01	In vitro/in vivo correlation of SR form and absolute BA compared to IV form
		LVM-PK-12	BE of 120 mg dose of the TBM and clinical trial SR forms and effect of food
		LVM-PK-19	BE of 120 mg dose of the TBM and clinical trial SR forms
		LVM-PK-14	BE of 120 mg dose of the Elan-TBM and clinical trial SR formulations
		LVM-PK-16	Comparison of SR formulation and oral solution
		LVM-PK-06	Effect of food on the BA of 40 mg levomilnacipran capsules
		LVM-PK-01	PKs following administration of single and multiple escalating doses
		LVM-PK-15	PKs following oral administration of 40, 80 or 120 mg
		F02695 LP 1 02	Interconversion of enantiomers
		LVM-PK-03	Mass balance and metabolism of [^{14}C] levomilnacipran
Population PK	Healthy and MDD	LVM-MS-01	Population PK analysis
Special populations	Hepatic Impairment	LVM-PK-05	Effect of hepatic impairment on single-dose PKs
	Renal Impairment	LVM-PK-02	Effect of renal impairment on single-dose PKs
	Age/Gender	LVM-PK-04	Effects of age and gender on PKs
PK interactions	CYP3A4/5 inhibition	LVM-PK-08	Effects of ketoconazole at steady state on the PKs of a single dose of levomilnacipran
	CYP3A4/2B	LVM-PK-	Effect of carbamazepine XR on the PKs of

PK topic	Subtopic	Study ID	*
	6 inducer	09	levomilnacipran SR
	CYP3A4 substrate	LVM-PK-10	Effect of a levomilnacipran SR at steady state on the PKs of alprazolam

* Indicates the primary aim of the study.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

Background

Levomilnacipran is a selective and potent norepinephrine and serotonin reuptake inhibitor for the treatment of MDD.

Absorption
Following a single120 mg oral dose of the TBM-formulation of levomilnacipran SR in healthy subjects the T_{max} occurred at 6.0 h following dosing and the $t_{1/2}$ was 13.8 h.

The absolute bioavailability of the clinical trial SR formulation of levomilnacipran was 100% (82 – 114%).

Following dose normalisation, the C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ values for the SR capsule formulation were 40.4%, 9% and 7.5% lower, respectively, than for an oral solution.

TBM SR formulations from both Forest and Elan (the primary and secondary manufacturing sites) were bioequivalent with the clinical trial formulation of SR levomilnacipran as the 90% CIs for C_{max} and AUC fell within the predefined confidence limits of 80 - 120%.

No studies specifically examined the bioequivalence of the proposed strengths of the TBM SR levomilnacipran capsules.

Food had no effect on the PKs of the TBM SR formulation.

Following single doses of the clinical trial SR formulation, C_{max} and $AUC_{0\text{-}inf}$ values increased dose-proportionally.

Levomilnacipran C_{max}, $AUC_{0\text{-}\tau}$ and C_{min} values increased dose-proportionally following treatment with multiple escalating once daily (QD) doses. Steady-state was achieved by the third dose on Day 3 and the accumulation indices were fairly stable over the dose range examined, ranging from 1.296 following the 300 mg dose to 1.486 at the 25 mg dose.

Distribution
The volume of distribution (Vd/F) values following single doses of 40 mg, 80 mg and 120 mg of the clinical trial SR formulation in healthy subjects were 405 L, 444 L and 429 L, respectively.

Binding of radiolabelled [14C]-F2695 to plasma proteins was low (~22 %) and binding to human serum albumin (HAS) and to alpha 1-acid glycoprotein (AAG) was very low, whereas, no binding to GG was detected.

Binding of [^{14}C]-F2695 to blood cells in buffer was low and non-saturable with the percentage bound ranging from 48% to 57%**.**

Given the volume of distribution following a single 40 mg dose of levomilnacipran is 405 L this would suggest that distribution of levomilnacipran to the tissues is extensive.

Metabolism

There was no interconversion of levomilnacipran to its opposite enantiomer in human plasma.

NADPH was found to be an essential component in levomilnacipran metabolism.

Multiple CYP enzymes (namely CYP2C8, 2C19, 2D6, 2J2 and 3A4) were implicated in the transformation of F2695 to F17400 with CYP3A4 being one of the major enzymes involved in this transformation.

Non-renal clearance was low with only 3.7% of a 60 mg oral dose of [^{14}C]F2695 being excreted in the faeces of healthy males.

The sponsor states that principal circulating metabolite of levomilnacipran, F17400, is inactive.

Circulating metabolites of levomilnacipran identified in healthy males were levomilnacipran glucuronide, F17400 and F17400 glucuronide. The plasma exposure for these metabolites represented 10.7%, 14.4% and 21.8%, respectively, of the plasma exposure of the parent drug.

The C_{max}, AUC_{0-12} and T_{max} values of levomilnacipran glucuronide in plasma following the administration of 60 mg oral dose of [^{14}C] F2695 were 18.7 ng/mL, 126 ng.h/mL and 3 h, respectively. For F17400 these values were 17.7 ng/mL, 164 ng.h/mL and 6 h, respectively, and for F17400 glucuronide were 29.2 ng/mL, 250 ng.h/mL and 4 h, respectively.

Excretion
93.4% and 3.8% of total radioactivity following a single 60 mg oral dose of [^{14}C] F2695 was excreted in the urine and faeces, respectively.

Renal clearance was identified as the primary route of excretion with 93.4% of a 60 mg oral dose of [^{14}C] F2695 excreted in the urine, with 58% representing unchanged levomilnacipran and 18% representing F17400, whereas, <5% corresponded to each of other metabolites.

Variability of pharmacokinetics
Estimates of the inter-individual variability on CL/F, Vc/F and Ka were 26.0%, 25.6% and 55.4%, respectively. Additive and proportional residual error terms for Phase I data of 13% and 43%, respectively.

Pharmacokinetics in the target population
No studies specifically examined the PKs of levomilnacipran in subjects with MDD.

Impaired hepatic function
Levomilnacipran C_{max} was 26%, 8%, and 28% higher in patients with mild, moderate and severe hepatic impairment, respectively, in comparison to healthy subjects, whereas AUC_{∞} was -1%, 9% and 32% higher, respectively.

Impaired renal function
In subjects with mild, moderate and severe renal impairment, levomilnacipran C_{max} was 4% lower and 19% and 44% higher, respectively, compared to subjects with normal renal function, whereas, AUC_{0-inf} was 23%, 93%, and 180% higher, respectively, for the 3 groups with renal impairment compared to normal subjects. Median T_{max} was delayed by 1.5, 3.5 and 1.5 h in subjects with mild, moderate, and severe renal impairment, respectively, and mean $t_{1/2}$ was longer by 17.3, 19.1, and 27.7 h, respectively.

Age and gender
The sponsor states that neither age nor gender had a statistically significant effect on levomilnacipran C_{max} or $AUC_{0-\tau}$; however, on examining using the more commonly accepted 90% CI limits of 80 to 125%, the data suggest that there is an increase in

levomilnacipran C_{max} (24% increase), AUC (26% increase) and C_{min} (35% increase) in elderly compared to young subjects and that levomilnacipran C_{max} (17% increase) is higher in female than male subjects.

Drug-drug interactions
Co-administration of levomilnacipran with steady state ketoconazole increased the mean levomilnacipran C_{max} by about 39%, and the mean AUC_{0-t} and AUC_{0-inf} by about 57% each. In addition, co-administration delayed the median T_{max} of levomilnacipran from 6 to 8 h and caused a reduction of the clearance from 22 to 14 L/h.

Levomilnacipran C_{max} and $AUC_{0-\tau}$ were 26.4% and 28.9% lower, respectively when administered concomitantly with carbamazepine XR compared to when levomilnacipran SR was administered alone. By contrast, the C_{max} and $AUC_{0-\tau}$ for carbamazepine were only slightly lower following co-administration.

Steady-state levomilnacipran had no effect on the PKs of alprazolam following a single-dose administration of a 1 mg alprazolam XR tablet. Co-administration of alprazolam had no effect on the steady-state PKs of levomilnacipran.

Population PK studies
The PopPK analysis indicated that PK data were best described by a one compartment PK model with first order absorption of drug from an oral dosing compartment. Creatinine clearance on CL/F and body weight on Vc/F were identified as significant covariates in the final PK model.

Limitations of the PK studies
No studies specifically examined the bioequivalence of the proposed strengths of the TBM SR levomilnacipran capsules.

No studies specifically examined dose proportionality for the proposed strengths of the TBM SR levomilnacipran capsules.

No studies specifically examined the PKs of levomilnacipran in subjects with MDD.

Questions arising from the PK studies
Why was 90% CI acceptance range of 70% to 143% used in Study LVM-PK-04 rather than the more typical 80-125% range as specified in *Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr*)?

Pharmacodynamics

Studies providing pharmacodynamic data

Table 6 below shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 6: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	PopPK/PD in patients with MDD	LVM-MS-04	Effect on MADRS-CR score following 8 weeks treatment
Secondary Pharmacology	Thorough QT	LVM-PK-07	Effects on cardiac repolarisation in healthy subjects

* Indicates the primary aim of the study.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Background

Levomilnacipran is a potent and selective SNRI.

The exact mechanism of the antidepressant effect of levomilnacipran is unknown.

Primary PD

PopPK/PD modelling of data from patients with MDD provided the following estimates: following 8 weeks of treatment either with levomilnacipran or placebo the mean percentage change from baseline in MADRS-CR was -41.2%, indicating an overall improvement in MDD; the median change from baseline MADRS-CR score following 8 weeks treatment with placebo was -12.4; and following 8 weeks treatment with 120 mg levomilnacipran SR the decrease in baseline score over placebo was 3.25.

Secondary PD

Thorough QT analysis in healthy subjects identified the following: for the primary endpoint of the study, which utilised Day -1 exercise data for heart-rate correction, the upper limit of the two-sided 90% CI of the time-matched ΔΔQTcNi was higher than 10 ms at 2, 3, 8 and 16 h post-dose of 120 mg/day levomilnacipran SR on Day 11, whereas, the upper limit of the two-sided 90% CI of the time-matched ΔΔQTcNi for levomilnacipran 300 mg/day on Day 24 was higher than 10 ms only at 16 h post-dose; and the upper limits of the 90% CI for the largest time-matched ΔΔQTcNi following three further analyses, which used different forms of QT correction, were under 10 ms for both levomilnacipran 120 mg/day and 300 mg/day.

Time course of pharmacodynamic effects

The decrease in Montgomery-Åsberg Depression Rating Scale, Clinician Rated (MADRS-CR) score[26] identified following the initial treatment with levomilnacipran SR or placebo gradually increased over the following weeks of treatment.

Relationship between drug concentration and PD effects

Changes in MADRS-CR showed a statistically significant linear relationship with exposure, specifically, two-week lagged steady-state area-under-the-curve (AUC_{ss}).

Following 8 weeks of treatment with 40 mg, 80 mg and 120 mg levomilnacipran SR the placebo corrected change in change from baseline (CFB)-MADRS-CR scores for the 3 doses were -1.10, -2.19 and -3.25, respectively.

Treatment with levomilnacipran SR resulted in placebo-adjusted changes from baseline in vital signs of +7.15 bpm for pulse rate, +2.83 mmHg for systolic blood pressure (SBP) and +2.72 mmHg for diastolic blood pressure (DBP). These changes were not dose dependent.

During the initial phase of treatment, a statistically significant relationship was identified between nausea and exposure. In addition the incidence of vomiting, dizziness, headache, urinary hesitation in males and erectile dysfunction also appeared to demonstrate some evidence of a weak positive correlation with exposure.

During the maintenance phase of treatment incidence of nausea, vomiting, dizziness, hyperhidrosis, and erectile dysfunction were all higher in the active treatment population over the placebo population, but were not significantly correlated with exposure.

Although there was a statistically significant relationship between the incidence of constipation and male urinary hesitation and exposure, the increase in incidence over the therapeutic dose range was only modest (less than 7%).

[26] This is a ten-item diagnostic questionnaire which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders.

Limitations of PD studies

No PD studies, other than the combined PopPK/PD study, specifically examined the effects of levomilnacipran SR on MDD.

No studies examined the PD interaction of levomilnacipran with other drugs.

Questions arising from the PD studies

Given the sponsor's justification for the aberrant results of the primary endpoint analysis in Study LVM-PK-O7 (please see section *Secondary pharmacodynamic effects* of this report for more information), why was the Day -1 exercise data for heart-rate correction chosen for the primary endpoint analysis at the study's outset?

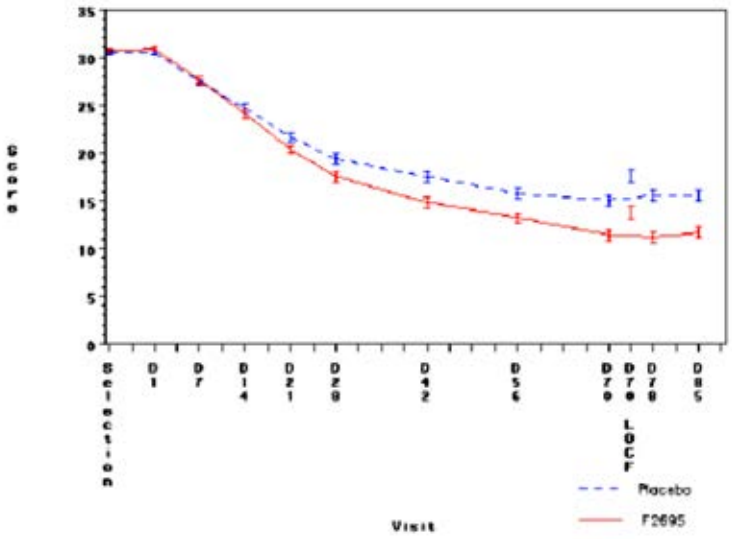
Dosage selection for the pivotal studies

The Phase III program selected 40, 80 and 120 mg per day which included doses lower and higher than the 75 mg and 100 mg per day flexible dosing which was assessed in the earlier Phase II study F02695 LP 2 02 (see Section Study F02695 LP 2 02 for study summary together with Table 7 and Figure 2). The doses of milnacipran approved for use in fibromyalgia are 100 to 200 mg per day.

Table 7: F02695 LP 2 02 MADRS total score: Change from baseline MMRM analysis (FAS)

	Placebo n=277	F2695 n=276
Model Change=Baseline+Centre group+Visit+Treatment+Visit*Treatment+Visit*Baseline Test for Visit*Treatment effect, p <0.0001		
Adjusted change from baseline to day 70 LSMeans (SE)	-14.5 (0.56)	-18.7 (0.56)
Adjusted change from baseline to day 70 difference between treatment groups Test for Treatment effect, p <0.0001 LSMeans (SE) = -4.2 (0.79) [LSM 95%CI]: [-5.7; -2.6]		

Figure 2: F02695 LP 2 02 MADRS Total score: Values over time (FAS)



Comments: Study F02695 LP 2 02 was a supportive efficacy study and not a dose-finding study. There was no detailed discussion in the dossier on how the decision was made to select the 40, 80 and 120 mg doses for the Phase III program. The Sponsor has been asked to comment on this.

Efficacy

Studies providing efficacy data

The dossier included five short term, double-blind, randomised, placebo-controlled studies. Two studies were fixed dose: LVM-MD-01 (40, 80 and 120 mg/day) and LVM-MD-10 (40 and 80 mg/day). Two were flexible dose: LVM-MD-03 and LVM-MD-02 (40-120 mg/day). There was also one Phase II study (F02695 LP202) which assessed a flexible dose of 75-100 mg/day. All studies were conducted in the US and Canada apart from the Phase II study.

Evaluator's conclusions on efficacy for MDD

All short term studies had 8 weeks of double-blind treatment apart from the Phase II study which had 10 weeks. Dose titration in the Phase III studies started at 20 mg/day for 2 days and in the fixed dose studies was titrated to 40 at Day 3-4, 80 by Day 5-7 and 120 mg (only Study LVM-MD-01) from Day 8. In the flexible dose studies, titration to 40 mg was at Day 3 to 7, 80 mg at Day 8-28 and 120 mg from Day 29.

The primary efficacy endpoint in all studies was the change from baseline to study endpoint (8 weeks in the Phase III studies and 10 weeks in the Phase II study) in the MADRS total score as rated by a trained clinician. The SDS total score was the key secondary endpoint and used as a measure of functional impairment. The change from baseline to Week 8 was analysed on the intent-to-treat (ITT) population which was defined as all randomised patients who took at least one dose of study medication and had at least one post baseline efficacy assessment. There was consistency of design and analyses across the studies.

Patients had MDD meeting the DSM-IV-TR criteria with an MADRS total score of ≥ 30 in Studies LVM-MD-01, LMV-MD-02 and LVM-MD-03 and a MADRS total score of ≥ 26 in Study LVM-MD-10. The Phase II study eligibility was based on the HAMD-17 (>22).

Four of the short term studies were positive and one was negative (LVM-MD-02). The Phase II study, which was positive, is only considered supportive primarily due to differences in doses assessed and inclusion criteria. The least squares (LS) mean difference (levomilnacipran versus placebo) in the change from baseline to Week 8 in the MADRS total score was in the range of -3 to -5 (Table 8). Results were robust being supported by sensitivity analyses and the secondary endpoint of SDS total score (Table 9).

Table 8: Primary efficacy parameter' Change from baseline to end point in the MADRS total score (MMRM) in the positive studies-ITT population

	LVM-MD-01				*LVM-MD-10*			*LVM-MD-03*		*F02695 LP 2 02*	
	Placebo (N = 175)	*40 mg/d (N = 176)*	*80 mg/d (N = 177)*	*120 mg/d (N = 176)*	*Placebo (N = 185)*	*40 mg/d (N = 185)*	*80 mg/d (N = 187)*	*Placebo (N = 214)*	*40-120 mg/d (N = 215)*	*Placebo (N = 277)*	*75-100 mg/d (N = 276)*
Baseline, Mean ± SD	35.6 ± 4.5	36 ± 4.1	36.1 ± 3.9	36.0 ± 3.9	31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5	35.2 ± 3.8	35.0 ± 3.6	30.5 ± 3.7	30.9 ± 4.1
Change, LS mean (SE)	−11.6 (0.97)	−14.8 (0.99)	−15.6 (1.00)	−16.5 (1.02)	−11.3 (0.77)	−14.6 (0.79)	−14.4 (0.79)	−12.2 (0.78)	−15.3 (0.79)	−14.5 (0.56)	−18.7 (0.56)
LSMD (95% CI)	—	−3.23 (−5.9, −0.5)	−3.99 (−6.7, −1.3)	−4.86 (−7.6, −2.1)	—	−3.30 (−5.5, −1.1)	−3.14 (−5.3, −1.0)	—	−3.10 (−5.3, −0.9)	—	−4.2 (−5.7, −2.6)
p-Value[a]	—	**0.0186**	**0.0038**	**0.0005**	—	**0.0027**	**0.0043**	—	**0.0051**	—	**< 0.0001**

Note: Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.

a Analyses were based on the MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MADRS = Montgomery-Åsberg Depression Rating Scale; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SD = standard deviation; SE = standard error.

Table 9: Secondary efficacy parameter Change from baseline to end point in the SCS score (MMRM) in the positive studies-ITT population

	LVM-MD-01				LVM-MD-10			LVM-MD-03		F02695 LP 2 02	
	Placebo (N = 175)	40 mg/d (N = 176)	80 mg/d (N = 177)	120 mg/d (N = 177)	Placebo (N = 185)	40 mg/d (N = 185)	80 mg/d (N = 187)	Placebo (N = 214)	40-120 mg/d (N = 215)	Placebo (N = 277)	75-100 mg/d (N = 276)
Baseline, Mean ± SD	21.5 ± 4.8	21.1 ± 4.8	21.4 ± 4.9	21.3 ± 5	16.4 ± 6.1	16.7 ± 6.6	17.6 ± 6.0	19.7 ± 5.2	20.1 ± 5.0	20.8 ± 3.8	21.3 ± 3.9
Change, LS mean (SE)	−7.2 (0.74)	−8.6 (0.75)	−9.7 (0.77)	−9.7 (0.78)	−5.4 (0.66)	−7.3 (0.68)	−8.2 (0.66)	−5.4 (0.57)	−8.0 (0.58)	−7.7 (0.44)	−11.1 (0.43)
LSMD (95% CI)	—	−1.41 (−3.4, 0.6)	−2.51 (−4.5, -0.5)	−2.57 (−4.6, −0.5)	—	−1.83 (−3.6, −0.0)	−2.72 (−4.5, −1.0)	—	−2.63 (−4.2, −1.1)	—	−3.4 (−4.6, −2.2)
p-Value[a]	—	0.1687	**0.0151**	**0.0141**	—	**0.0459**	**0.0028**	—	**0.0010**	—	**< 0.0001**

Note: Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.

a Analyses were based on the MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS-CR total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures; N = number of patients in the ITT Population; SDS = Sheehan Disability Scale; SD = standard deviation; SE = standard error.

Levomilnacipran was found to have a positive effect on MADRS response and remission rates in studies LVM-MD-01 (only the 120 mg dose), LVM-MD-10 and F02695 LP 2 02. However no significant effects on these clinically relevant endpoints were found in studies LVM-MD-02 and LVM-MD-03 (Table 10). The sponsor states this is due to the higher MADRS entry criteria in studies LVM-MD-01, -02 and -03 and the short trial duration. The evaluator agrees that these are possible explanations for the lack of effect.

Table 10: MADRS response rates at end point (LOCF) in the positive studies-ITT population

	LVM-MD-01				LVM-MD-10			LVM-MD-03		F02695 LP 2 02	
	Placebo (N = 175)	40 mg/d (N = 176)	80 mg/d (N = 177)	120 mg/d (N = 177)	Placebo (N = 185)	40 mg/d (N = 185)	80 mg/d (N = 187)	Placebo (N = 214)	40-120 mg/d (N = 215)	Placebo (N = 277)	75-100 mg/d (N = 276)
Baseline, Mean ± SD	35.6 ± 4.5	36.0 ± 4.1	36.1 ± 3.9	36.0 ± 3.9	31.0 ± 3.8	30.8 ± 3.4	31.2 ± 3.5	35.2 ± 3.8	35.0 ± 3.6	30.5 ± 3.7	30.9 ± 4.1
MADRS response n (%)	51 (29.1)	64 (36.4)	66 (37.3)	73 (41.5)	62 (33.5)	90 (48.6)	87 (46.5)	63 (29.4)	90 (41.9)	117 (42.2)	163 (59.1)
Odds ratio (95% CI)[a]	—	1.44 (0.92, 2.27)	1.51 (0.96, 2.37)	1.79 (1.15, 2.81)	—	1.87 (1.23, 2.85)	1.74 (1.15, 2.66)	—	1.72 (1.15, 2.56)	—	2.15 (1.48, 3.11)

Note: Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.

a Analyses were based on logistic regression model with treatment group and corresponding baseline value as explanatory variables in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03. Analyses were based on Model Response = Baseline + Visit + Treatment + Visit*Treatment + Visit*Baseline' and 'at Week 10' in Study F02695 LP 2 02.

CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; mg/d = milligrams per day; N = number of patients in the ITT Population; n = number of responders; SD = standard deviation.

Subgroup analyses of age (< 55/≥ 55 years) and race (White/non-White) were hampered by small numbers is some groups. The responses in males and females showed variation between studies. Those with more severe depression (MADRS ≥35) tended to have a higher treatment response.

The dossier included one 52 week, open-label extension study (LVM-MD-04) which primarily assessed safety. Due to the open-label design, lack of comparison group and the high discontinuation rate (53%) no long term efficacy conclusions can be drawn from this study.

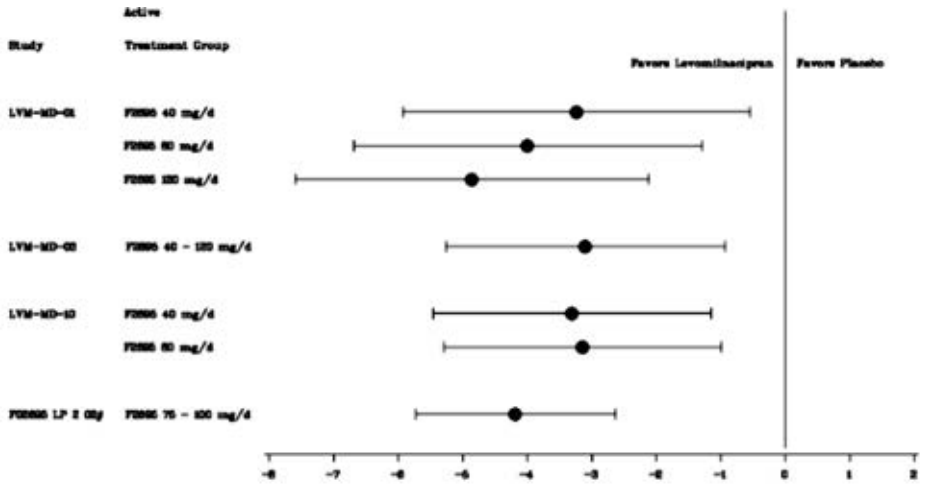
There was one relapse prevention study (LVM-MD-05) which was negative. Consequently, there are no data demonstrating persistence of efficacy beyond 8 weeks (limited supportive evidence to 10 weeks from Study F02695 LP 2 02). EMA (2013) guidelines on products for treatment of depression state that for *authorisation it should be shown that a short-term effect can be maintained during the index episode*. It is noted that the FDA has requested that the sponsor conduct another relapse prevention study with altered design. The sponsor has been asked to comment on this.

The dossier included two other studies, one on generalised anxiety disorder which was terminated prematurely due to non-supportive preclinical data, and the other on fatigue associated with MDD which indicated no positive effect.

The data from the fixed dose Study LVM-MD-01 pointed towards increased efficacy with increasing dose (40, 80, 120 mg/day). This was more noticeable in those with more severe depression (MADRS ≥ 35). The dose response was not evident in Study LVM-MD-10 when only 40 and 80 mg/day were assessed (Figure 3). These studies were not powered for inter-dose comparisons and there were no statistical analyses of this. With a flexible dosing regimen in Study LVM-MD-03, 44% of patients were titrated to the highest dose of 120 mg. The other flexible dose study was negative. The data in the dossier have not characterised the minimum effective dose.

The clinical development program did not include any active control groups despite guidelines recommending their inclusion (EMA 2013).

Figure 3: Treatment differences and 95% CIs of change from baseline in MADRS total score endpoint (MMRM)-ITT population



Note: Analysis based on observed cases using a mixed model for repeated measures with treatment group, pooled study center (nested within Study), visit, and treatment group-by-visit interaction, as fixed effects and baseline and baseline-by-visit as covariates using an unstructured covariance matrix to model the covariance of within-patient scores.

Endpoint was Week 8 in Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in Study F02695 LP 2 02.

All values in the levomilnacipran group were statistically significant versus placebo.

CI = confidence interval; F2695 = levomilnacipran; ITT = intent to treat; MADRS = Montgomery-Åsberg Depression Rating Scale; mg/d = milligrams per day; MMRM = mixed-effects model for repeated measures.

Safety

Studies providing evaluable safety data

There were no pivotal safety studies.

The studies which provided evaluable safety data were allocated into 5 groups (Table 11). Group 1 included the 5 short term placebo controlled studies, Group 2 the single long term (48 weeks) safety study, Group 3 the single relapse prevention study, Group 4 the healthy subject studies (19 studies) and Group 5 the two studies in other indications. Groups 1, 2 and 3 were pooled to provide the 'all levomilnacipran-treated patient' group.

Safety analyses were conducted on the Safety Population which was defined as all randomised subjects who received at least one dose of study medication. The end of double-blind treatment was defined as the last dose prior to commencing the down-titrated double-blind medication (or the last non-missing value if there was no down titration).

Table 10: Levomilnacipran clinical studies

Group 1: Short-term, Placebo-Controlled Studies	
Group 1A: US Short-term, Placebo-Controlled Studies	*Group 1B: Non-US Short-term, Placebo- Controlled Study*
Fixed-dose Studies: LVM-MD-01 LVM-MD-10[a] **Flexible-dose Studies:** LVM-MD-02 LVM-MD-03	**Flexible-Dose Study:** F02695 LP 2 02[b]
Group 2: Long-term, Open-label Study	
LVM-MD-04	
Group 3: Relapse-Prevention Study	
LVM-MD-05[a]	
Group 4: Clinical Pharmacology and Biopharmaceutic Studies in Healthy Subjects	
BA/BE Studies	
F02695 GE 1 02 F02695 LP 1 01 LVM-PK-06 LVM-PK-12	LVM-PK-14 LVM-PK-16 LVM-PK-19
PK Studies	
F02695 GE 1 01 F02695 LP 1 02	LVM-PK-03[c] LVM-PK-01 LVM-PK-15
Intrinsic Factors	
LVM-PK-02 LVM-PK-04	LVM-PK-05
Extrinsic Factors	
LVM-PK-08 LVM-PK-09	LVM-PK-10
PK/PD Study	
LVM-PK-07	
Group 5: Studies in Other Indications	
F02695 LP 2 01[d]	LVM-MD-06

a Study also conducted at sites in Canada.
b Studies conducted worldwide.
c Study also known as F02695 PO 1 01.
d Study was prematurely terminated by the sponsor due to administrative reasons.

There were 26 identified patients who participated in more than one levomilnacipran study. Data from these subjects were included in the safety analyses.

In the short-term, placebo-controlled studies the following safety data were collected:

- General adverse events (AEs) which were assessed at all visits. Data on treatment emergent AEs (TEAEs) were provided.
- AEs of particular interest, including cardiovascular, suicidality, genitourinary, narrow angle glaucoma, abnormal bleeding, serotonin syndrome/neuroleptic malignant syndrome, hyponatraemia and hepatoxicity, were analysed by standardised MedDRA queries.
- Clinical laboratory tests, including haematology, chemistry and urinalysis (not in F02695 LP 2 02), and pregnancy tests which were assessed at screening and weeks 4 and 8 (or 10 in F02695 LP 2 02).
- Vital signs (including orthostatic blood pressure and body weight) at all visits and physical examination (at screening and final visits).
- ECGs at screening and weeks 4 and 8 (or 10 in F02695 LP 2 02).

- Columbia–Suicide Severity Rating (C–SSRS)[27] (not in F02695 LP 2 02) at all visits.
- Arizona Sexual Experiences (ASEX) as a measure of sexual dysfunction in Study LVM-MD-02.

The open-label, long-term and relapse prevention studies collected the same safety data at regular intervals during the studies. The healthy subject studies provided data on serious AEs (SAEs).

Patient exposure

There were 1583 patients in Group 1 (short term studies), 825 in Group 2 (long term extension study), 734 in Group 3 open-label (233 double-blind period) and 637 in Group 4 (clinical pharmacology and biopharmaceutic studies) who received levomilnacipran (Table 11 below). In the phase I studies, 371 subjects received a single dose, 209 multiple doses and 57 both single and multiple doses. Doses ranged from 20 to 300 mg per day for up to 36 days.

Table 11: Distribution of subjects in the levomilnacipran studies-Safety population

Study	*Placebo*	*Levomilnacipran*
Group 1—Short-term, Placebo-Controlled Studies		
Group 1A Fixed-dose studies		
LVM-MD-01	176	537
LVM-MD-10	186	376
Group 1A Fixed Dose subtotal	**362**	**913[a]**
Group 1A Flexible-dose studies		
LVM-MD-02	182	175
LVM-MD-03	217	217
Group 1A subtotal	***761***	***1305***
Group 1B		
F02695 2 02	279	278
Group 1B subtotal	***279***	***278***
Group 1 total	***1040***	***1583***
Group 2—Long-term, Open-label Study		
LVM-MD-04 (New Exposure)		825 (356)[b]
Group 3—Relapse-Prevention Study		
LVM-MD-05		
Open-label period		734
Double-blind period	112	233
Group 4—Clinical Pharmacology and Biopharmaceutic Studies in Healthy Subjects		
Single-dose studies	6	371
Multiple-dose studies	82	209
Single-dose and multiple-dose	8	57
Group 4 Total	***96***	***637***

a A total of 366, 367, and 180 patients received levomilnacipran 40 mg, 80 mg, and 120 mg, respectively.
b Patients who received placebo during the lead-in study.

In Groups 1, 2 and 3 (MDD patients) there were 2673 patients who received levomilnacipran (40 to 120 mg/day) with a total treatment exposure of 941.7 patient-

[27] The C–SSRS is an instrument that reports the severity of both suicidal ideation and behaviour. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C–SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behaviour is classified on a 5-item scale: 0 (no suicidal behaviour), 1 (preparatory acts or behaviour), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

years. There were 367 patient exposed to levomilnacipran for 48 weeks or longer (Table 12).

Table 12: Summary of overall exposure (Groups 1, 2 and 3), safety population

Exposure	*Group 1 + 2+ 3 LVM 40-120 mg/d*	*Group 1*		*Group 2*	*Group 3*		
		Placebo	*LVM 40-120 mg*	*LVM 40-120 mg*	*Open-label*	*Double-blind*	
					LVM 40-120 mg	*Placebo*	*LVM 40-120 mg*
Treatment duration, n							
≥ 1 day	2673	1040	1583	825	734	112	233
≥ 8 weeks	1940	675	957	709	556	93	193
≥ 24 weeks	737	—	—	511	—	53	104
≥ 48 weeks	367	—	—	296	—	—	—
Patient-years of exposure	941.7	152.3	218.2	502.3	138.6	41.6	82.7

LVM = levomilnacipran.

Group 1 = 5 short term studies Group 2 = long term open-label extension study (LVM-MD-04) Group 3 = relapse prevention study (LVM-MD-05)

Comment: Table 12 states that in Group 2 there were 296 patients exposure for ≥48 weeks while in Groups 1, 2 and 3 there were 367 patients with this exposure duration. Given there were no other studies apart from LMV-MD-04 that had ≥ 48 weeks treatment duration (Study LVM-MD-05 was 38 weeks), the evaluator is unsure how the number exposed to ≥ 48 weeks from Groups 1,2 and 3 can be greater than the number exposed in Group 2. In addition, the exposure numbers provided in the sponsor's Summary of Clinical Safety are different to those in the FDA clinical evaluation report. The sponsor has been asked to comment on these points. The numbers, as they are reported, meet the ICH E1 requirements for a safety data base.

The mean treatment duration in the short term studies (Group 1) was 50.3 days (range 3 to 77 days). In the flexible dose studies (LVM-MD-02 and -03), 46% received 120 mg, 34% 80 mg and 19% 40 mg as the final daily dose. In the long term study (Group 2), the mean treatment duration was 222 days and the mean daily dose was 83 mg with a final daily dose of 120 mg, 80 mg, 40 mg and 20 mg in 47%, 26%, 27% and 0.4%, respectively. In study LMV-MD-04 open-label period, the mean daily dose was 79 mg and 47% had a final daily dose of 120 mg.

Safety issues with the potential for major regulatory impact

Safety issues relating to the SNRI class effects have been discussed in relevant prior sections. There were no additional major safety signals.

Postmarketing data

There were five quarterly Periodic Adverse Drug Event reports in the dossier covering the period from 25 July 2013 (US authorisation date) to October 2014. The sponsor's Summary of Clinical Safety included a review of these for the first year (to 23 July 2014). During this time the estimated exposure was 10,237 patient-years. There were 659 adverse drug reaction reports in 322 patients. Psychiatric disorders were most frequent (20%) with the most common being anxiety, insomnia, agitation and suicidal ideation (11 cases). There were 3 suicides, one after 2 days levomilnacipran treatment and data in the others were lacking.

Thirteen per cent of adverse drug reactions (ADRs) were gastrointestinal with nausea being the most frequent event. There were two casas of intestinal haemorrhage (data lacking on these cases). The most frequent neurological ADRs were dizziness and

headache. There were two cases of serotonin syndrome, one of whom was also taking bupropion. There was one seizure reported 4 days after commencing levomilnacipran. Other events reported included fatigue and asthenia and drug ineffective.

There was one case of 'drug withdrawal syndrome' reported which was described as sadness and weeping after abrupt cessation of levomilnacipran 40 mg. Of the 12 cases of hypertension, 4 were serious. There were 17 cases of tachycardia/increased heart rate (HR) of which two were serious. There was one cardiac failure and three cases of atrial fibrillation. One patient with atrial fibrillation (AF) died. This 75 year old female had an artificial heart valve and history of AF. The cause of death was not confirmed.

There was one case of raised liver enzymes. Renal and urinary ADRs (5.5%) were most frequently urinary hesitation and urinary retention with one case being serious and requiring catheterisation.

In the period 25 July to 24 October 2014 there were 224 events reported of which 29 were considered serious. There were 4 new cases of serotonin syndrome. Overall, there were no new findings and the events were consistent with those from the prior reporting periods.

Evaluator's conclusions on safety

In the MDD studies there were 2673 patients exposed to levomilnacipran with 367 exposed for 48 week or longer (this number is to be confirmed by the sponsor). The total MDD patient exposure was 941.7 patient-years.

Group 1 studies included the 5 short term, placebo controlled studies (1583 levomilnacipran and 1040 placebo-treated patients), Group 2 included the single long term (48 weeks) safety study (825 patients), and Group 3 the single relapse prevention study (734 open-label and 233 levomilnacipran and 112 placebo-treated in the double-blind period). There were also 637 healthy subjects in the clinical pharmacology and biopharmaceutic studies.

The mean treatment duration in the short term studies was 50 days. In the long term study, the mean treatment duration was 222 days and the mean daily dose was 83 mg with a final daily dose of 120 mg, 80 mg, 40 mg and 20 mg in 47%, 26%, 27% and 0.4%, respectively.

There was one death in the clinical development program post-randomisation. A female was diagnosed with Stage IV gastric adenocarcinoma after 223 days of levomilnacipran treatment in the extension Study LVM-MD-04. She had received placebo in the feeder study. The other death (from drowning) occurred during screening.

The rate of SAEs was slightly lower with levomilnacipran than placebo in the short term studies (0.7% versus 1.3%) with a comparative rate of 5.0 versus 9.2 per 100 patient-years exposure. The SAE rate in the 48 week study was 7.2 per 100 patient years. SAEs deemed treatment-related included aggression/violent outburst, suicidal ideation, prostatitis, seminal vesiculitis and non-cardiac chest pain, plus one post-study case of a premature and small-for-dates baby. There was one case of a seizure with encephalopathy classed as not treatment-related.

The rate of treatment emergent AEs (TEAEs) that led to discontinuation was higher with levomilnacipran than placebo (8.8% versus 3.2%) in short term studies and in the long term study the rate was 13%. The most frequent events were nausea, vomiting, dizziness, headache, hyperhidrosis, rash or urticaria, urinary disorders (hesitation, retention, and dysuria), tachycardia, palpitations, hypertension, testicular pain and erectile dysfunction.

The adverse event profile was consistent with other SNRIs. TEAEs which occurred at a notably higher rate than placebo were nausea, constipation, tachycardia, increased heart

rate, palpitations, vomiting, dizziness, urinary hesitation, hyperhidrosis, increased BP, erectile dysfunction, ejaculation disorder and testicular pain.

No increased risk was found of the class effects of serotonin syndrome, mania/hypomania, hostility or aggression, discontinuation syndrome, suicidality (also assessed using the C-SSRS) or abnormal bleeding. There was one case of rhabdomyolysis with elevated liver function tests (LFTs) for which other causes were postulated but not confirmed.

Dose response on AE rates was not evident, apart from with erectile dysfunction and urinary hesitancy.

TEAEs were generally mild to moderate. Severe TEAEs occurred in 6% of short term and 13% of long term study patients treated with levomilnacipran.

Mild mean increases in liver enzymes were noted however there was no evident dose response and levels generally reduced despite ongoing treatment. Clinically significant increases in ALT and/or aspartate aminotransferase (AST) of ≥ 3x upper limit of normal (ULN) occurred in <1% of subjects. Discontinuation due to LFT abnormalities was infrequent (2 in Group 1) and there were no cases meeting Hy's law criteria for potential drug-induced liver injury. There were no other remarkable findings on laboratory analyses.

Levomilnacipran was seen to increase the mean heart rate (7 beats per minute (bpm) in Group 1 and 9 bpm in Group 2). The rate of potentially clinically significant increase in HR in the levomilnacipran groups ranged from 0.4 to 0.9%. This resulted in a moderately high rate of TEAEs of tachycardia or increased heart rate although discontinuation from this cause was less common (0.6% in Group 1). There were two SAEs relating to increased heart rate in the long term study. In the fixed dose studies, increased heart rate was greater with 120 mg than with 40 to 80 mg.

Over the short term treatment period, there were also increases in mean SBP (3.0 mmHg) and mean DBP (3.2 mmHg). This increase did not appear dose related. The increase with longer term treatment was similar (3-4 mm Hg). Sustained hypertension in Group 1 occurred in 1.8% versus 1.2% patients in the levomilnacipran and placebo groups, respectively and was 0.8% in Group 2. The rate of orthostatic hypotension was only marginally higher than placebo (11.6% versus 9.7%) and no dose response was evident.

While there was a small decrease in mean body weight in the short term studies and the rate of potentially clinically significant weight decrease was not markedly different (1.6% versus 1.0%).

While the upper bound of the 90% CI for the primary QTc endpoint in the Thorough QT trial for levomilnacipran 120 mg and 300 mg was slightly greater than the 10 ms threshold, this was not confirmed on secondary endpoints. The ECG findings from the Phase III program showed an increase in QTcB but not on QTcF. The effect on QTcB is likely due to the increased heart rate associated with levomilnacipran and in such cases QTcF is the more reliable correction. Overall, the data from the Phase III program do not point towards an appreciable effect on QTc interval and the effect on heart rate and blood pressure is believed to be of greater clinical relevance.

Subgroup analysis found increased constipation and hypertension in those aged 55 years and over. Nausea was more frequent in females.

There were 15 pregnancies during the clinical development program with two SAEs; preeclampsia and premature/small-for-dates baby.

Treatment with levomilnacipran was tapered down prior to ceasing. During this period there was no evidence of a discontinuation syndrome as assessed by comparing rates of newly emergent AEs between the levomilnacipran and placebo groups. Due to the

importance of withdrawal effects and rebound depression, the sponsor has been asked to provide further information on this safety issue.

Post-marketing data for the period from July 2013 to October 2014 with an estimated 10,000 patient-years exposure was presented. The most frequent events reported were psychiatric disorders (anxiety, insomnia, agitation and suicidal ideation) followed by gastrointestinal disorders (nausea) and neurological (dizziness and headache). No new safety signals were identified during this period.

Long term safety was consistent with data from the short term studies. However, drawing definitive conclusions is difficult due to the lack of a comparison group.

There is an increased exposure with moderate to severe renal impairment which will impact on dosing recommendations. There is also a requirement for a lower dose when co-administration with strong CYP3A4 inhibitors (such as ketoconazole).

Safety has not been established in patients with other psychiatric conditions, clinically significant or unstable cardiovascular disease, pregnancy or breastfeeding due to clinical trial exclusions.

The rate of adverse events with the Elan site to-be-marketed formulation was higher than the clinical trial formulation and this signal needs further clarification.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of levomilnacipran SR in the proposed usage are:

- Efficacy over placebo for short term treatment of major depressive disorder as measured by the MADRS total score (3 pivotal and one supportive study). Efficacy over placebo was also found on functional impairment as measured by the secondary endpoint of SDS total score.
- Safety was in line with that of other SNRIs and no new safety signals were evident.

First round assessment of risks

The risks of levomilnacipran SR in the proposed usage are:

- Common adverse events of nausea, constipation, hyperhidrosis, vomiting, increased heart rate, tachycardia, palpitations and erectile dysfunction.
- Treatment discontinuation due to adverse events (approximately 9-13% compared to 3% with placebo).
- Cardiovascular effects of hypertension and increased heart rate. Data on the use of levomilnacipran in patients with significant cardiovascular disease are lacking.
- Urinary retention and hesitation.
- Sexual dysfunction adverse events particularly in males.
- Mild increases in liver enzymes although there was no evidence of drug-induced liver injury.
- Other SNRI class related effects: suicidal thoughts and behaviour, serotonin syndrome, abnormal bleeding, mania, discontinuation syndrome, mydriasis and risk of narrow angle glaucoma.
- Lack of efficacy data on long term maintenance and relapse prevention.

- Drug-drug interactions with strong CYP3A4 inhibitors such as ketoconazole which will require lower levomilnacipran dosing.
- Moderate to severe renal impairment needs a reduced dose.
- Tapering down of dose required due to the risk of discontinuation syndrome.
- Due to clinical trial exclusions there are no data on patients < 18 years or > 80 years, with suicide risk, or pregnant or lactating women.

First round assessment of benefit-risk balance

Levomilnacipran extended release capsules (40 to 120 mg per day) demonstrated statistically significant short term efficacy (as measured by MADRS-CR) in adult outpatients with MDD in three of 4 placebo-controlled studies. Two of the positive studies were fixed dose (40, 80 and 120 mg) and one had flexible dosing (40 to 120 mg). One short term flexible dose study was negative. There was one additional Phase II short term study which provided supportive efficacy data. The studies found a LS mean difference (levomilnacipran – placebo) in the change from baseline to Week 8 in the MADRS total score of between -3 and -5. Overall, the results were robust, confirmed on sensitivity analyses and supported by secondary endpoints, in particular the SDS as a measure of functional impairment. Data were suggestive of greater response with the highest dose of 120 mg/day however there were no formal inter-dose comparisons.

By contrast, separation from placebo on the clinically relevant endpoints of MADRS response (≥ 50% reduction) and remission (total score ≤ 10) rates was variable. Significantly higher rates were found with levomilnacipran compared to placebo in studies LVM-MD-10 and F02695 LP 2 02, while this positive effect was not seen in LVM-MD-02 and LVM-MD-03 nor with the lower two doses in LVM-MD-01. The sponsor stated this is due to the short trial duration and the higher MADRS entry criteria (MADRS ≥ 30) in Studies LVM-MD-01, -02 and -03 compared to MADRS ≥ 26 in Study LVM-MD-10. The evaluator agrees that these are possible explanations for the lack of effect.

The only controlled, long term efficacy data comes from the relapse prevention study which was negative. Levomilnacipran and placebo failed to separate in the rate of relapse (14% versus 21%). These rates were lower than anticipated over the 24 month period (20% versus 38%). It is noted that the FDA have requested a repeat of the relapse prevention study with longer period of stabilisation prior to randomisation.

The Australian and New Zealand clinical practice guidelines for the treatment of depression state that treatment duration following a first episode of depression should be for 12 months and for recurrent episodes should be 3 years or more *following discussion of the potential benefits and burden of treatment*.[28] In addition, the Australian Therapeutic Guidelines on psychotropics state that for treatment of depression *antidepressants should be continued for at least 6 months, and preferably up to 12 months.* For treatment of recurrent depression longer term prophylactic treatment is recommended and this *should probably be continued for at least 3 to 5 years*.[29]

Efficacy of levomilnacipran has been established for a treatment period of 8 weeks however there are no comparative, long term efficacy data. In light of EMA guidelines on depression which state that *longer double-blind trials are necessary to demonstrate that the*

[28] RANZCP (2004). Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression. Australian and New Zealand clinical practice guidelines for the treatment of depression. *Aust NZ J Psychiatry*. 38:389–407.

[29] Therapeutic Guidelines Limited (2013). Psychotropic Expert Group. *Therapeutic guidelines: psychotropic. Version 7.* Melbourne.

acute effect is maintained during an episode[30], this is a major gap in the efficacy data submitted.

In addition, the development program did not include any active controls despite three arm trials which include placebo and active controls being recommended (EMA 2013). The sponsor has been asked to comment on this.

The dosage in the clinical efficacy and safety studies commenced at 20 mg and was titrated up to 40 mg within days. The recommended dosage range is 40 to 120 mg. In the fixed dose studies, efficacy was seen with the lowest dose of 40 mg, however the minimum effective dose was not characterised. It is acknowledged that the population PK exposure response showed a trend for increased clinical response with increased exposure without an increase in adverse events or changes in vital signs. Nonetheless, the sponsor has been asked to comment on the minimum effective dose and discuss whether there should be further clinical assessment of the 20 and 40 mg doses.

The safety of levomilnacipran was assessed in approximately 2600 patients with MDD of which around 300 received treatment for up to 48 weeks. There are notable safety risks with levomilnacipran, however the data were consistent with the class effects of SNRIs and no new safety signals were evident. The numerous risks associated with the product have been adequately covered in the draft product information. One issue is the higher rate of TEAEs in the bioequivalence study comparing the Elan site to-be-marketed formation with the clinical trial formulation. This finding needs further elucidation and a question has been raised.

The positive efficacy data, together with a safety profile which is similar to currently approved drugs in the same class, suggest that levomilnacipran has a positive benefit-risk balance for short term treatment of depression. In spite of this, the evaluator finds that at present the overall benefit-risk balance of levomilnacipran is unfavourable due to the following issues:

- The lack of long term, controlled data on efficacy in relapse prevention given treatment of depression is recommended for at least 6 to 12 months duration.
- The need for further elucidation of the minimum effective dose.
- The need for further information on the possible increased rate of adverse events with the Elan site to-be-marketed formulation compared to the clinical trial formulation.
- Comments on the draft PI and Consumer Medicines Information (CMI) need to be addressed.

First Round Recommendation Regarding Authorisation

It is currently not recommended to authorise levomilnacipran SR 40-120 mg in the treatment of major depressive disorder until the questions raised in (see below) and comments on the draft PI and CMI have been satisfactorily addressed.

[30] EMA (2013). Guideline on clinical investigation of medicinal products in the treatment of depression. EMA/CHMP/185423/2010 Rev 2. May.

Clinical Questions

Pharmacokinetics

Question 1

Why was 90% CI acceptance range of 70% to 143% used in Study LVM-PK-04 rather than the more typical 80-125% range as specified in Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)?

Pharmacodynamics

Question 1

Given the sponsor's justification for the aberrant results of the primary endpoint analysis in Study LVM-PK-O7 (please see section *Secondary pharmacodynamic effects* of this report for more information), why were the Day -1 exercise data for heart-rate correction chosen for the primary endpoint analysis at the study's outset?

Efficacy

Question 1

The Phase II study F02695 LP 2 02 assessed flexible dosing 75-100 mg/day and the Phase III program assessed doses lower and higher than this from 40 to 120 mg/day. It is not clear from the dossier how the decision was made to select this dose range for the Phase III program. Please discuss.

Question 2

The dossier does not contain clinical efficacy studies which assessed the minimum effective dose of levomilnacipran. There were also no inter-dose comparisons in the fixed dose short term studies. In the flexible dose studies, the majority of the active treatment group were titrated to the highest possible dose. The design would result in subjects with no or little response to active treatment being escalated to the highest dose. Nonetheless, there was a lack of clear evidence of a dose response with levomilnacipran. Please discuss these points and comment on whether there are any plans to assess the efficacy and safety of a lower dose such as 20 mg per day.

Question 3

In Study P02695 LP 2 02, there was GCP non-compliance noted at one site in South Africa with a resultant exclusion of data from this site in the analysis. Please discuss if there were any other issues with GCP compliance in the clinical development program.

Question 4

Study LVM-MD-05 failed to show a significant effect on relapse prevention. It was noted that the relapse rates were lower than the estimated ones used in the sample size calculations. It is also noted that the US FDA clinical evaluation stated the study may have been hampered by an insufficient time of clinical stability (2 weeks) prior to the randomised withdrawal phase. Consequently, there has been a request by the FDA to repeat this study with altered design. Please discuss any insights on the reasons for the failure of this study, the planned future studies in relapse prevention and rationale for design changes.

Question 5

The development program did not include any active controls in the efficacy studies despite three arm trials which include placebo and active controls being recommended in

European guidelines on the clinical investigation of medical products in the treatment of depression (EMA 2013). Please comment on the rationale for omitting active controls.

Question 6

Efficacy analyses in subgroups did not include an assessment of response by previous antidepressant use despite the fact that at least 40% of study participants had not previously been treated with an antidepressant. Please discuss the efficacy in treatment naïve patients compared to those who had previously received antidepressants.

Question 7

Please outline the plans for paediatric development.

Safety

Question 1

In the sponsor's Summary of Clinical Safety it states that in Group 2 (Study LVM-MD-04) there were 296 patients exposed for ≥ 48 weeks while in Groups 1, 2 and 3 there were 367 patients. Given there were no other studies apart from LMV-MD-04 that had ≥ 48 weeks treatment duration, the evaluator is unsure how the number exposed for ≥ 48 weeks from Groups 1, 2 and 3 can be greater than the number exposed in Group 2. In addition, the exposure numbers provided in the sponsor's Summary of Clinical Safety are different to those in the FDA clinical evaluation report. Please comment on these points and discuss how the exposure to levomilnacipran was calculated.

Question 2

Study LVM-PK-14 assessed the bioequivalence of the proposed to-be-marketed SR formulation (Elan site formulation) with the clinical SR formulation (120 mg single dose crossover study). In this study it was noted that the to-be-marketed formulation had a higher rate of TEAEs than the clinical trial formulation (86.2% versus 67.8%) with higher rates of vomiting, dizziness, dysuria and testicular pain. While bioequivalence was demonstrated on C_{max} and AUC, there was a significantly shorter median T_{max} and also a longer $t_{½}$ with the Elan formulation. Please discuss these findings and whether there should be further clinical investigation of this particular formulation if its use is still proposed.

Question 3

During the tapering down period it was noted that there was no evidence of a discontinuation syndrome as assessed by comparing rates of newly emergent AEs between the levomilnacipran and placebo groups. Nonetheless, due to the known risks of withdrawal effects and rebound depression with this class of medications, could the sponsor please discuss further if there is any evidence of these important safety issues with levomilnacipran.

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of levomilnacipran in the proposed usage are unchanged from those identified in the First round.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of levomilnacipran in the proposed usage are unchanged from those identified the First round.

Second round assessment of benefit-risk balance

The predominant issues after the first round of evaluation were in relation to the lack of long term, controlled data on efficacy in relapse prevention; lack of assessment of the minimum effective dose; possible increased adverse event rate with the Elan site to-be-marketed formulation compared to the clinical trial formulation; and a number of comments on the draft PI and CMI.

The evaluator believes that the clinical program did not adequately define the minimum effective dose, however it is accepted that the lower response to the 40 mg dose points to little additional benefit being derived from further assessment of doses lower than this. The evaluator agrees that that the data are suggestive of a better response with the highest dose of 120 mg, although this is only a numerical trend due to the lack of formal inter-dose comparisons.

No further information was provided on the possible increased rate of adverse events with the Elan site to-be-marketed formulation compared to the clinical trial formulation. The evaluator accepts the bioequivalence of the two formulations and that the higher TEAE rate with the Elan site formulation may be a chance finding due to the study not being powered to assess such effects. Nonetheless, it is recommended that this is monitored should the product be approved.

Comments on the draft PI and CMI have largely been addressed and only a few minor points remain.

There was GCP non-compliance at a single site in one study and, while no further issues were identified in the clinical study reports, the sponsor has yet to provide confirmation that this was the only case for the clinical development program.

The clinical development program did not fully follow the European guidelines, which have been adopted by the TGA, in respect to use of active comparators in assessment of clinical efficacy. This is an inadequacy in the program.

The main deficiency in the clinical data remains the lack of long term, controlled data on efficacy in relapse prevention given treatment of depression is recommended for at least 6 to 12 months duration. A second relapse prevention study has been planned with the FDA and is scheduled for completion in 2017. The design is acceptable and the data from this study are a necessary component for efficacy determination.

In summary, as concluded after the first round evaluation, while the data indicate that levomilnacipran has a positive benefit-risk balance for short term treatment of depression, until there is provision of positive longer term efficacy data, the evaluator finds that the overall benefit-risk balance of levomilnacipran is unfavourable given the proposed usage.

Second round recommendation regarding authorisation

It is not recommended to authorise levomilnacipran SR 40-120 mg in the treatment of major depressive disorder due to the lack of positive longer term efficacy data. In addition, data still need to be provided regarding GCP compliance in the clinical development program and two comments in need to be addressed.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (AUS-RMP version 1.0 dated 26 January 2015 (data lock point 23 July 2014)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 13.

Table 13: Sponsor's summary of ongoing safety concerns

Risk	Details
Important identified risks	Effect on blood pressure Effect on heart rate Urinary hesitation and retention
Important potential risks	Suicidal ideations and behaviours Serotonin syndrome Abnormal bleeding Discontinuation of treatment Seizures Hyponatraemia Angle closure glaucoma
Important missing or limited information	Pediatric use Geriatric use Use during pregnancy, labour and in nursing mothers Long term use Use in patients with severe underlying cardiovascular disease Use in hepatic impaired patients Use in renal impaired patients

Pharmacovigilance plan

The sponsor has proposed routine pharmacovigilance to monitor all the safety concerns. No additional pharmacovigilance activity has been proposed.

Risk minimisation activities

Routine risk minimisation has been proposed to mitigate all the safety concerns. No additional risk minimisation has been considered necessary by the sponsor.

Reconciliation of issues outlined in the RMP report

Table 14 summarises the first round evaluation of the RMP, the sponsor's responses to the issues raised and the TGA's evaluation of the sponsor's responses.

Table 14: Reconciliation of issues outlined in the first round RMP Evaluation Report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the non-clinical and clinical evaluators and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*The Marketing Authorisation Holder (MAH) evaluated the consolidated requests and has not detected any additional safety consideration for inclusion into RMP.*	The nonclinical evaluation report has made several recommendations to the safety specification of the RMP. The sponsor should update the RMP documents as recommended.
2. The sponsor should advise whether its application has been rejected or withdrawn in any overseas jurisdictions and if so, reasons should be provided.	*This application has not been rejected or withdrawn in any overseas jurisdictions.*	The sponsor's response is satisfactory.
3. It is noted that the sponsor has provided relevant advice on several class effects of SNRIs in the PI. Nonetheless, the sponsor should include the following safety concerns that have been found commonly related to SNRIs on the list of safety concerns in the RMP and undertake to monitor and report these events in the Periodic Safety Update Reports (PSURs): Use in patients with a history	*a. Use in patients with a history of bipolar disorder and/or other mental disorders;* *Major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar*	The sponsor's response is acceptable. The sponsor should update the AUS-RMP accordingly.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
of bipolar disorder and/or other mental disorders; Sexual dysfunction.	*disorder. Activation of mania/hypomania in patients with bipolar disorder is a class effect observed in antidepressants.* *A review of US spontaneous reports for levomilnacipran with data obtained from Actavis, our US partner, was conducted for Fetzima, which was authorised in the management of depression by the FDA on 23 July 2013. Since the market launch of Fetzima, 2 cases in which bipolar disorder had been either reported as an indication or as medical history were retrieved. In one case, a female patient had received Fetzima for bipolar disorder and experienced irritability. In the second case, a female with a history of bipolar disorder experienced mood swings while receiving Fetzima.* *Irritability and mood swings suggest activation of mania/hypomania in these patients with underlying bipolar disorder.* *In addition, 5 cases coded 'mania' (Preferred Term (PT)) were retrieved. Although none of the patients have a history of bipolar disorder, the possibility of an undiagnosed underlying bipolar disorder that could have triggered the mania/hypomania as suggested by the class effect could not be excluded.* *Activation of mania/hypomania in patients with a history or family history of bipolar disorder, mania, or hypomaniais included in the warning section of Fetzima Product Information. Consequently, the MAH will add the risk 'Activation of mania/hypomania in patients*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	with bipolar disorder' as important potential risk in the RMP. However, the MAH considers the wording 'and/or other mental disorders' to be too vague and does not specifying the disorder. Consequently the MAH proposes not to include this wording in the RMP. *b. Sexual dysfunction.* *No serious adverse event referring to sexual dysfunction was reported during the clinical development. Since the market launch of Fetzima in the US, 23 cases of sexual dysfunction (PTs: Sexual dysfunction, Erectile dysfunction, Ejaculation disorder, Testicular pain, Organic erectile dysfunction, Psychogenic erectile dysfunction, Epididymitis, Seminal vesiculitis, Ejaculation failure, Ejaculation delayed and Premature ejaculation) were reported. All 23 cases were non-serious and, where information was available, events of sexual dysfunction had resolved upon discontinuation of Fetzima.* *As per the RMP Guidance, only the serious adverse reactions that may have an impact on the individual patient, public health, benefit-risk balance of the product or likely to be considered a contraindication or warning and precaution need to be added as identified/potential risks.* *The 23 cases reported do not fulfil the above described conditions; therefore the MAH proposes not to include sexual dysfunction as a risk in the RMP.*	
4. It is recommended that the	*Targeted follow-up*	The sponsor's

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
sponsor uses targeted follow-up questionnaires for the following important potential risks: Suicidal ideation and behaviours; Serotonin syndrome; Seizures.	*questionnaires will be implemented for the following important potential risks: suicidal ideation and behaviours; serotonin syndrome and seizures.*	response is satisfactory. The sponsor should update the AUS-RMP accordingly.
5. Long-term use is listed as missing information. As a proportion of patients with major depression require long-term treatment, the sponsor should provide justification as to why enhanced surveillance is not required to monitor the safety of long-term use of levomilnacipran.	*Like most newly approved drugs, safety data for 1 year have been provided for evaluation of Fetzima. Since the product launch in December 2013, no safety concern regarding the long-term use (greater than 1 year) was brought to the attention of MAH.* *Enhanced surveillance is usually put in place at the beginning of the marketing (from 6 to 12 months after the marketing authorisation). Long-term use is currently considered as missing information in the RMP, and the MAH proposes to perform a specific safety analysis in patients treated with levomilnacipran for more than 1 year in the future* Periodic Benefit-Risk Evaluation Reports (PBRERs).	The sponsor's response is satisfactory. The sponsor should update the AUS-RMP to include this specific safety analysis.
6. In regard to the proposed routine risk minimisation activities, the following recommendations are made with regard to the draft product information document: Co-administration with MAO inhibitors: the approved PIs for other SNRIs in Australia appear to contain the following additional information: '*Cases of serious reactions, such as potentially life threatening serotonin syndrome (characterised by neuromuscular excitation,*	*a. The Product Information of Fetzima will be updated accordingly.* *b. The Product Information of Fetzima will be updated accordingly.* *c. The Product Information of Fetzima will be updated accordingly.*	The sponsor's response is satisfactory. However, the evaluator has noted that the advice on angle closure has been deleted from the updated PI. It is recommended that the advice is reinstated as follows: '*The pupillary dilation that occurs following use of many antidepressant drugs including Fetzima may trigger acute angle*

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
altered mental status and autonomic dysfunction) have been reported in patients receiving an SNRI in combination with MAOIs[31] and RIMA[32], and in patients who have recently discontinued an SNRI and have been started on a MAOI'. It is recommended that the Delegate considers the adequacy of PI in the context of the information provided for products in the same class. Depression, suicidal ideation and behaviour: the approved PIs for other SNRIs in Australia appear to contain the following additional advice: '*Prescriptions for (product name) should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.*' It is recommended that the Delegate considers the adequacy of PI in the context of the information provided for products in the same class. Angle closure glaucoma: '*The pupillary dilation that occurs following use of many antidepressant drugs including FETZIMA® may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy*.' The wording is confusing as patent iridectomy is a procedure, not a state or a condition.		*closure glaucoma in a patient with anatomically narrow angles who has not had a patent iridectomy*.' The other PI recommendations remain for the final determination by the Delegate.

[31] Monoamine oxidase
[32] Reversible inhibitors of monoamine oxidase A

Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed most of the issues identified in the RMP evaluation report. Outstanding issues are detailed below.

Outstanding issues

Issues in relation to the RMP

Details on the following outstanding issues are provided in Table 14 above.

Recommendation 1: The nonclinical evaluation report has made several recommendations to the safety specification of the RMP. The sponsor should update the RMP documents as recommended.

Recommendation 6: The sponsor's response is satisfactory. However, the evaluator has noted that the advice on angle closure attack has been deleted from the updated PI. It is recommended that the advice is reinstated as follows:

'*The pupillary dilation that occurs following use of many antidepressant drugs including FETZIMA® may trigger acute angle closure glaucoma in a patient with anatomically narrow angles who has not had a patent iridectomy*.'

The other PI recommendations remain for the final determination by the Delegate.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

The AUS-RMP version 1.0 dated 26 January 2015 (data lock point 23 July 2014), to be revised to the satisfaction of the TGA, should be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no quality issues which would preclude registration of levomilnacipran. A quality summary will be provided to the committee (see Quality findings above).

Nonclinical

There are no nonclinical objections to registration of levomilnacipran as proposed by the sponsor**.** The nonclinical evaluator noted that the primary pharmacology studies

supported the proposed mechanism of action and provided evidence of antidepressant effects in vivo.

There was some indication that levomilnacipran may induce QT prolongation however the evaluator concluded that the weight of evidence indicates QT interval prolongation is unlikely to occur at the maximum human recommended dose of 120 mg/day.

The toxicity profile was similar to that for the racemate milnacipran. The effects observed in liver were mild and reversible, and are unlikely to occur clinically based on the anticipated exposures. CNS and renal effects, related to the pharmacology of levomilnacipran, may occur clinically. The nonclinical data indicate that levomilnacipran has a low genotoxic and carcinogenic potential and is not teratogenic.

Adverse effects on fetal and postnatal growth and development were noted and may have been secondary to maternotoxicity. Pre and postnatal death also occurred which may be a direct effect of levomilnacipran. Levomilnacipran did not impair male or female fertility in Wistar rats at estimated relative exposures of ≤ 8 times based on body surface area.

Levomilnacipran was not teratogenic in rats or NZW rabbits at doses which produced maternal toxicity characterised by reduced body weight gain and food intake (relative exposure 8 times in rats and 0.8 to 3.8 times in rabbits, based on AUC). Maternal toxicity was associated with reduced pup weight and/or delayed ossification of the sternebrae (rats) or phalanges (rabbits). Administration of levomilnacipran from GD6 and throughout lactation in rats led to increased stillbirths (100 mg/kg/day, estimated relative exposure of 8 times) and postnatal death on PND1 (≥6 0 mg/kg/day, estimated relative exposure of 5 times). Similar outcomes were observed for milnacipran at doses that also induced maternal toxicity, with similar findings also reported for other SSRIs and SNRIs. In addition, pup growth and physical development were delayed in the offspring of dams that received ≥ 20 mg/kg/day PO levomilnacipran. The no-effect level for decreased pup weight and delayed growth and development was 7 mg/kg/day, which was associated with an estimated relative exposure of ≤ 0.5 times.

The evaluator recommended Pregnancy Category C is considered to better reflect the nonclinical and clinical data rather than the proposed Category of B3. Based on that recommendation, the Pregnancy Category of other registered SNRIs was referred for clinical reconsideration.

Clinical

Pharmacology

Levomilnacipran is highly bioavailable with absolute bioavailability approximating 100%. It is formulated in a slow release preparation with $t_{½}$ approximately 13.8 h and T_{max} occurring at 5 to 6 h. Steady state was achieved after the third dose with once daily dosing. It is proposed that the product be manufactured in 2 facilities. Bioequivalence of product from these two sites was demonstrated with respect to AUC and C_{max} however there were minor differences in T_{max}.

Food did not significantly affect the C_{max} or AUC of levomilnacipran. Pharmacokinetics are linear within the dose range of 25 mg to 300 mg. Vd is approximately 420 L. Binding to plasma proteins is low (approximately 22%). Conversion to levomilnacipran's opposite enantiomer does not occur in human plasma.

Levomilnacipran is primary excreted as unchanged drug in urine (approximately 58%) with non-renal clearance of 3.7% in faeces. Multiple CYP enzymes (namely CYP2C8, 2C19, 2D6, 2J2 and 3A4) were implicated in the transformation of levomilnacipran. The principal metabolite, N-desethyl levomilnacipran is inactive. CYP3A4 is the major enzyme involved

in that transformation. Other metabolites identified were levomilnacipran glucuronide and N-desethyl levomilnacipran, which accounted for 10.7% and 14.4% of the plasma exposure of levomilnacipran in a mass balance study. Estimates of the inter-individual variability on clearance (CL/F), Vc/F and Ka were 26.0%, 25.6% and 55.4%, respectively.

In subjects with mild, moderate and severe hepatic impairment levomilnacipran C_{max} was increased by 26%, 8%, and 28% respectively, in comparison to healthy subjects whereas $AUC_{0\text{-}inf}$ was -1%, 9% and 32% higher, respectively. This suggests dose adjustment is not needed for patients with hepatic impairment. In subjects with mild (creatinine clearance (CrCL) 60-89 mL/min), moderate (CrCL 30-59 mL/min and severe renal impairment (CrCL 15- 29 mL/min), levomilnacipran C_{max} was 4% lower and 19% and 44% higher, respectively, compared to subjects with normal renal function, whereas, $AUC_{0\text{-}inf}$ was 23%, 93%, and 180% higher, respectively, for the 3 groups with renal impairment compared to normal subjects. Mean $t_{1/2}$ was longer by 17.3, 19.1, and 27.7 h, respectively. The sponsor has proposed dose adjustment for patients with moderate or severe renal impairment and that it is not given to patients with end stage renal disease.

Compared to healthy adults aged < 45 years the AUC of milnacipran increased 26% in subjects aged > 65 years and was 14% higher in women compared to men.

Concomitant administration of ketoconazole, a strong CYP 3A4 inhibitor, with levomilnacipran was associated with an increase in mean AUC for milnacipran of 57%. Concomitant administration with steady-state carbamazepine, a strong CYP inducer, was associated with a 28.9% reduction in the AUC for levomilnacipran. Alprazolam, another CYP3A4 substrate had no effect on the PK of levomilnacipran, nor did levomilnacipran affect the PK of alprazolam.

Levomilnacipran did not have a clinically significant effect on QT interval at doses up to 300 mg daily. Vital signs were monitored in patients in the Phase III efficacy and safety studies. Modelling predicted an increase in heart rate of around 7 bpm and increases in diastolic and systolic blood pressure of around 2 to 3 mmHg which were not dependent on the dose of levomilnacipran given (from 40 mg to 120 mg daily).

Population modelling from the 3 Phase III clinical trials examined the time course of onset of action, assessed using change in MADRAS-CR score (an efficacy measure) over time. It was concluded that levomilnacipran effects increased over the 8 weeks of treatment with some effect apparent (a mean 12.7% reduction) at the end of Week 1. This analysis indicated that following 8 weeks of treatment with 40 mg, 80 mg and 120 mg levomilnacipran SR the placebo corrected change in CFB-MADRS-CR score for the 3 doses were -1.10, -2.19 and -3.25, respectively (Table 15). Increasing dose was not associated with increasing heart rate or blood pressure but was associated with an increased incidence of nausea, vomiting, dizziness, headache, and in males, urinary hesitation and erectile dysfunction during the initial treatment phase. During the maintenance phase of treatment the incidences of nausea, vomiting, dizziness, hyperhidrosis, and erectile dysfunction were all higher in the active treatment population over the placebo population, but were not significantly correlated with exposure.

Table 15: Typical drug effect at median AUC_{ss} by levomilnacipran dose

	placebo	40 mg	80 mg	120 mg
AUCss (ng.hr/mL)	0	1701	3401	5102
Change from baseline MADRS-CR	-12.4	-13.5	-14.5	-15.6
Change from placebo	--	-1.10	-2.19	-3.25

Efficacy

No formal dose finding studies were conducted however a range of doses was assessed in the pivotal efficacy and safety studies. The sponsor stated that after having assessed 75 to 100 mg/day dose range in Phase II studies the dose range was chosen to be lower and

higher than this. In addition, the dose range of 40 to 120 mg/day of levomilnacipran was estimated to result in concentrations comparable to the approved milnacipran dose of 100 to 200 mg/day.

There were 5 double-blind, controlled studies and one open, uncontrolled, long term study. Four of these studies were short term, with 8 week double-blind treatment periods. There was one randomised withdrawal study. Statistically significant benefits were demonstrated in all 4 short term studies (Studies -01, -10 and -03 and -02) but not in the randomised withdrawal study (Study -05).

Studies -01, -10 and -03 were identified as pivotal and these are described in section *Pivotal efficacy studies*. These studies were conducted from 2009 to 2012. Study -02 was an earlier study, having been conducted from 2006 to 2007 and assessed a different dose (flexible 75 to 100 mg), had slightly different selection criteria (based on HAMD and SDS rather than MADRS), had no documented rater training, and had one site with GCP non-compliance. For these reasons efficacy data from that study are only considered supportive.

The pivotal studies were all conducted in the USA and Canada and had a similar design. They were multi-centre, randomised, double-blind, and placebo-controlled. Each study had a 1 week run-in period during which patients received single-blind placebo, followed by an 8 week double-blind treatment period then a 2 week down-taper period.

The studies enrolled adult subjects aged to 65 years who met the DSM-IV-TR criteria for MDD confirmed on a Mini International Neuropsychiatric Interview (MINI) with a major depressive episode of at least 8 weeks duration and a score of ≥3 0 on the MADRS-CR scale and ≥ 26 on the MADRS-Self-Rated scale. This scale is widely used to assess symptom severity in studies of MDD. The MADRS questionnaire includes questions on the following symptoms: 1. Apparent sadness; 2. Reported sadness; 3. Inner tension; 4. Reduced sleep; 5. Reduced appetite; 6. Concentration difficulties; 7. Lassitude; 8. Inability to feel; 9. Pessimistic thoughts; 10. Suicidal thoughts. The maximum score is 60 with higher scores equating to more severe symptoms. Scores of 20 to 34 are generally considered to moderate depression and scores > 34 to severe depression.

Patients could be enrolled with a first episode of depression. Exclusion criteria of note were: treatment with antidepressants within 2 weeks of visit 1; Axis 1 disorders other than MDD within 6 months before visit 1; non-response to ≥ 2 antidepressants; history of narrow angle glaucoma; and symptoms of urinary obstruction or previous urinary retention.

The primary efficacy parameter was the change from baseline to Week 8 in the MADRS-CR total score. Secondary efficacy measures included the Sheehan Disability Scale, Hamilton Rating Scale for Depression (17 item) and Clinical Global Impression-Improvement. Additional efficacy outcomes included the MADRS-CR response rate (≥ 50% reduction in total score) and remission rate (total score ≤ 10) as well as change from baseline, response rate and remission rate (score ≤ 7) on the HAMD-17. Response rates (MADRS-CR, HAMD-17 and CGI-I) and remission rates (MADRS-CR and HAMD-17) were analysed using a logistic model with the treatment group and the corresponding baseline score (the baseline CGI-S score was used for CGI-I) as explanatory variables for the LOCF approach only (from study reports).

The primary efficacy analysis used a mixed model for repeated measures (MMRM) with treatment group, pooled study centre, visit, and treatment group–by-visit interaction as fixed effects and the baseline and baseline-by-visit interaction as the covariates. Analysis was based on observed values of post-baseline scores. There was no imputation for missing values. To control the type 1 error rate the Hochberg multiple comparison procedure was used.

Results for the primary efficacy parameter in these studies are tabulated below (Table 16).

Table 16: Primary Efficacy Parameter: Change From Baseline to Endpoint in the MADRS Total Score (MMRM)—ITT Population

	Baseline Mean ± SD	*Change LS mean (SE)*	*LSMD (95% CI)*	*p-Value*[a]
LVM-MD-01				
Placebo	35.6 ± 4.5	−11.6 (0.97)	—	—
40 mg/day	36.0 ± 4.1	−14.8 (0.99)	−3.23 (−5.92, −0.54)	0.0186
80 mg/day	36.1 ± 3.9	−15.6 (1.00)	−3.99 (−6.69, −1.29)	0.0038
120 mg/day	36.0 ± 3.9	−16.5 (1.02)	−4.86 (−7.59, −2.12)	0.0005
LVM-MD-10				
Placebo	31.0 ± 3.8	−11.3 (0.77)	—	—
40 mg/day	30.8 ± 3.4	−14.6 (0.79)	−3.30 (−5.46, −1.15)	0.0027
80 mg/day	31.2 ± 3.5	−14.4 (0.79)	−3.14 (−5.29, −0.99)	0.0043
LVM-MD-03				
Placebo	35.2 ± 3.8	−12.2 (0.78)	—	—
40-120 mg/day	35.0 ± 3.6	−15.3 (0.79)	−3.10 (−5.26, −0.94)	0.0051
F02695 LP 2 02				
Placebo	30.5 ± 3.7	−14.5 (0.56)	—	—
75-100 mg/day	30.9 ± 4.1	−18.7 (0.56)	−4.2 (−5.7, −2.6)	< 0.0001

Note: Endpoint was Week 8 in the 3 pivotal Studies LVM-MD-01, LVM-MD-10, and LVM-MD-03 and Week 10 in the supportive Study F02695 LP 2 02.

a p-Value was obtained from an MMRM model with treatment group, pooled study centers, visit, and treatment-group-by-visit interaction as factors and baseline MADRS total score and baseline-by-visit interaction as covariates.

CI = confidence interval; ITT = intent to treat; LS = least squares; LSMD = least squares mean difference; MADRS = Montgomery-Åsberg Depression Rating Scale; MMRM = mixed-effects model for repeated measures; SD = standard deviation; SE = standard error.

MDRS-CR response rates in these studies are shown below (Table 17).

Table 17: MDRS-CR response rates in the 4 studies of levomilnacipran versus placebo

	Levomilnacipran (mg/day)				Placebo
	40	80	120	Flexible dose	
LVM-MD-01	36.4%	37.3%	41.5%*		29.1%
LVM-MD-010	48.6% *	46.5%*			31.9%
LVM-MD-03				41.9%*	29.4%
Fo2695 LP 2 02				38.5%	34.3%

*statistically significant

Response by previous receipt of antidepressant treatment for each of these studies is shown in Table 18. Approximately 40% of patients enrolled in these studies had not previously received antidepressant treatment. While there were differences in the extent of difference in mean change from baseline in MADRS-CR scores across the groups, in each of the studies and in all these subgroups there was a greater reduction from baseline in mean MADRS-CR scores for patients given levomilnacipran than in patients given placebo. Statistical analysis of this result was not provided.

Table 18: Summary of treatment difference[1] based on change from baseline in MADRS-CR total score at the end of treatment by previous antidepressant usage ITT population

Study	Not previously treated with antidepressants		Previously treated with antidepressants	
	Placebo	Levomilnacipran	Placebo	Levomilnacipran
LVM-MD-01	N= 78	N=271 - 1.7	N=97	N=258 - 4.4
LVM-MD-02	N=79	N=91 - 2.2	N=102	N=83 - 0.3
LVM-MD-03	N=122	N=106 - 3.2	N=92	N=109 - 1.7
LVM-MD-10	N=79	N=156 - 3.1	N=106	N=216 - 2.2
F02695 LP 2 02	N=34	N=39 - 2.3	N=160	N=175 - 5.8

[1] treatment difference is calculated as the mean change of F2695 minus the mean change of Placebo

LVM-MD-01: 3 fixed doses: 40 mg/d, 80 mg/d, 120 mg/d; actual value and change from baseline are based on assessment at Day 56
LVM-MD-02: flexible dose: 40 - 120 mg/d; actual value and change from baseline are based on assessment at Day 56
LVM-MD-03: flexible dose: 40 - 120 mg/d; actual value and change from baseline are based on assessment at Day 56
LVM-MD-10: 2 fixed doses: 40 mg/d, 80 mg/d; actual value and change from baseline are based on assessment at Day 56
F02695 LP 2 02: flexible dose: 75 - 100 mg/d; actual value and change from baseline are based on assessment at Day 70

The relapse prevention study was randomised, double-blind and placebo-controlled. This study was conducted in 2 phases: 12 weeks of open-label levomilnacipran (flexible dose) followed by a 24 week fixed-dose double-blind treatment phase in which patients were randomised to either levomilnacipran or placebo (at a ratio of 2:1). Only patients who met the criteria for MADRS response (MADRS total score of ≤ 12 and CGI-I score of ≤ 2 at Weeks 10 and 12) at the end of the open-label treatment period were randomised (at Week 12) in a 2:1 ratio to levomilnacipran or placebo. These patients continued on the dose (40, 80 or 120 mg/day) that was being taken at the end of the open-label period and this dose was fixed during the double-blind 24 week treatment period. Placebo-treated patients had their open-label levomilnacipran dose tapered down during the first week of double-blind treatment. At the end of the double-blind treatment period there was a 2 week double-blind taper down phase. The total study duration was up to 39 weeks. Patients could be included in this study with MADRS scores ≥ 22 rather than 30 as with the short term studies. Other entrance criteria were similar to those of the short term studies.

The primary efficacy endpoint was the *time to relapse* from randomisation during the double-blind treatment period. Relapse was defined as 1 or more of the following:

1. MADRS total score ≥ 22 at 2 consecutive visits; or
2. Increase of 2 or more points in CGI-I score compared with the CGI-I score at visit 9 (end of open-label treatment period) at 2 consecutive visits; or
3. Premature discontinuation due to insufficient therapeutic response; or
4. MADRS item 10 score ≥ 4.

Patients who had not relapsed at the end of the double-blind treatment period and those who prematurely discontinued from the double-blind treatment period for reasons other than insufficient therapeutic response were censored in the analysis of the primary efficacy parameter.

Of the 1066 patients screened, 734 were enrolled and 494 completed open-label treatment. Of these 348 were randomised to double blind treatment (235 to levomilnacipran and 113 to placebo) with 342 receiving study medication in the double-blind period and included in the ITT analysis. During double-blind treatment (ITT population) 13.9% of patients taking levomilnacipran and 20.5% taking placebo relapsed.

The hazard ratio for the time to relapse was 0.68 (95% CI: 0.40, 1.17) which was not statistically significant (p=0.165) indicating that the study failed to meet its primary objective.

The open, long term study (Study -04) was primarily designed to assess safety and tolerability. It was a flexible dose, 52 week extension study which enrolled 828 patients who had participated in Studies -01, -10 and -03. Patients were titrated up to a maximum dose of 120 mg daily. A total of 384 (46.5%) patients completed the open-label period. The reasons for premature discontinuation were: consent withdrawal (14.3%); adverse event (13.0%); lost to follow-up (10.5%); protocol violation (8.1%); and insufficient therapeutic response (6.8%). Protocol violations were high (40.5%) with the main reason be taking prohibited concomitant medication other than a prohibited antidepressant, anxiolytic, or antipsychotic) for more consecutive days than allowed per protocol (18.5% of protocol violations).

Safety

In the MDD studies there were 2673 patients exposed to levomilnacipran with 367 exposed for 48 weeks or longer. The total MDD patient exposure was 941.7 patient-years. The mean treatment duration in the short term studies was 50 days.

In the long term study, the mean treatment duration was 222 days. Additionally substantial post-market data from both levomilnacipran and melnacipran are available.

The adverse event profile was consistent with other SNRIs. In clinical trials the rate of SAEs was slightly lower with levomilnacipran than placebo in the short term studies (0.7% versus 1.3%) with a comparative rate of 5.0 versus 9.2 per 100 patient-years exposure. The SAE rate in the 48 week study was 7.2 per 100 patient years. SAEs deemed treatment-related included aggression/violent outburst, suicidal ideation, prostatitis, seminal vesiculitis and non-cardiac chest pain, plus one post-study case of a premature and small-for-dates baby. There was one case of a seizure with encephalopathy classed as not treatment-related.

The rate of TEAEs that led to discontinuation was higher with levomilnacipran than placebo (8.8% versus 3.2%) in short term studies and in the long term study the rate was 13%. The most frequent events were nausea, vomiting, dizziness, headache, hyperhidrosis, rash or urticaria, urinary disorders (hesitation, retention and dysuria), tachycardia, palpitations, hypertension, testicular pain and erectile dysfunction.

TEAEs which occurred at a notably higher rate than placebo were nausea, constipation, tachycardia, increased heart rate, palpitations, vomiting, dizziness, urinary hesitation, hyperhidrosis, increased BP, erectile dysfunction, ejaculation disorder and testicular pain.

One death in a patient taking levomilnacipran during an extended treatment period was reported and this was due to gastric adenocarcinoma.

The clinical program did not identify an increased risk of the SNRI class effects of serotonin syndrome, mania/hypomania, hostility or aggression, discontinuation syndrome, suicidality (also assessed using the C-SSRS) or abnormal bleeding. There was one case of rhabdomyolysis with elevated LFTs for which other causes were postulated but not confirmed.

Clinical evaluator's recommendation

The clinical evaluator did not recommend authorisation of levomilnacipran SR 40-120 mg in the treatment of major depressive disorder due to the lack of positive longer term efficacy data. In addition, data still need to be provided regarding GCP compliance in the clinical development program and two comments in need to be addressed.

Risk management plan

The final RMP evaluation will be provided to the Advisory Committee on Prescription Medicines (ACPM). Recommendations for additional amendments to the PI and safety specification have been made. Were milnacipran to be approved for registration the evaluator has recommended for following condition of registration:

> *The AUS-RMP version 1.0 dated 26 January 2015 (data lock point 23 July 2014), to be revised to the satisfaction of the TGA, should be implemented.*

Risk-benefit analysis

Delegate's considerations

The demonstration of efficacy for levomilnacipran is less than is recommended for a new antidepressant. The mean difference between any dose of levomilnacipran and placebo in the short term studies ranged from 3.1 to 4.2 on a 60 point scale. While statistically significant this difference is quite small and would not generally be considered clinically significant. A better assessment of the proportion of patients likely to derive a short term clinically significant from treatment is the clinical response rate. Unfortunately the studies were not designed to assess this very important endpoint as a primary efficacy measure. It was instead one of many additional efficacy measures. While no integrated assessment of MADRS-clinical response rate was provided in the integrated efficacy analysis, results by study suggest a number needed to treat (NNT) of between 6 (Study MD-010 40 mg/day) and 45 (Study LP202 flexible dose).

No correlation between dose of levomilnacipran and difference from placebo in response rate was apparent, though for all doses of levomilnacipran the difference from placebo was positive in each of the pivotal studies and in the earlier supportive study. Not all these results were statistically significant. The large number of additional efficacy endpoints including the MADRS-CR suggests that multiplicity effects would require considerable statistical management in order to be valid.

While the demonstration of efficacy is limited by the lack of primacy of a clinically meaningful endpoint the major concern is that comparative efficacy has been demonstrated only in short term studies. This may be acceptable in jurisdictions where milnacipran is approved for use as an antidepressant and where provisional approval is possible but this is not the case in Australia. Australian treatment guidelines[33] recommend that if there is a favourable response, antidepressants should be continued for at least 6 months, and preferably up to 12 months, after a single episode of major depression as there is a high risk of relapse during this period. Only short term efficacy has been demonstrated and the extent of clinically meaningful efficacy, even in the short term is not clear.

The sponsor has advised that the clinical development program was based on the FDA guidelines for the clinical evaluation of Antidepressant drugs 1997, and all initial planned short-term and long-term studies for adult MDD indication for US submission had been performed accordingly. The TGA has adopted the current EMA guideline.[34] That guideline states that the typical design to demonstrate efficacy and safety of an antidepressant remains a randomised, double-blind, placebo controlled, parallel group study comparing change in the primary endpoint. Inclusion of a well-accepted standard as an active control is strongly recommended. The results must be robust and clinically meaningful. This

[33] Therapeutic Guidelines – Psychotropic
[34] EMA/CHMP/185423/2010 Rev. 2, *Guideline on clinical investigation of medicinal products in the treatment of depression.*

requires besides statistically significant results the incorporation of responder/remitter analyses to adequately assess clinical relevance. It has to be shown that initial response to treatment is maintained in at least one study following a randomised withdrawal design or an extension study for 6 months.

In the randomised withdrawal study the primary efficacy measure was time to relapse. This was assessed over 24 weeks of double-blind, placebo-controlled treatment. The relapse rate was lower than anticipated (13.9% of patients taking levomilnacipran and 20.5% taking placebo) consequently the study was underpowered to determine a difference in time to relapse. At the request of the FDA another randomised withdrawal study is being conducted. The design has been altered with a longer open-label treatment phase (20 weeks) and response stabilisation phase (12 weeks). The inclusion criteria have also been changed with patients needing to have a minimum of 3 episodes of MDD, with 2 in the past 5 years, and a MADRS baseline score of ≥ 26. The sample size is 640 in the open-label treatment phase and 308 in the double-blind treatment phase (1:1 levomilnacipran versus placebo). The primary efficacy endpoint is the time to first relapse during double-blind treatment. That study is due for completion in 2017.

The program for levomilnacipran did not include active control treatments. The absence of an active control arm limits assessment of the validity of the studies and to some extent, of the relative efficacy of levomilnacipran compared with other antidepressant treatments.

Safety does not appear to be a significant issue, though it is likely that class effects of SNRI's will be identified with levomilnacipran at some time.

The Delegate was inclined to agree with the clinical evaluator in that levomilnacipran SR 40 to 120 mg should not be approved for the treatment of major depressive disorder due to the lack of positive longer term efficacy data.

Summary of Issues

Efficacy has not been demonstrated beyond an initial 8 week treatment period. Current Australian guidelines on the treatment of depression recommend at least 6 months treatment. The current guideline on the clinical investigation of medicinal products for the treatment of depression recommends a demonstration of prevention of relapse (of the index episode) in a 6 month randomised withdrawal study. While other recommendations in that guideline have not been followed these are minor compared to the above.

Proposed action

The Delegate was not in a position to say, at this time, that the application for Fetzima (levomilnacipran) should be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The nonclinical evaluator has noted fetal effects at maternotoxic doses in animals and has recommended pregnancy category C rather than B3 which was proposed by the sponsor and which is in place for milnacipran.

   Category B3 is for drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Category C is for drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Currently most SSRIs are category C. Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.

SSRIs have also been implicated in an increased risk of persistent pulmonary hypertension in the neonate.

At this stage the Delegate proposes Pregnancy Category C for levomilnacipran. The pregnancy category for other SNRIs including milnacipran will be discussed with the Pharmacovigilance and Special Access Branch of the TGA. Does the committee agree with this approach?

2. Prevention of relapse from an acute episode of depression and prevention of recurrence have not been demonstrated with levomilnacipran. The randomised withdrawal study intended to show prevention of relapse did not demonstrate a statistically significant difference from placebo for its primary efficacy endpoint. While a second randomised withdrawal study is planned the Delegate is inclined to not approve levomilnacipran for the treatment of depression until prevention of relapse from an acute episode of depression has been adequately demonstrated. The Delegate is prepared to accept open, uncontrolled data for longer term efficacy. Does the committee agree with this approach?
3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Advice sought: Pregnancy Category

In the nonclinical evaluation report of Levomilnacipran, dated 28 July 2015, changing Pregnancy Category B3 (not considered the most appropriate) to Pregnancy Category C was recommended.

The sponsor agreed to this change and the proposed PI submitted later was modified accordingly to Pregnancy Category C.

The sponsor will follow the TGA/ACPM final advice for Pregnancy Category.

Summary of the issue

Efficacy has not been demonstrated beyond 8 weeks treatment period. According to the TGA, the current Australian guidelines on the treatment of depression recommend a demonstration of prevention of relapse (of the index episode) in a 6 month randomised withdrawal study.

Prevention of relapse from an acute episode of depression and prevention of recurrence have not yet been demonstrated with levomilnacipran. The randomised withdrawal study intended to show prevention of relapse did not demonstrate a statistically significant difference from placebo for its primary efficacy endpoint. However, a second randomised

withdrawal study is currently ongoing and is projected to be completed with results available in early 2017.

Response

Fetzima is already approved in the US by the FDA and in Canada by Health Canada based on the significant results of Fetzima on the reduction of the depressive symptoms compared to placebo in 3 double-blind, controlled clinical studies having exposed patients for 8 weeks. The FDA concluded that the sponsor had provided sufficient evidence of efficacy and levomilnacipran had a safety profile consistent with its pharmacology. In addition, the FDA requested a post-marketing commitment study and the sponsor agreed to conduct a maintenance of efficacy trial with an adequate period of stabilization (PMC).

Health Canada, who reviewed the file after the FDA, concluded that the efficacy of Fetzima was established primarily in three 8 week placebo-controlled studies. Long-term maintenance of effect has not been established.

The discussions with the FDA highlighted some potential reasons related to the relapse study design that may have contributed to the non-statistical significance of the study. The new study (LVM-MD-15 - NCT02288325) has been designed in compliance with the most recent recommendations. It is currently ongoing, and the study is projected to be completed with results available in early 2017.

The FDA reviewer commented that '*It is very unusual for an antidepressant with multiple positive short-term studies to not demonstrate a difference from placebo in a maintenance study*.' Considering that the different antidepressants with similar mechanism of action have demonstrated a positive effect over placebo in both short-term and long-term maintenance studies, it is unlikely that levomilnacipran, which has demonstrated a positive effect in 3 short-term studies, would not demonstrate a significant difference over placebo in such study assessing the prevention of relapses.

The FDA and the Health Canada have acknowledged the lack of data on relapse prevention at the time of market approval and have incorporated this into the approved labelling. It is stated in the PI for Fetzima that the efficacy of Fetzima for the treatment of MDD beyond 8 weeks was not established.

Additional data supporting the long-term efficacy of levomilnacipran

During the clinical development program, all subjects having completed both the double-blind treatment and the double-blind down-taper periods of one of the lead-in, short-term studies (LVM-MD-01, LVM-MD-02, or LVM-MD-03) were eligible to enter a multicenter, open- label, flexible dose (40 to 120mg/day) extension study (LVM-MD-04). The study report for LVM-MD-04 was submitted in the original file. A high-level summary of this study is provided below:

- The primary objective of this study was the evaluation of long-term safety and tolerability of levomilnacipran. The following efficacy assessments were collected but not grouped into primary, secondary, or additional categories: Montgomery-Åsberg Depression Rating Scale, Clinical Global Impressions–Severity, and Clinical Global Impressions–Improvement.
- All patients independent of the allocated treatment in the lead-in study were started with levomilnacipran from the titration regimen (20 mg on the first 2 days) up to 40 mg/day. During the study, patients were evaluated for a potential dose increase based on the Investigator's judgment of the patient's response and the absence of dose-limiting adverse events (AE). At the end of the study, which had maximum 48 weeks duration, the patients entered a down-taper period during which their drug was gradually tapered over a period of up to 4 weeks.

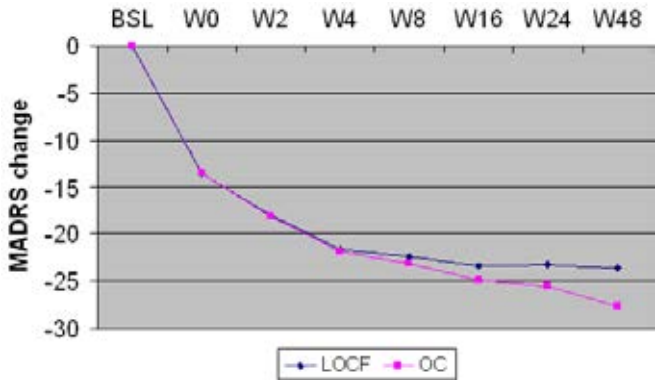
- A total of 828 patients completed one of the lead-in studies, and signed an Informed Consent Form (ICF) for this extension study (Enrolled Population); 825 patients received at least 1 dose of open-label investigational product (Safety Population); and 813 patients had at least 1 post-Visit 1 assessment of the MADRS total score (ITT Population). 384 patients (46.5%) completed the study. The most frequent reasons for discontinuation were withdrawal of consent (14.3%), AE (13.0%) and lost to follow-up (10.5%). Premature discontinuation of the study due to insufficient therapeutic response was reported in 6.8% patients. A total of 490 patients entered the open-label down-taper period.
- Most patients (77.5%) had a history of recurrent major depression and the mean duration of MDD was approximately 12 years. Approximately 26% of patients with previous antidepressant use were considered non-responders (either poor or no change to at least 1 antidepressant) and approximately 11% of patients with previous antidepressant use were intolerant to therapy (discontinued at least 1 antidepressant due to an adverse event).
- The mean final daily dose of levomilnacipran was approximately 88 mg/day. Almost half of the patients (46.8%) received 120 mg/day as the final daily dose. The mean treatment duration was approximately 222 days with a median of 280 days. A total of 385 patients had treatment exposure ≥ 316 days.
- *Results*: the efficacy analysis assessed the evolution of the MADRS total score throughout the whole study treatment exposure. Study results are provided in the tables below, and a graph summarises the evolution of MADRS total scores over the whole duration of the long-term study.

Table 19: Change from baseline in the MADRS total score (LOCF and OC) ITT population

MADRS Time Point Statistic	*F2695 SR 40-120 mg/day (N = 813)*			
Lead-in study baseline				
Mean ± SD	35.9 ± 4.1			
	LOCF		*OC*	
	n	*Change*	*n*	*Change*
Week 0				
Mean ± SD	813	−13.5 ± 10.7	813	−13.5 ± 10.7
Week 2				
Mean ± SD	813	−17.9 ± 9.9	753	−18.1 ± 9.8
Week 4				
Mean ± SD	813	−21.6 ± 9.3	765	−21.9 ± 9.1
Week 8				
Mean ± SD	813	−22.4 ± 9.6	715	−23.1 ± 9.2
Week 16				
Mean ± SD	813	−23.3 ± 9.8	608	−24.9 ± 8.8
Week 24				
Mean ± SD	813	−23.2 ± 10.5	516	−25.5 ± 9.3
Week 48				
Mean ± SD	813	−23.6 ± 10.8	381	−27.6 ± 8.5

Note: Baseline is the corresponding baseline in the lead-in studies LVM-MD-01, LVM-MD-02, or LVM-MD-03.
F2695 = levomilnacipran; ITT = intent to treat; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; N = number of patients in the ITT Population; n = number of patients with available analysis value at both baseline and a specific time point in the ITT Population; OC = observed cases; SD = standard deviation; SR = sustained release.

Figure 4: MADRS change over time



Note: Baseline (BSL) to W0 corresponds to the overall change in MADRS total score during the lead-in studies (LVM-MD- 01, LVM-MD-02, or LVM-MD-03); W0 through W48 corresponds to the change during the open-label study (LVM-MD- 04).

The Clinical Global Impression assessing the severity of the disease also changed over time, in the same direction as the MADRS total scores (Table 20).

Table 20: Change from baseline to Week 48 in the CGI-S scores (LOCF and OC) ITT Population

CGI-S Time Point Statistic	*F2695 SR 40-120 mg/day (N = 813)*			
Lead-in study baseline				
Mean ± SD	4.8 ± 0.6			
	LOCF		*OC*	
	n	*Change*	*n*	*Change*
Week 0 (Visit 1 of Study LVM-MD-04)				
Mean ± SD	813	−1.3 ± 1.3	813	−1.3 ± 1.3
Week 48				
Mean ± SD	813	−2.5 ± 1.4	381	−3.0 ± 1.1

CGI-S = Clinical Global Impressions–Severity; F2695 = levomilnacipran; ITT = intent to treat; LOCF = last observation carried forward; N = number of patients in the ITT Population; n = number of patients with available analysis value at both baseline and a specific time point in the ITT Population; OC = observed cases; SD = standard deviation; SR = sustained release.

More than half of the patients met the criteria for MADRS remitters, MADRS responders, and CGI-I responders at Week 48 using the LOCF and OC approaches.

Table 21: Response and remission rates as measured by the MADRS and CGI-I scales at Week 48 (LOCF and OC) ITT population

	F2695 SR 40-120 mg/day (N = 813) n/N1 (%)	
	LOCF	*OC*
MADRS remission rate (total score ≤ 10)	433/813 (53.3)	262/381 (68.8)
MADRS response rate (≥ 50% reduction from baseline of the corresponding lead-in study)	597/813 (73.4)	335/381 (87.9)
CGI-I response rate (CGI-I score ≤ 2)	608/813 (74.8)	344/381 (90.3)

CGI-I = Clinical Global Impressions–Improvement; F2695 = levomilnacipran; ITT = intent to treat; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; N = number of patients in the ITT Population; n = number of patients in a specific category; N1 = number of patients in the ITT Population with available values at a specific time point; OC = observed cases; SR = sustained release.

In all 813 patients who received long-term extension of levomilnacipran up to Week 48, the MADRS total score decreased consistently over the course of the study and the Clinical Global Impressions–Severity scores also decreased, indicating the majority of patients responded to treatment.

Furthermore, the change from baseline in total MADRS score from the beginning of the short term studies (LVM-MD-01/02/03) and throughout the long-term extension Study LVM-MD- 04, as outlined above provide additional support for the efficacy of Fetzima after 8 weeks of treatment.

Additionally, a second randomised withdrawal study (LVM-MD-15) is currently ongoing and will conclude in 2017 which will adhere to the requirements as outlined in the EMA Guidance.

The sponsor commits to make the data from this study available to TGA upon study completion.

With the data from this study pending, the applicant believes that Fetzima can be approved with appropriate statements in the labelling indicating that efficacy of Fetzima for the treatment of MDD beyond 8 weeks was not established, similar to the statement in the labelling approved by FDA and Health Canada. Once Study LVM-MD-15 is completed, this data will be submitted to revise the labelling to include long term data.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Fetzima extended release capsules containing 20 mg, 40 mg, 80 mg and 120 mg of levomilnacipran.

The ACPM taking into account the submitted evidence of pharmaceutical efficacy, safety and quality considered this product to have an overall negative benefit–risk profile.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *The nonclinical evaluator has noted foetal effects at materno-toxic doses in animals and has recommended pregnancy category C rather than B3 which was proposed by the sponsor and which is in place for milnacipran.*

   Category B3 is for drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

   Category C is for drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

   Currently most SSRIs are category C. Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. SSRIs have also been implicated in an increased risk of persistent pulmonary hypertension in the neonate.

At this stage the delegate proposes Pregnancy Category C for levomilnacipran. The pregnancy category for other SNRIs including milnacipran will be discussed with the Pharmacovigilance and Special Access Branch of the TGA. Does the committee agree with this approach?

The ACPM was of the view that while Fetzima does not wholly fulfil definition of Category C as there are no human pregnancy data; however, there is an acknowledged class effect of SNRIs (serotonin syndrome, mania/hypomania, hostility or aggression, discontinuation syndrome, suicidality or abnormal bleeding) which would require the use of Category C.

2. *Prevention of relapse from an acute episode of depression and prevention of recurrence have not been demonstrated with levomilnacipran. The randomised withdrawal study intended to show prevention of relapse did not demonstrate a statistically significant difference from placebo for its primary efficacy endpoint. While a second randomised withdrawal study is planned the delegate is inclined to not approve levomilnacipran for the treatment of depression until prevention of relapse from an acute episode of depression has been adequately demonstrated. The delegate is prepared to accept open, uncontrolled data for longer term efficacy. Does the committee agree with this approach?*

The ACPM noted that while statistically significant benefits were demonstrated in all 4 short term studies (Studies -01, -10 and -03 and -02), the randomised withdrawal study (Study -05) did not show such a benefit. Thus efficacy has not been demonstrated beyond the initial 8 week treatment period. Only short term statistically significant efficacy has been demonstrated and the extent of clinically meaningful efficacy, even in the short term is not clear.

The ACPM noted;

- The current Australian therapeutic guidelines on the treatment of depression recommend at least 6 months treatment, after a favourable initial response, and common Australian clinical practice extends this to a year and sometimes longer.
- The current TGA adopted EMA Guideline on the clinical investigation of medicines for the treatment of depression recommends a demonstration of prevention of relapse (of the index episode) in a 6 month randomised withdrawal study.

In the randomised withdrawal study the primary efficacy measure was time to relapse. The relapse rate was lower than anticipated (13.9% of patients taking levomilnacipran and 20.5% taking placebo). Consequently the study was underpowered to determine a difference in time to relapse.

The ACPM noted that, at the request of the FDA, another randomised withdrawal study is being conducted. The sponsor stated this will be available in early 2017.

The program for levomilnacipran did not include active control treatments. The absence of an active control arm limits assessment of the validity of the studies and to some extent, of the relative efficacy of levomilnacipran compared with other antidepressant treatments.

Safety does not appear to be a significant issue, though it is likely that class effects of SNRI's will be identified with levomilnacipran at some time.

The ACPM was of the view that a review of the pregnancy classifications currently applied to the individual antidepressant medicines might now be timely. Most classes of antidepressant medicines have now been used for some time and research and analysis of their effects have clarified those effects.

Outcome

Based on a review of quality, safety and efficacy, TGA decision to reject the application to register Fetzima (levomilnacipran hydrochloride) 20 mg, 40 mg, 80 mg and 120 mg extended release capsules for:

> *Treatment of episodes of major depressive disorder. The efficacy of Fetzima was established in randomized, double-blind, Placebo-controlled trials of up to 8 weeks (See CLINICAL TRIALS). The efficacy of Fetzima for the treatment of MDD beyond 8 weeks was not established.*

Reasons for Decision

Firstly while the pivotal short term studies demonstrated a statistically significant improvement in measures of depression when compared with placebo treatment, none of these studies had an active control arm. The TGA adopted EMA guideline[35] states that the dossier should include parallel group studies against placebo and active comparator (generally accepted standard treatment). Three- arm or multi-arm studies are strongly recommended for pivotal studies in Phase III of development, as the trials will be internally validated and the problem of assay sensitivity can be addressed. Thus, the Delegate is not satisfied that the pivotal studies have internal validity and therefore the results may not be clinically meaningful.

Secondly due to the character of major depression, longer double blind trials are necessary to demonstrate that the acute effect of a medicine is maintained during an episode. This pertains to prevention of relapse within an episode of acute depression. The randomised withdrawal study intended to show prevention of relapse (LVM-M D-05) did not demonstrate a statistically significant difference from placebo for its primary efficacy endpoint of time to relapse. Thus current evidence suggests that levomilnacipran when taken as intended is no better than placebo in the prevention of relapse. The *Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders* (2015)[36] includes as part of Recommendation box 7 that maintenance antidepressant treatment should be continued for at least six months and up to one year.

It notes that this is particularly important if a recurrent pattern of illness has been established.

The Delegate notes that while the study intended to demonstrate prevention of relapse was a failed study, a new prevention of relapse study is underway and it is anticipated to be completed in 2017. This is an indication that the sponsor is aware that such data are required to support effective use of levomilnacipran in the treatment of MDD. The sponsor has indicated that there was evidence supporting long-term efficacy in the open-label, flexible dose extension study, LVM-M D-04 however this was an open study with no placebo control and included only those patients who volunteered to continue treatment. These design features limit the ability of the study to distinguish between continued efficacy of the medicine and a placebo response.

While the indications sections of the PI documents for Fetzima in both the USA and Canada advise that efficacy was established in 8 week studies these indications do not contain an explicit statement to advise on the continuing treatment of patients who initially respond to Fetzima.

[35] EMA/CHMP /185423/2010 Rev. 2 Guideline on clinical investigation of medicinal products in the treatment of depression

[36] https://www.ranzcp.org/Files/Resources/Publications/CPG/Clinician/Mood-Disorders-CPG.aspx

Thirdly Fetzima was associated with the following serious adverse events which were considered treatment-related in clinical trials: aggression/violent outburst, suicidal ideation, prostatitis, seminal vesiculitis and non-cardiac chest pain. Less serious treatment-related adverse effects associated with Fetzima were: nausea, vomiting dizziness, headache, hyperhidrosis, rash or urticaria, urinary disorders (hesitation, retention, and dysuria), tachycardia, palpitations, hypertension, testicular pain and erectile dysfunction. Given the failure to demonstrate efficacy of Fetzima in treatment of MDD beyond 8 weeks and that treatment for up to 12 months is regularly required in the management of MDD it is an unacceptable risk to allow patients to commence treatment for MDD with Fetzima given the risks from that treatment that have been identified.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

Transcript of the Reasons for the Delegate of the Minister's decision

In your [the sponsor's] appeal documentation, you [the sponsor] have cited a number of grounds in support of your appeal. Delegate of the Minister addresses each of those issues in turn. Although raised later in your [the sponsor's] Grounds for Appeal (page 19) the Delegate of the Minister deals first with the matter of Indications.

(i) Revised Indications You [the sponsor] submits that:

The application initially identified the indication as: *Treatment of major depressive disorder (MDD).*

However, as the [initial decision] Delegate of the Secretary acknowledges in the decision letter, Pierre-Fabre amended the indication in its Pre-ACPM Response dated 19 January 2016 to:

> *Treatment of episodes of major depressive disorder (MDD). The efficacy of FETZIMA was established in randomized, double-blind, placebo-controlled trials of up to 8 weeks (see CLINICAL TRIALS). The efficacy of Fetzima® for the treatment of MDD beyond 8 weeks was not established.*

The Delegate of the Minister accepts that prior to the Delegate's decision you [the sponsor] amended the proposed Indications and that the Delegate was aware of that amendment when making her decision. The Delegate of the Minister returns to the matter of Indications below.

Use of Guidelines

(ii) Concerning which guidelines may be used by the TGA in the evaluation of an application for registration of a medicine.

You [the sponsor] have submitted that:

> *First, Pierre Fabre contends that in this case it has been very difficult to anticipate which guidelines the decision-making process would rely upon other than the relevant TGA adopted EMA guidelines. In relation to these particular guidelines the 2002 version should have been applied given the dates the studies were conducted. There are some important differences between the 2002 and 2013 versions that have a direct bearing on this appeal. These differences are discussed below.*

> *Second, Pierre Fabre contends that only the formally adopted EMA guideline should be relied upon. To this end the purpose of the Freedom of lnformation Act 1982 needs to be raised. The purpose is primarily twofold. To provide for a scheme to allow any person reasonable access to the documents of a government agency (subject to a public interest test in relation to exemption), and to provide a scheme whereby any person is put on notice, by allowing them access to the operational guidelines of a government agency, as to what is required of them in applying for government approval and then protecting the actions of that person if a policy or guideline is invoked by that agency in circumstances where it was not first made publicly available within the terms of the FOI Act (ie. updated and published annually by the agency).*
>
> *The RANZCP and Therapeutic Guidelines Limited guidelines fall into this latter category as they have not been formally adopted and published by the TGA as guidelines the regulator will rely on.*
>
> *This protection is encapsulated in Section 10 which provides that a person shall not be prejudiced by the unpublished operational information (e.g. rule, guideline or practice) of an agency if the person engages in conduct relevant to that performance or function and at the time of engaging in that performance or function the person was unaware of the unpublished information but lawfully could have avoided that prejudice had he or she been aware of the unpublished information.*
>
> *In this case, Pierre Fabre was not aware that the TGA would place reliance on any guideline other than those formally adopted by the TGA and published on its website. In addition, if there was a conflict between an adopted guideline and any other guideline, the adopted guideline would take precedence.*

The Delegate of the Minister deals with your [the sponsor's] second contention first. The Delegate of the Minister does not accept that the TGA should rely only upon formally adopted guidelines. Policy information, such as guidelines, manuals and handbooks play an important role in administrative decision making. The TGA adopts various guidelines from time to time including from the EMA. However, a Delegate is not required to only utilise the guidance set out in relevant guidelines from the EMA in determining whether the quality, efficacy and safety of a particular medicine has been demonstrated satisfactorily. A Delegate is also entitled to take into account guidelines and information published by other scientific and medical authorities if they are relevant to the issues being determined. In the case of an application seeking to register a medicine for use in the treatment of major depressive disorder, the guidelines published by the RANZCP and the Australian Therapeutic Guidelines-Psychotropic are relevant.

The Delegate of the Minister has noted your reference to section 10 of the Freedom of Information Act.

Section 10(1) refers to the circumstance of a person engaging in conduct relevant to the performance of the function or the exercise of the power while not being aware of relevant unpublished operational information of the agency.

Section 10 (2) states:

> '*The person must not be subjected to any prejudice only because of the application to that conduct of any rule, guideline or practice in the unpublished information, if the person could lawfully have avoided that prejudice had he or she been aware of the unpublished information*.'

The Delegate of the Minister also notes that section SA (1) of the FOI Act defines an agency's operational information as information held by the agency to assist the agency to perform or exercise the agency's functions or powers in making decisions or

recommendations affecting members of the public (or any particular person or entity, or class of persons or entities).

Importantly Section SA (2) exempts from *operational information* that is available to the public otherwise than by being published by (or on behalf of) the agency.

The Delegate of the Minister has verified that the Clinical Practice Guideline of the Royal Australian and New Zealand College of Psychiatrists titled Mood Disorders (December 2015) is a document available to the public.[37]

The initial Delegate referred to Australian treatment guideline[38] in the request to the Advisory Committee on Prescription Medicines for advice, but not in the decision letter.

Concerning guidelines published by Therapeutic Guidelines Limited, the history of this organisation may be found at: https://www.tg.org.au/the-organisation/history-of-therapeutic- guidelines/-accessed 30 June 2016).

It may be noted that Therapeutic Guidelines have evolved out of activities dating back to January 1978 when a group of enthusiastic individuals came together to develop *Antibiotic Guidelines* in response to the worrying and emerging problem of antibiotic resistance. A guideline titled Psychotropic was first published in 1989. Therapeutic Guidelines are widely respected and are an accepted part of the Australian medical culture. They are used in all Australian medical and pharmacy schools, and are used extensively in public teaching hospitals and in community medical and pharmacy practices. The electronic integrated compilation of guidelines (eTG complete) was first made available in 2002 and hospitals, libraries, training providers and healthcare providers today comprise a large proportion of users.

The Delegate of the Minister has noted that the Royal Australian College of General Practitioners states that '*Therapeutic Guidelines provide clear, concise, independent and evidence-based recommendations for patient management that have been developed by Australia's leading medical experts*.' [39]

The Delegate of the Minister has verified that the Therapeutic Guidelines-Psychotropic[40] is a document available to the public otherwise than by being published by (or on behalf of) the agency.

Given the history and very wide distribution of Therapeutic Guidelines in Australia the Delegate of the Minister considers that your company should have followed up with the publisher to obtain this guideline, notwithstanding that your company '*held serious doubts about its status given that there had been no evidence that it had been formally adopted by the TGA*.', particularly as '*Our Head Office has requested the reference to those guidelines*' (as reflected in the e-mail stream provided as Attachment 9 to your appeal) and the means to access them was provided to you [the sponsor] in response by the TGA.

The Delegate of the Minister now deals with your [the sponsor's] first contention '*that in this case it has been very difficult to anticipate which guidelines the decision-making process would rely upon other than the relevant TGA adopted EMA guidelines. In relation to these particular guidelines the 2002 version should have been applied given the dates the studies were conducted*.'

[37] https://www.ranzcp.org/Files/Resources/Pu blications/CPG/Clinician/Mood-Disorders- CPG.aspx - accessed 30 June 2016
[38] Therapeutic Guidelines - Psychotropic
[39] see http://www.racgp.org.au/yourracgp/membership/offers/tg/ accessed 30 June 2016
[40] Depression in adults. Psychotropic Guideline. eTG complete. Published June 2013, amended February 2015. Therapeutic Guidelines Limited. https://tgldcdp.tg.org.au/viewTopic?topicfile=depression (accessed 5 July 2016)

Your [the sponsor's] Grounds for Appeal acknowledge that the adopted 2013 Guideline includes some important guidances not contained in the 2002 Guideline.

Your [the sponsor's] Grounds for Appeal acknowledge that the adopted 2013 Guideline includes '*That the dossier should include parallel group studies against placebo and active comparator (generally accepted standard treatment). Three-arm or multi-arm studies are strongly recommended for pivotal studies in Phase III of development, as the trials will be internally validated and the problem of assay sensitivity can be addressed*. ' You [the sponsor] submit that the previously adopted 2002 Guideline did not specify any need for an active comparator.

The Delegate of the Minister draws attention to the publication in September 2009 of the EMA's '*Concept paper on the need for revision of note for guidance on clinical investigation of medicinal products in the treatment of depression with regard to treatment resistant depression*.' That paper (section 3, page 314) foreshadows that the proposed update of the guidance document should discuss '*Inclusion of an active comparator in clinical trials, is there a gold standard acceptable as active control'* and '*study duration (short-term efficacy, maintenance of effect)*'

The Delegate of the Minister further draws attention to release for consultation on 22 September 2011 of 'European Medicines Agency Guideline on clinical investigation of medicinal products in the treatment of depression. Draft. EMA/CHMP/185423/2010 Rev. 2 previously (CPMP/EWP/518/97, Rev. 1) 22 September 2011. End of consultation (deadline for comments) 31 March 2012.'

That document clearly foreshadows important changes needed for the assessment of treatments of depression. They include:

- Inclusion of a well-accepted standard as an active control is strongly recommended (Executive Summary page 6/22); Three-arm trials including both a placebo and an active control are recommended (4.1.1. page 9); '*Three-arm or multi-arm studies are strongly recommended for pivotal studies in Phase III of development, as the trials will be internally validated and the problem of assay sensitivity can be addressed. The aim of the studies should be superiority over placebo or active comparator or demonstration of at least a similar balance between benefit and risk of the test product in comparison with an acknowledged standard antidepressant agent (when both are superior over placebo)*' (4.1.2. page 11/22).
- *'It should be shown that initial response to treatment is maintained in at least one study following a randomised withdrawal design or an extension study of six months'* (Executive summary; page 6/22); '*For authorisation it should be shown that the short-term effect can be maintained during the episode. For this a randomised withdrawal study, allowing studying relapse is probably the best design. In this design, responders to treatment of sufficient duration with the test product, are (re-)randomised to test product or placebo*' (4.1.2 page 10/22).

The Delegate of the Minister draws the conclusion that in the period September 2009 to September 2011 the publications of the European Committee for Medicinal Products for Human Use had clearly put developers of antidepressant medicines on notice of the need to meet emerging guidance not included in the adopted 2002 Guideline.

The Delegate of the Minister is of the view that although the clinical studies submitted in the dossier had finished between 2010 to December 2012 and that to undertake clinical studies in depression is an expensive exercise it should have been clear to your company in 2012 that its set of studies very likely no longer met regulatory expectations. Further, the Delegate of the Minister notes that there is no provision in the legislation for the Delegate to apply retrospective or out-dated criteria in reaching a decision.

(iii) Duration of efficacy studies

You [the sponsor] have noted that the Delegate in the reasons for rejection stated:

'*Due to the character of major depression, longer double blind trials are necessary to demonstrate that the acute effect of a medicine is maintained during an episode. This pertains to prevention of relapse within an episode of acute depression'*.

You [the sponsor] have submitted that:

'*This characterisation of major depression by the Delegate is inconsistent with the TGA-adopted EMA 2013 Guideline. This Guideline makes a distinction between treatment in the acute phase, the continuation phase and the maintenance phase. A distinction is also made in the design of the trials to demonstrate efficacy of the anti-depressant drug product in each of these phases*.'

For the acute phase, the EMA 2013 guideline advocates short-term randomised double-blind parallel group trials (section 4.2.1): *'The duration of these trials is around 6 weeks (at least 4 weeks have been needed to clearly separate active treatment from placebo, in some programs 8 weeks have been studied' (p.9).* In section 4.1.1, the guideline provides the ethical rationale for limiting the duration of the study - the use of placebo when performing studies during acute episodes being a *'controversial issue' (p.7).* The Guideline says*, 'Precautions to minimise impact of the study should be taken however, e.g. by limiting the duration of the study - generally a duration of about 6 weeks should be sufficient and a longer duration should be justified'.*

For the continuation phase, treatment is meant to prevent deterioration during the index episode. The EMA 2013 Guideline says*, 'For authorisation, it should be shown that the short-term effect can be maintained during the index episode. For this a randomised withdrawal study, allowing to study relapse prevention is probably the best design'.* The period after (re) randomisation of the responders to treatment, the guideline says is usually of 6 months duration as this corresponds with the average duration of an episode of depression (p.8).

The purpose of treatment in the maintenance phase is to prevent new episodes (recurrence prevention) and *'is not a mandatory part of a registration package for treatment of MDD episodes* (p.8 EMA 2013 guideline)*.* But in the reasons for rejection, the Delegate relies on the RANZCP guidelines to claim that *'maintenance antidepressant treatment should be continued for at least 6 months and up to one year. It notes that this is particularly important if a recurrent pattern of illness has been established ...'.* Here there is a clear inconsistency between the TGA-adopted EMA 2013 guidelines and the RANZCP guidelines on which the [initial] Delegate relies in the decision, which should have been accommodated by the [initial] Delegate in the reasoning.

The duration of the studies submitted by Pierre-Fabre in support of the efficacy of levomilnacipran in the acute phase (8 week studies) and the continuation phase (the 6 month relapse withdrawal study, LVM-MD-05) is completely consistent with the duration requirements for treatment in these phases prescribed by the EMA 2013 Guideline.

The Delegate in using the Australian and NZ clinical practice guideline (RANZCP 2004) (which says that maintenance anti-depressant treatment should be continued for at least 6 months and up to one year), to support the case that longer double-blind trials are necessary to demonstrate that the acute effect of a medicine is maintained during an episode, confuses clinical practice with clinical investigation. The EMA 2013 Guideline in fact states*, 'Generally a solely placebo-controlled extension study is not recommended, as there is a risk that the results will be ambiguous with regard to the question of maintenance of effect'* (p.8).

Pierre-Fabre contends that the [initial] Delegate's use of therapeutic guidelines for the treatment of depression in the evaluation of the efficacy of a new anti-depressant is

inappropriate. The treatment requirements in clinical practice cannot be directly extrapolated to a placebo controlled investigational study. That the evaluator requires that the placebo-controlled double- blind trials are longer than 8 weeks *'at least 6 months and up to one year',* Pierre Fabre contends is inconsistent with the TGA-adopted EMA 2013 Guideline and furthermore, unethical.'

The Delegate of the Minister is of the view that the use of the words '*maintained during an episode'* by the Delegate has led to a misunderstanding. The Delegate of the Minister thinks it is clear that when taken as a whole, the paragraph refers to a '*randomised withdrawal study*' also known as a '*relapse prevention study*'. Your [the sponsor's] submitted Study LVM-MD-05 was such a study. It is mutually acknowledged that LVM-MD-05 failed to meet its objective.

(iv) Design of efficacy studies 'lack of active controls in efficacy studies'

Your company has submitted that:

'*Whilst Pierre Fabre acknowledges that the application was lodged after the introduction of the 2013 version of the EMA guidelines on 1 June 2014, it was clear, (as described above) from the information in the dossier that the pivotal studies were conducted and completed well before this date. Consequently, at the time the studies were designed and conducted, the relevant TGA adopted EMA guideline was CPMP/EWP/518/97, Rev. I , 2002, 'Note for guidance on clinical investigation of medicinal products in the treatment of depression'* (attachment 9a). In relation to the first limb of the Delegate's reasons for rejection, the 2013 version of the EMA guidelines relied on by the Delegate states '*that the dossier should include parallel group studies against placebo and active comparator (generally accepted standard treatment). Three- arm or multi-arm studies are strongly recommended for pivotal studies in Phase III of development, as the trials will be internally validated and the problem of assay sensitivity can be addressed. Thus, I am not satisfied that the pivotal studies have internal validity and therefore the results may not be clinically meaningful*. '

However, the 2002 version, at, 3.0 'Assessment of Efficacy Criteria, 3.1 'Short-term trials', did not specify any need for an active comparator.

In terms of study design, the 2002 version of the guideline provides at 5.2 'Study design', that '*comparison with a standard product in an adequate dose <u>is generally needed</u>*. 'Then at 6.0 'Strategy', 6.4 'Short-term trials': '*the dossier should also include parallel group studies against placebo and/or active comparator*'.

Pierre Fabre therefore contends that the TGA adopted EMA guidelines that were applicable at the time the pivotal studies were conducted and completed did not mandate active controls in the efficacy studies.

It should also be noted that the current EMA 2013 guideline in 4.1.1 'Use of placebo' states: '*Clinical studies should provide unambiguous evidence of the antidepressant activity and of the effective dose or dose range. In depression, comparisons between a test medicinal product and reference substances are difficult to interpret since there is a high and variable placebo response in depression. Actually in about one-third to two-thirds of the trials, in which an active control is used as a third arm, the effect of the active control could not be distinguished from that of placebo'* (p.7).

The Delegate of the Minister refers to comments above concerning the various guidelines. In the Delegate of the Minister's view, an application to register a new antidepressant would be greatly enhanced by the inclusion of reports of three-arm active comparator pivotal studies. In the case of your [sponsor's] application, the [initial] Delegate has accepted that the pivotal studies submitted by you [the sponsor] have satisfied about short term (to 8 weeks) efficacy: What is lacking is evidence of efficacy beyond that 8 weeks and more generally robust information about what happened to patients at the end of the

down-taper. The Study LVM- MD-04 had major deficiencies and did not provide this evidence. As noted above, the Study LVM-MD-05 was a failed study.

(v) Deficiencies in the scientific evaluation

Your [the sponsor's] submission in this regard relates to approvals in two other jurisdictions:

'*As indicated above at International Regulatory Status, levomilnacipran has been approved for the treatment of major depressive disorder (MDD) in the USA in July 2013. It was approved for the short-term symptomatic relief of major depressive disorder (MDD) in Canada in May 2015.*

In the USA the approval was conditional on the Sponsor performing another relapse prevention study to evaluate the longer term (i.e. maintenance) efficacy of levomilnacipran in the treatment of adults with MDD. The final report of that study is due by 25 March 2019.

However, the approval in Canada (Canadian Summary Basis of Decision (SBD) document is at Attachment 10), recognised that the efficacy of FETZIMA was established in three 8 week placebo-controlled studies. It also recognised that long-term maintenance of effect has not been established.

Consequently, the Canadian approval is relevant as the indication and basis for approval in Canada closely aligns with the revised indication for Australia.'

Concerning the conditional approval in the United States of America, that jurisdiction has provision for types of conditional registration. Such a provision does not exist in Australia. Under the Australian legislation, conditions may be applied only after the Secretary has been satisfied as to the quality, efficacy and safety of the medicine and the medicine has been included on the Australian Register of Therapeutic Goods. The Delegate of the Minister is not able to place weight on the licensing in the United States of America.

In Canada, the medicine is authorised as '*Fetzima (levomilnacipran extended-release capsules) is indicated for short-term symptomatic relief of major depressive disorder (MDD). The efficacy of Fetzima was established in randomized, double-blind, placebo-controlled trials of up to 8 weeks (see CLINICAL TRIALS). Long-term maintenance of effect has not been established*.'

You [the sponsor] seek to highlight some points from the Canadian Summary Basis of Decision.

The authorisation in Canada reflects the nature of the limited data available about the use of levomilnacipran. Efficacy has not been established beyond eight weeks. The design of the pivotal studies involved following the experiences of the study subjects for only a further two weeks during a double-blind tapering-down period. Beyond that point, no robust information exists about the fate of those patients. Importantly, it is not known whether they subsequently had an adequate response to another antidepressant or experienced adverse events upon switching. The results of studies LVM-MD -04 and -05 do not provide this information.

Although there may be some differences between guidelines, treatment of depression with antidepressants clearly requires treatment beyond eight weeks and usually of the order of six to twelve months. Switching between antidepressants requires careful clinical attention. Keks et al.[41] provide clinical guidance about switching between one SNRI medicine (levomilnacipran belongs to this class) and another SNRI medicine (Table 3, page 80). That advice includes that: '*A washout period of 2-5 half- lives (most frequently 2-5*

[41] Keks N, Hope J, Keogh S. Switching and stopping antidepressants. Australian Prescriber 2016; 39 (3): 76-83.

days) between cessation of previous drug and the introduction of a new drug is the safest switching strategy from the point of view of drug interactions. In the indicated instances a washout period is not essential if switching is carried out cautiously and under close observation, and clinical considerations such as illness severity support harm-benefit considerations. Cautious cross taper (when the dose of the first drug is being reduced and the dose of the second drug is being increased at the same time so that the patient is taking both antidepressants) may be used in the indicated instances if appropriate and safe.'

The authorisation in Canada of *'short term symptomatic relief of a major depressive disorder*' is inconsistent with the appropriate treatment of a major depressive disorder as the patient will be required to a switch to another antidepressant for continuation of needed treatment. The switch may expose the patient to withdrawal symptoms from levomilnacipran and will require close clinical supervision.

Because of the nature of the condition Major Depressive Disorder the Delegate of the Minister is of the view that *'short term symptomatic relief of a major depressive disorder*' which must be followed by an obligatory switch to another antidepressant is not '*a specific therapeutic use of the goods*' and therefore does not meet the definition of an '*indication*' for the purposes of the Act.

In summary, the Delegate of the Minister places no weight on the authorisation in Canada.

(vi) Delegate's consideration of efficacy

As part of your [the sponsor's] Grounds for Appeal concerning the amended proposed Indications you [the sponsor] state:

"The evidence from the pivotal studies supporting the efficacy of levomilnacipran for up to 8 weeks is clearly recognised throughout the evaluation.

The clinical evaluator found as follows:

'*Levomilnacipran extended release capsules (40 to 120 mg per day) demonstrated statistically significant short term efficacy (as measured by MADRS-CR) in adult patients with MDD in three of four placebo-controlled studies.....Overall, the results were robust, confirmed on sensitivity analyses and supported by secondary endpoints, in particular the SDS as a measure of functional impairment. Data were suggestive of greater response with the highest dose of 120 mg/day, however there were no formal inter-dose comparisons*.' (First round assessment of benefit-risk balance).

However, whilst re-iterating these views within the report the clinical evaluator referred to the 2013 EMA guidelines, incorrectly claiming that longer double blind trials are necessary to demonstrate that the acute effect is maintained during an episode and that this is a major gap in the efficacy data submitted. As discussed above, the 2013 EMA guidelines do not mandate studies beyond 8 weeks for licensing purposes. The clinical evaluator stated:

Efficacy of levomilnacipran has been established for a treatment duration of 8 weeks, however there are no comparative, long term efficacy data. In light of EMA guidelines on depression which state that longer double-blind trials are necessary to demonstrate that the acute effect is maintained during an episode (EMA 2013), this is a major gap in the efficacy data submitted.

In the Request for ACPM Advice, the [initial] Delegate also clearly acknowledged that efficacy had been demonstrated up to 8 weeks. However, misinterpreted the 2013 EMA guidelines, as did the clinical evaluator, in claiming that the guidelines *'recommend'* a demonstration of prevention of relapse during 6 months treatment for licensing purposes. The [initial] Delegate found:

> *Efficacy has not been demonstrated beyond an initial 8 week treatment period. Current Australian guidelines on the treatment of depression recommend at least 6*

months treatment. The current guideline on the clinical investigation of medicinal products for the treatment of depression recommends a demonstration of prevention of relapse (of the index episode) in a 6 month randomised withdrawal study. While other recommendations in that guideline have not been followed these are minor compared to the above.

However, at the ACPM stage there appears to be no recognition in the ACPM minutes that the committee was aware of the amendment to the indication proposed by Pierre-Fabre. For example, at page 4 of the minutes the committee finds:

Whilst short term studies show efficacy, and it is likely this effect will continue beyond the 8 weeks demonstrated in clinical practice, the longer term studies are suboptimal.

In the decision the [initial] Delegate acknowledges that:

While the pivotal short term studies demonstrated a statistically significant improvement in measures of depression when compared with placebo treatment, none of these studies had an active control arm.

As discussed above, an active control arm is not mandated by the relevant TGA adopted EMA guidelines that were current at the time the pivotal studies were conducted and completed. Pierre Fabre therefore contends that, in relation to the statutory test of efficacy under S.25(1)(d) of the Act, the scientific evidence supporting efficacy for up to 8 weeks arising from the evaluation is overwhelming and that levomilnacipran should be approved for registration on the basis of the revised indication."

Later in your Grounds for Appeal you [the sponsor] note concerning efficacy that the [initial] Delegate based the decision on two matters. About these two matters you [the sponsor] submit:

- *Active comparator : the TGA adopted EMA guidelines that were applicable at the time the pivotal studies were conducted and completed (that is, 2002 version at 3.1) specified an active comparator as useful but not needed in the efficacy studies: 'Generally it is useful to add a placebo arm as well as an active comparator (p.7) and 'the dossier should include parallel group studies against placebo and/or active comparator (p.7);*
- *Long-term efficacy: the relevant TGA adopted EMA guidelines do not mandate that double blind parallel, placebo-controlled trials designed to demonstrate efficacy in the acute phase should be continued beyond 8 weeks for at least 6 months and up to one year to demonstrate relapse and recurrence prevention for licensing purposes. Relapse prevention was investigated in a 6 month randomised withdrawal study as required by the EMA 2013 Guideline (LVM-MD-05). The prevention of new episodes or recurrence prevention requiring long term studies of 6 months up to one year was not investigated as 'it is not a mandatory part of a registration package for treatment of MDD episodes' (section 4.1.2, p.8). Elsewhere stated in the guidelines as 'not required for licensing, though of major interest' (section 4.2.2, p.10).*

The Delegate of the Minister has made clear above that a long term double-blind placebo controlled trial is not a mandatory party of the adopted 2012 Guideline. That does not mean that positive results from such a study would not be valuable. Attention to this type of study diverts from the need for a convincing result from a relapse prevention study, which the Delegate of the Minister considers necessary to satisfy the Secretary of the medicine's efficacy and safety.

(iiv) Delegate's consideration of safety:

Your [the sponsor's] Grounds for Appeal also note that the [initial] Delegate based the decision on matters relating to safety.

You [the sponsor] quote the [initial] Delegate:

Fetzima was associated with the following serious adverse events which were considered treatment-related in clinical trials: aggression/violent outburst suicidal ideation, prostatitis, seminal vesiculitist and non-cardiac chest pain. Less serious treatment-related adverse effects associated with Fetzima were: nausea, vomiting, dizziness, headache, hyperhydrosis, rash or urticaria, urinary disorders (hesitation, retention, dysuria), tachycardia, palpitations, hypertension, testicular pain and erectile dysfunction. Given the failure to demonstrate efficacy of Fetzima in treatment of MDD beyond 8 weeks and that treatment for up to 12 months is regularly required in the management of MDD it is an unacceptable risk to allow patients to commence treatment for MDD with Fetzima given the risks from that treatment that have been identified.

Concerning this you [the sponsor] submit:

First, in relation to AE's there appear to be no new adverse reactions than previously known. Second, the [initial] Delegate has predicated the risk profile based on use well beyond 8 weeks which does not accord with the revised indication. Last, in the 'Request for ACPM Advice' the [initial] Delegate acknowledged that the adverse event profile for levomilnacipran was consistent with other SNRIs, and that the clinical program did not identify an increased risk of the SNRI class effects of serotonin syndrome, mania/hypomania, hostility or aggression, discontinuation syndrome, suicidality or abnormal bleeding. In fact, at 'Discussion' the [initial] Delegate did not raise safety as an issue at all.

As indicated above, in relation to safety the ACPM found:

- *"The adverse event (AE) profile was consistent with other SNRI's. In clinical trials the rate of serious AEs was slightly lower with levomilnacipran than placebo in the short term studies.*
- *Treatment emergent AEs which occurred at a notably higher rate than placebo included nausea, constipation, tachycardia, increased heart rate, palpitations, vomiting, dizziness, urinary hesitation, hyperhidrosis, increased BP, erectile dysfunction, ejaculation disorder and testicular pain.*
- *The ACPM noted that no significant concerns have been reported yet since approval and use in USA (2013) and Canada (2015).*
- *Overall, the safety profile is as expected for this class of medicines and, although known class adverse effects have not been clearly identified in the trials these would be expected.*

Consequently, if the scientific evidence appears unequivocal that the AE profile for levomilnacipran was no worse than that for other SNRI's Pierre Fabre can only speculate as to why the [initial] Delegate has chosen safety as the third limb of the reasons for rejection. However, it is clear that without it the [initial] Delegate could not adequately claim an unacceptable risk-benefit trade-off."

The Delegate of the Minister does not consider the safety profile of levomilnacipran as revealed in the short term efficacy studies to be a ground for refusing registration. In the Delegate of the Minister's view, however, registration cannot be approved in Australia until the Secretary is satisfied of the medicine's safety in longer-term use.

(iiiv) In a Conclusion to your [the sponsor's] Grounds for Appeal you state:

Pierre-Fabre therefore strongly contends that the decision of the Delegate of the Secretary is not the correct or preferable decision. The decision-making process has been fundamentally flawed because of the following.

Pierre-Fabre could not have reasonably anticipated that the TGA would place reliance on any guideline other than those formally adopted by the TGA and published on its website. In particular the evaluation of the application has relied upon guidelines that:

- *cannot be found on the TGA website (not formally adopted);*
- *came into effect after the pivotal studies were conducted;*
- *came into effect after the application was lodged;*
- *were inconsistent in relation to selection and title at various stages of the evaluation process;*
- *were inconsistent in relation to the TGA adopted EMA guidelines.*

The [initial] Delegate's reasons for rejection include the lack of Active controls in the efficacy studies - the TGA adopted EMA guidelines that were applicable at the time the pivotal studies were conducted did not mandate active controls in the efficacy studies;

The Delegate's reasons for rejection include the need for efficacy studies beyond eight weeks - this is not supported by the TGA adopted EMA 2013 guideline and appears to be confusing clinical practice with clinical investigation and furthermore, unethical;

The Delegate's reasons for rejection conclude that it is an unacceptable risk to allow patients to commence treatment for MDD with Fetzima given the identified risks from that treatment - this does not appear to be consistent with the [initial] Delegate's findings that:

- *There appear to be no new adverse reactions than previously known;*
- *The Delegate has predicated the risk profile based on use well beyond 8 weeks which does not accord with the revised indication;*
- *The Delegate has acknowledged in her 'Request for ACPM Advice' that the adverse event profile for levomilnacipran was consistent with other SNRI's and that the clinical development program did not identify an increased risk of the SNRI class effects.*

Pierre-Fabre amended the indication in its Pre-ACPM Response to more accurately reflect the results of the clinical development program to:

> *Treatment of episodes of major depressive disorder (MDD). The efficacy of FETZIMA was established in randomized, double-blind, placebo-controlled trials of up to 8 weeks. The efficacy of FETZIMA for the treatment of MDD beyond 8 weeks was not established.*

Fetzima has been approved for major depressive disorder in the USA (July 2013) and for short-term symptomatic relief of major depressive order in Canada (May 2015);

The Canadian approval, for an indication similar to that now proposed for Australia, recognised that efficacy was established on the basis of the same data package submitted in Australia, i.e. three, 8 week placebo-controlled studies.'

In the Delegate of the Minister's view, the Conclusion is a recitation of matters that the Delegate of the Minister has considered above.

(ix) Review of decision by the Administrative Appeals Tribunal

If you [the sponsor] are dissatisfied with the Delegate of the Minister's decision then, subject to the Administrative Appeals Tribunal Act 1975, you [the sponsor] can make an application to the Administrative Appeals Tribunal for a review of this decision.

Outcome from appeal to the Administrative Appeals Tribunal

The sponsor appealed to the Administrative Appeals Tribunal (AAT) for review of the TGA's decision to not register Fetzima.

The sponsor later withdrew their application to the AAT.

Attachment 1. Product Information

The PI for Fatzima approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report.

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