Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for Agomelatine

Proprietary Product Name: Valdoxan

Submission No: PM-2009-00483-3-1

Sponsor: Servier Laboratories (Australia) Pty Ltd

October 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	5 August 2010
Active ingredient(s):	Agomelatine
Product Name(s):	Valdoxan
Sponsor's Name and Address:	Servier Laboratories (Australia) Pty Ltd 8 Cato Street Hawthorn Vic 3122
Dose form(s):	Film-coated tablet
Strength(s):	25 mg
Container(s):	Blister pack
Pack size(s):	28 or 56
Approved Therapeutic use:	The treatment of major depression in adults including prevention of relapse.
Route(s) of administration:	Oral
Dosage:	The recommended dose is 25 mg once daily taken in the evening. The dose may be increased to 50 mg once daily (2 x 25 mg) taken in the evening if clinically indicated.
ARTG Number (s)	159712

Product Background

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has noted that Major Depressive Disorder (MDD) is reported to be the most common mood disorder.[1] Depressive disorders tend to be chronic and both relapse and recurrence are seen frequently.

The presumed mechanism of action of the majority of antidepressants in the treatment of MDD is thought to be via inhibition of neuronal reuptake of monoamines (mainly serotonin and noradrenaline), with a resultant increase in monoamine neurotransmission in the central nervous system (CNS).

The agomelatine molecule possesses a new pharmacological mechanism of action, which combines its melatonin MT_1 and MT_2 agonist properties with a serotonin 5-HT_{2C} antagonist effect. The 5-HT_{2C} receptors is considered a relevant target with regard to antidepressant therapy, as several currently used antidepressant drugs have 5-HT_{2C} receptor antagonist properties (for example, mianserin and mirtazapine).

There have been two submissions to register agomelatine in Australia.

[1] Valdoxan EPAR: http://www.ema.europa.eu/humandocs/PDFs/EPAR/valdoxan/H-915-en6.pdf - accessed 18 June 2010.

First Submission (2005):

At the first presentation in April 2007 the Australian Drug Evaluation Committee (ADEC) recommended rejection on the grounds of lack of established clinical efficacy, concerns regarding safety especially at the higher 50 mg dose (inadequate patient exposure) and inadequate pharmacokinetic characterisation of agomelatine. Further, the Committee supported its Pharmaceutical Subcommittee (PSC) recommendation that the sponsor should provide an absolute bioavailability study to support registration.

Second Submission (2009):

That first submission was withdrawn and the current submission, containing new efficacy and safety data, was considered by the ADEC in August 2009. Deficiencies were again identified by the ADEC which again recommended rejection of the submission on the grounds that efficacy and safety have not been adequately demonstrated.

In making this recommendation, the ADEC agreed that the results of the newly presented relapse study (041) showed that in patients who satisfactorily respond to agomelatine 25 mg or 50 mg daily, continuation of agomelatine at the same dose prolongs that response. This contrasts to the previously presented relapse study (021) which failed to show a significant benefit for agomelatine over placebo.

However, ADEC considered that there continued to be a lack of robust evidence to support the efficacy of agomelatine in treating episodes of depression. ADEC noted that the new submission includes an active controlled study of agomelatine against sertraline. However, the primary aim of this study was to compare the time course of effect of the two treatments on various circadian/sleep-wake cycles, and evidence of antidepressant efficacy was a secondary outcome only.

Thus, although the antidepressant effect of agomelatine was statistically superior (but of uncertain clinical relevance) to that of sertraline in terms of the HAM-D total score and CGI severity of illness score during the first 6 weeks of treatment, these data can only be regarded as supportive of efficacy.[2,3]

The second submission initially provided no new placebo-controlled data regarding the short-term efficacy of agomelatine. Accordingly, the situation with respect to use in this setting is largely unchanged from the original submission, that is, the efficacy of agomelatine is statistically significantly superior to placebo but this difference is of doubtful clinical relevance.

Overall therefore, acceptance of efficacy rests primarily on the one of the two relapse prevention studies which demonstrated a benefit for agomelatine over placebo. This was not considered by ADEC to be an adequate basis upon which to recommend registration.

In terms of safety, the committee continued to be concerned about the lack of adequate patient exposure at the higher 50 mg dose, with data provided for only 44 patients treated with 50 mg daily for more than 12 months. Also of concern was the incidence of potentially clinically significant transaminase elevations (>3 x the upper limit of normal [ULN]). There is some evidence that the incidence of this adverse event is increased at higher agomelatine doses.

The committee noted that the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve from time zero to infinity (AUC_{∞}) of agomelatine are considerably higher in females (3.4× and 5.0× the male values respectively at the 50 mg therapeutic dose), but terminal

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[2] The Hamilton Rating Scale for Depression (HAM-D): This is a questionnaire administered to the subjects by trained health care professionals. The Ham-D score (range 0 to 53) is calculated from an equal-weight summary of 17 items, and higher total scores indicate more severe depression. Each question is rated from 0 to 2, 3, or 4 for severity.

[3] CGI-S = Clinical Global Impression - Severity. The investigator rates the severity of a subject's condition on a 7-point scale 1=not ill, 2=very mild, 3=mild, 4=moderate, 5=marked, 6=severe, and 7=extremely severe.

half life did not differ between the sexes. This finding is of particular concern given this medicine is likely to be extensively used in young females, many of whom will also be using oral contraceptives, and that it cannot be excluded that the observed increases in liver enzymes are dose related.

Submission 2 (2009) – supplementary clinical data:

The sponsor submitted further data to address the deficiencies identified by the ADEC in the above resolution. These consisted of the results of a short term, active-controlled study and a Periodic Safety Update Report (PSUR) containing the initial post-marketing data following marketing of agomelatine in the European Union (EU). These were considered in conjunction with the earlier evaluations.

The areas of major concern which had previously been identified were:

- An insufficient demonstration of efficacy in treatment of depression in placebo-controlled trials.
- Lack of long term safety data for the 50 mg dose

As noted in the TGA-adopted EU guideline for products to treat depression, randomised, double-blind comparisons versus placebo are needed to permit adequate evaluation of efficacy, though showing superiority over an active comparator could be an acceptable alternative.[4]

The Submission 2 data set contained only clinical data. The clinical evaluator was requested to also consider:

- Initial clinical evaluation
- Supplementary clinical evaluation of initial submission
- Initial delegate's overview
- ADEC Minutes concerning the first submission
- Second clinical evaluation
- Second delegate's overview
- ADEC Minutes concerning the second submission

The recommended dose is 25 mg once daily taken in the evening. The dose may be increased to 50 mg once daily (2 x 25 mg) taken in the evening if clinically indicated.

Regulatory Status

The original application to register Valdoxan in the EU via the centralised procedure was withdrawn after an unfavourable opinion from the CHMP. Subsequently, additional data were submitted (essentially the same data that were submitted to the TGA in August 2009) and Valdoxan was approved by the EMA on 19 February 2009.

The indication in the EU is for *Treatment of major depressive episodes in adults.*

No submission has been made in the USA. A submission to Health Canada was withdrawn in 2005.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

[4] EMEA, Committee for Proprietary Medicinal Products (CHMP), 25 April 2002. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Depression CPMP/EWP/518/97 Rev 1 (pdf,160kb)

II. Quality Findings

Introduction

An earlier application to register agomelatine was withdrawn following a negative recommendation from ADEC. Amongst other things, ADEC recommended that the sponsor should submit an absolute bioavailability study. The present resubmission includes an absolute bioavailability study (Study 066), which is evaluated below. There are no additional quality data as all other quality aspects were cleared in respect of the previous application, and no changes to these data have been made.

Drug Product

Valdoxan tablets contain the active ingredient agomelatine 25 mg and the following excipients: lactose, starch - maize, povidone, sodium starch glycollate, stearic acid, magnesium stearate, silica - colloidal anhydrous, hypromellose, iron oxide yellow (CI77492), glycerol, macrogol 6000, and titanium dioxide (CI77891), shellac, indigo carmine (CI73015) and propylene glycol.

Bioavailability

Agomelatine is only very slightly soluble in aqueous solution over the physiological pH range, but it is classified as a high solubility drug in accordance with the BCS because its dose/solubility ratio is about 100 mL.[5]

Agomelatine is rapidly and well absorbed (>80%) after oral administration but the estimated bioavailability (based on a population pharmacokinetic analysis) is only about 3% due to a high first pass effect. Furthermore, bioavailability is variable due to inter-individual differences in cytochrome P450 (CYP) 1A2 activity.

Agomelatine is rapidly oxidised, primarily in the liver, by the cytochromes CYP1A2 (90%) and CYP2C9/CYP2C19 (10%). The major metabolites are hydroxylated and demethylated agomelatine, which are not pharmacologically active. They are rapidly conjugated and eliminated in the urine. Urinary excretion of unchanged agomelatine is negligible.

Food has no significant effect on the extent of absorption of agomelatine, but it reduces C_{max} by about 20-30%.

Study 066 was an assessment of the absolute bioavailability of the oral 25 mg tablet of agomelatine in healthy male volunteers. It was a Phase I single centre, randomised, open, two-way cross-over study. Treatment A consisted of an agomelatine 25 mg tablet, identical to that proposed for registration. Treatment B consisted of agomelatine 0.025 mg/mL in 5% glucose. A volume of 40 mL was infused over a period of one hour corresponding, nominally, to 1 mg of agomelatine. However, the batch assayed at only 92.4%. It is not clear whether the volume of infusion was adjusted so that the dose administered was 1 mg or whether the dose administered was only 0.924 mg. In the statistical analyses below, it has been assumed that the dose was 1 mg. If the dose was only 0.924 mg then the absolute bioavailability of the tablet becomes 0.9% rather than 1.0%. The difference is insignificant, so clarification of the dose will not be sought.

Thirty-six volunteers were screened. Of these, 24 healthy, male volunteers (23 Caucasian, one Maori), aged 18-36 years were enrolled and completed the study. All subjects were non-smokers.

Pharmacokinetic parameters were determined by non-compartmental analysis using actual sampling times. The area under the plasma concentration time curve from zero time to time t (AUC_t) was determined by the log-linear trapezoidal rule.

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[5] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

The reported data and statistical analyses thereof are summarised below. The evaluator confirmed these results by repeating the analysis of variance (ANOVA) calculations.

Table 1: Absolute bioavailability of agomelatine: ratio of dose adjusted geometric mean [including 90% Confidence Intervals]

Statistical analysis:		***ratio (%)***	***ratio (%)***
A vs B	Estimate	0.8% [0.6 – 1.2%]	1.0% [0.8 – 1.3%]

Note: A: tablet (25 mg), B: IV (1 mg)

The absolute bioavailability of the agomelatine 25 mg tablet proposed for registration is 1.0%. Pharmacokinetic results for the one Maori subject were within the range of results for Caucasian subjects.

Quality Summary and Conclusions

There were no objections in respect of chemistry and quality control to registration of this product.

III. Nonclinical Findings

Introduction

Servier Laboratories Australia Pty Ltd has applied to register Valdoxan tablets, which contain agomelatine as the active substance, for the treatment of major depression in adults including prevention of relapse. The product is a 25 mg film-coated tablet, with a maximum recommended dose of 50 mg once daily.

The submission is a re-submission; the previous registration application was withdrawn by Servier in 2007 pending resolution of biopharmaceutical and clinical (efficacy) issues. The sponsor has indicated that the current submission addresses these matters with recently completed studies.

The submission does not contain any new nonclinical data, as no changes have been made to this aspect of the dossier that was previously evaluated. The maximum recommended clinical dose (50 mg/day) has not changed since the original nonclinical submission was evaluated, so the animal/human systemic exposure ratios and safety margins previously calculated will suffice for the purposes of safety assessment.

Nonclinical Summary and Conclusions

The submission does not contain any new nonclinical data, as no changes have been made to this aspect of the original application.

The conclusion and recommendations of the original nonclinical evaluation report remain valid, and are reproduced below.

“The findings in the comprehensive package of nonclinical studies do not raise any concerns for the registration of agomelatine as proposed by the sponsor.

Pharmacological studies indicated that agomelatine is an agonist at MT_1 and MT_2 melatonin receptors and an antagonist at $5HT_{2c}$ receptors, and is active in animal models of depression, anxiety and desynchronisation of circadian rhythms. Pharmacokinetic studies in the species used for toxicity studies indicated widespread distribution, similar metabolic transformation pathways in animals and humans, and rapid, mainly hepatic, clearance. Metabolites are conjugated and renally excreted. Agomelatine induced the hepatic enzymes CYP2B1/2, 1A1/2, 3A1/2 and uridine diphosphate glucuronosyltransferases (UGT) (rats), CYP2B (monkeys) and CYP2B9/10 (mice).

The target organ for toxicity was the liver, observed as increased liver weight, discolouration and/or hepatocellular hypertrophy, hepatic enzyme induction, and increased incidences of hepatocellular adenomas (male and female mice) and hepatocellular carcinomas (male and female mice, male rats). The tumourigenic responses, observed only at doses producing high levels of liver enzyme induction, occurred at systemic exposures (plasma AUC) of about 10 fold or greater the anticipated clinical exposure, with exposures at the no-effect doses of 3-4 fold clinical exposure. Mechanistic studies found that agomelatine and phenobarbitone elicited similar enzyme inducing and proliferative hepatic responses. The genotoxicity profile of agomelatine was negative. The data suggest that the carcinogenic liability of agomelatine in humans is low.

The remaining toxicological findings with agomelatine, including reproductive toxicity, were relatively minor and observed only at high exposure ratios."

There were no nonclinical objections to the registration of agomelatine.

IV. Clinical Findings

Introduction

The original submission was withdrawn by the sponsor after unfavourable recommendations from the clinical evaluator, the Delegate, PSC and ADEC. Three main issues were identified:

- In respect of efficacy, the clinical evaluator and the Delegate considered that the short term (6 to 8 week) efficacy data were inconclusive as two of the six pivotal placebo-controlled studies were inconclusive and one was negative, and the supportive placebo-controlled study in patients aged ≥ 60 years was also negative. A meta-analysis of the six pivotal short term studies demonstrated a statistically significant treatment effect, but the magnitude of the effect was considered to be of doubtful clinical significance. Furthermore, the long term efficacy of agomelatine had not been established as the placebo-controlled relapse prevention study designed specifically to address this matter failed to show a statistically significant difference between agomelatine and placebo. ADEC agreed there was no dispute that agomelatine improved the 'Getting off to sleep' score, but this is not an antidepressant efficacy measure. ADEC considered that agomelatine may be efficacious in major depressive disease, but the current data did not demonstrate this sufficiently to allow a recommendation to register.
- In respect of safety, the number of patients exposed to long term treatment with agomelatine 50 mg was considered too small to satisfactorily demonstrate the safety of this dose for the proposed indication. Only 32 patients had received the 50 mg dose for ≥ 6 months, and none had received it for 12 months. In addition, the limited available data from the clinical studies showed that hepatic transaminase levels were higher with the 50 mg than the 25 mg dose, thus raising the possibility of dose-related liver toxicity.
- The PSC considered that an absolute bioavailability study on the tablet formulation proposed for registration was required to ensure that the product is optimally formulated. The Committee concluded that this is particularly relevant given the:
  - inherent low solubility, low bioavailability, possible saturable kinetics and short half life of agomelatine; and
  - significant intersubject and intrasubject variability observed in the various bioavailability and pharmacokinetic studies conducted with agomelatine.

The current 2009 submission seeks to address these three main issues. Other issues identified in the original submission but not specifically addressed by the new data include:

- Questionable suitability of once daily dosing: Valdoxan is proposed for once daily dosing, based on pharmacodynamic properties. However, the half life of agomelatine is about 1.5 hours, which is very short for a drug being proposed for once daily use.

- Inconclusive data in patients with renal impairment: In subjects with renal impairment (creatinine clearance [Clcr] < 30 mL/min, n=8) the C_{max} and AUC_{∞} were ~41% and ~24% higher, respectively, than in subjects with normal renal function. The results were regarded as inconclusive due to large intersubject variation.

The submission included the following studies, all of which were conducted in accordance with the principles of Good Clinical Practice (GCP) with appropriate ethics approval:

Pharmacodynamics

- CL1-054: A double-blind, controlled study of the effect of a single oral dose of agomelatine on the QT/QTc interval following the proposed maximum therapeutic dose of agomelatine (50 mg) and a supratherapeutic dose (400 mg), compared to placebo and a positive control (moxifloxacin) in healthy volunteers. This study also included blood sampling for the determination of agomelatine single dose pharmacokinetics.
- CL1-049: An 8 week, randomised, double-blind, placebo and active controlled study to assess sexual function and hormonal changes in healthy male volunteers treated with agomelatine (25 mg and 50 mg), paroxetine (20 mg) or placebo.
- CL3-046: A 6 week, randomised, double-blind, active controlled study (agomelatine versus sertraline), with an optional 18-week extension. The primary study aim was to compare the time course of the effect of the two treatments on various circadian/sleep-wake variables. A secondary objective was the provision of additional short term antidepressant efficacy and short- to medium-term safety data.

Pharmacokinetics

- PKH-066: A randomised, open, two-way crossover study to assess the absolute bioavailability of the 25 mg tablet proposed for marketing in healthy male volunteers. Bioavailability aspects of this study have been evaluated by the quality evaluator; other pharmacokinetic aspects and safety data are evaluated in this report.
- CL1-054 (described above).

Efficacy and safety

- CL3-041: A 1 year study consisting of an 8 to 10 week open-label agomelatine responder identification period, followed by a 24-week, randomised, double-blind, placebo-controlled maintenance treatment period, followed by an optional 20-week double-blind placebo-controlled extension period. The aim of this study was to assess the efficacy of maintenance therapy with agomelatine 25 or 50 mg in the prevention of depressive relapse. This study is very similar to Study CL3-021 in the original submission, which failed to show a significant effect of agomelatine on relapse rate over 26 or 44 weeks. The principal difference is that CL3-021 used a fixed dose of agomelatine 25 mg, whereas the new study allowed the agomelatine dose to be increased to 50 mg after 2 weeks, as recommended in the draft PI.
- CL3-046 (described above).

The submission also included:

- Meta-analyses of the short-term placebo- and active-controlled efficacy studies. These meta-analyses did not include any of the new studies, and are evidently the same ones that were included in the original submission. They will not be reviewed further.
- A *Clinical Overview*, *Summary of Biopharmaceutic Studies and Associated Analytical Methods*, and *Summary of Clinical Pharmacology Studies*. These took into account the new studies as well as those in the original submission.

- A *Summary of Clinical Efficacy* and *Summary of Clinical Safety*. The *Summary of Clinical Efficacy* did not include the optional 20-week double-blind extension of CL3-041. The *Summary of Clinical Safety* excluded most of the studies in the current submission, except for data from the first part of CL3-041 (that is, CL1-054, CL1-049, CL3-046, and the 20-week optional extension of CL3-041 were not included).
- An *Integrated Analysis of Safety* with a cut-off date of 31 March 2007 that contained the detailed supporting information for the *Summary of Clinical Safety*.
- An addendum to the *Summary of Clinical Safety*, dated February 2009, that examined cases of transaminase elevations but did not address any other safety data.
- A draft *Risk Management Plan* (to be assessed by the Office of Medicines Safety Monitoring [OMSM]). The *Risk Management Plan* referred to an update to the *Integrated Analysis of Safety*, with a cutoff date of 31 December 2007, which is stated to include CL3-046 and the 20-week optional extension of CL3-041. That update was not included in the submission, unless it is the update referred to above that only examined transaminase elevations.

Evaluator comments

A shortcoming of the submission was that the new clinical studies were not fully integrated into the various summaries, which impeded the evaluation process. Evaluation was also impeded by the reporting of CL3-041, which was covered by two separate but overlapping reports (one covered the open-label period and the first 24 weeks of randomised treatment; the second covered the first 24 weeks of randomised treatment and the optional 20 week extension). The evaluator was able to manually consolidate some of the safety data from the two reports to provide an assessment that covered the full 12 month treatment period (for example, for deaths and serious adverse events), but it was not feasible to do this for adverse events, adverse drug reactions or laboratory results.

Finally, as noted in the previous section and discussed later in this evaluation report, the new studies did not address all of the deficiencies that had been identified in the original submission.

Pharmacodynamics

CL1-054

CL1-054 was a randomised, double-blind, placebo- and positive- (moxifloxacin) controlled, 4×4 crossover study of the effect of a single oral therapeutic dose (50 mg) and a single oral supratherapeutic dose (400 mg) of agomelatine, given in the evening, on the population-corrected QT interval (QTcP) in healthy volunteers. Sixty subjects were randomised (29 male; 31 female; age 18-44 years), of whom 56 completed the study and provided evaluable QTcP data, based on electronically read, triplicate, 12-lead electrocardiograms (ECGs) recorded at intervals during the 24 hours before and after each dose. Treatment periods were separated by a 5 day washout.

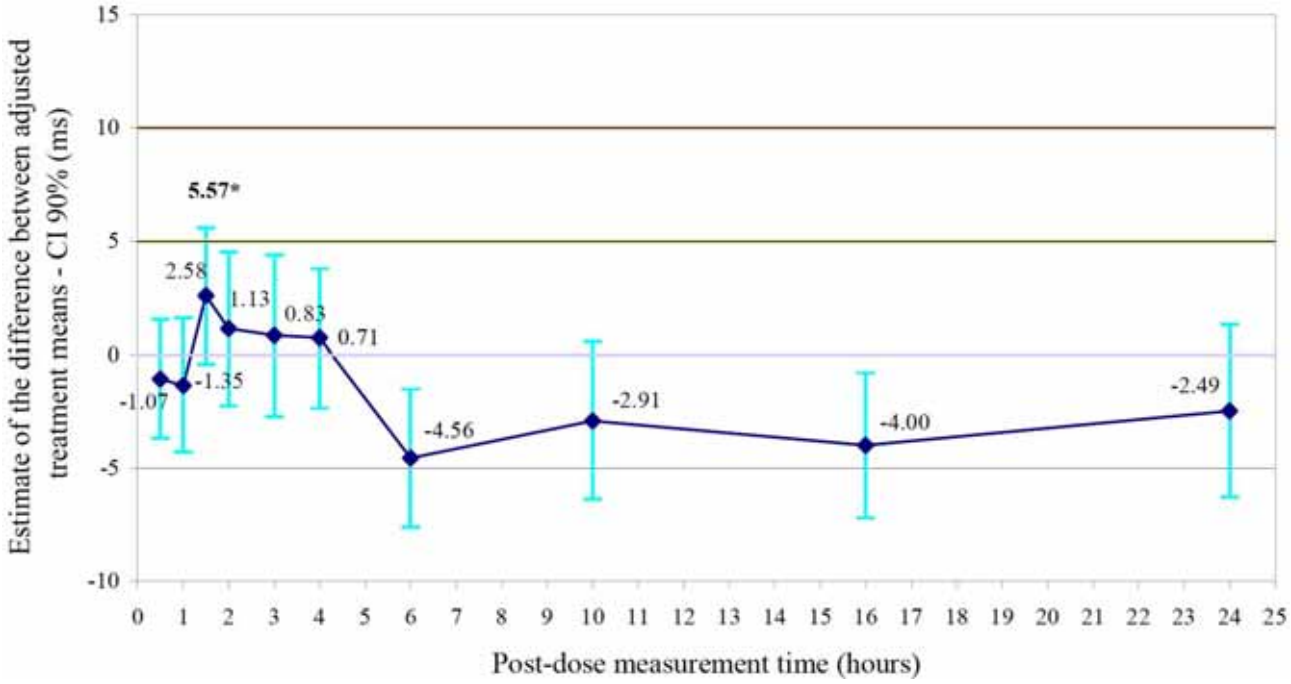
The primary assessment criterion was the QT interval corrected for heart rate according to a study male population-derived correction formula for male subjects and a study female population derived correction formula for female subjects (QTcP). The correction formulae were derived from the model that best fitted the relationship between the drug-free QT and RR intervals in males and females, respectively. At each post-dose time point, the mean and corresponding two sided 90% confidence intervals (CI) (providing an upper boundary equivalent to a one sided 95% CI) were calculated for the difference in change from baseline between active treatment and placebo, using a 4-way ANOVA. Secondary ECG criteria were: Fridericia-corrected QTc interval (QTcF); Bazett-corrected QTc interval (QTcB); QT interval corrected for heart rate according to individual derived correction formula (QTcI); uncorrected QT interval (QT); RR, PR and QRS intervals; heart rate (bpm) and ECG abnormalities.

The results for the primary criterion are depicted in Figure 1. The ANOVA estimate of the placebo-corrected QTcP change after administration of agomelatine 50 mg reached a peak value of 2.59 milliseconds (ms), 1.5 hours after the dose. At that point the upper boundary of the one sided 95%

CI was 5.57 ms. The corresponding estimate and upper 95% CI boundary for agomelatine 400 mg were 4.70 and 8.24 ms, 3 hours after the dose.

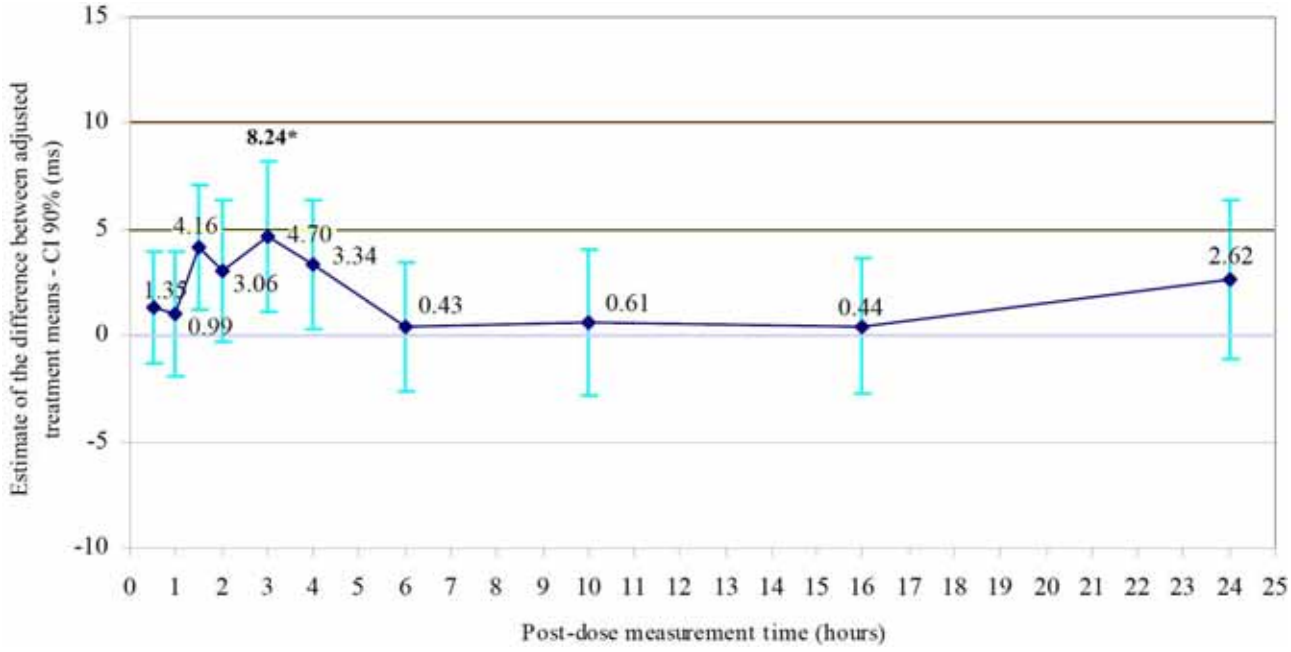
Figure 1: CL1-054: ANOVA-estimated (90% CI) placebo-corrected change in QTcP after single oral doses of agomelatine 50 mg, agomelatine 400 mg and moxifloxacin 400 mg.

Agomelatine 50 mg



* Highest 95% one sided CI upper bound

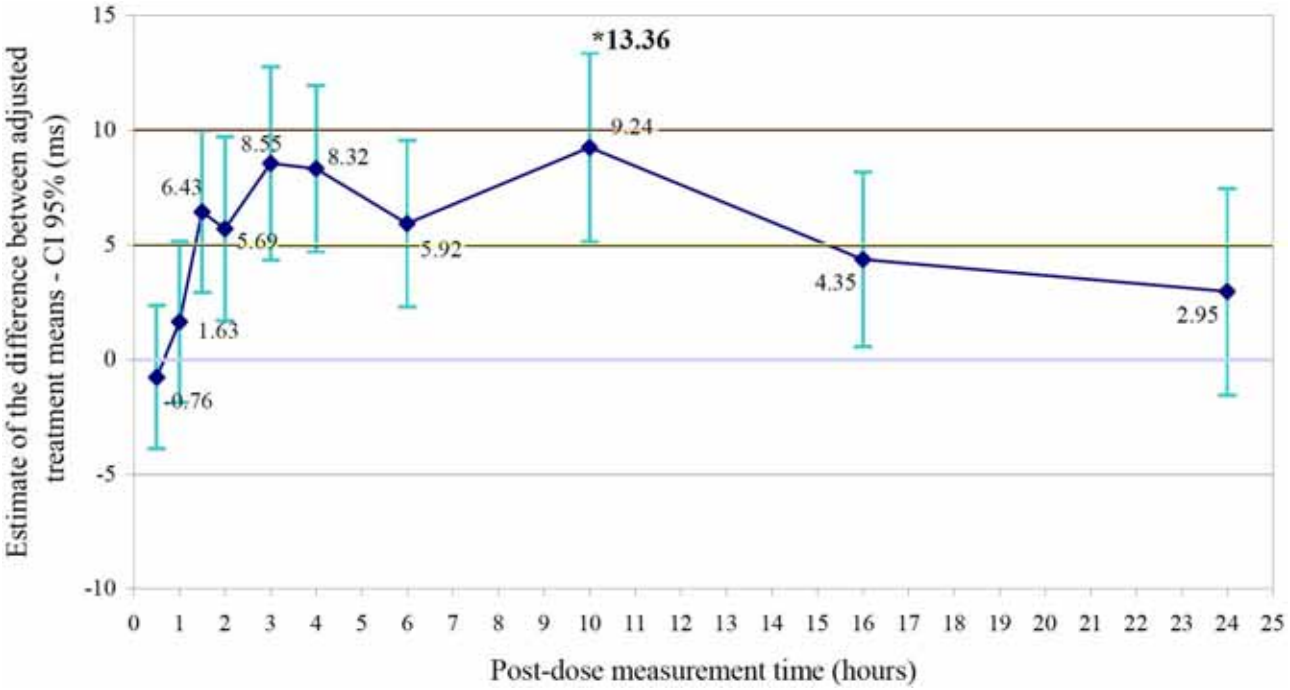
Agomelatine 400 mg



* Highest 95% one sided CI upper bound

Figure 1 (continued)

Moxifloxacin 400 mg



* Highest 95% one sided CI upper bound (added by evaluator)

Evaluator comments

This 'thorough QT/QTc study' was performed in accordance with the relevant ICH guideline on evaluation of proarrhythmic potential adopted by the EU.[6] This guideline has been adopted by the TGA with the explanatory comment that QT prolongation would be of regulatory concern if either the estimated QT prolongation is >5 ms or the upper bound of the 95% confidence interval of the prolongation is >10 ms. The agomelatine doses were chosen to represent the maximum recommended dose (50 mg), and a dose providing exposure equivalent to what would be expected in a person taking the maximum recommended dose in the presence of a strong inhibitor of both CYP1A2 and CYP2C9 (fluvoxamine) based on an interaction study in the original submission. Moxifloxacin is an antibiotic known to have an effect on QT/QTc interval and commonly used as positive control in 'thorough QT/QTc studies' because of its predictability. The 5 day washout period was more than adequate to allow elimination of both agomelatine (half life about 1 hour) and moxifloxacin (half life about 12 hours) between successive treatment periods. The timing of the ECGs was such as to adequately capture the maximum effect of both active treatments, based on their known pharmacokinetic profiles and confirmed by blood sampling within the study.

The study results demonstrate that the use of agomelatine is unlikely to be associated with clinically relevant QT prolongation. There was some evidence of a small, dose-related effect of agomelatine on placebo-corrected QTcP change, although this was not borne out by an analysis of placebo-corrected QTcP change versus agomelatine plasma concentration. In any case, the magnitude of the effect was below the threshold of concern even at the 400 mg dose (that is, the mean QTcP increase was <5 ms at all time points and the upper boundary of the one sided 95% CI for QTcP increase was <10 ms at all time points). By contrast, the corresponding values exceeded the threshold of

[6] EMEA, Committee for Medicinal Products for Human Use (CHMP), November 2005. Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, CHMP/ICH/2/04, http://www.tga.gov.au/docs/html/euguide/euad_clin.htm.

concern at several time points after the administration of moxifloxacin, demonstrating the sensitivity of the study design. Results for the secondary criteria supported those for the primary criteria.

CL1-049

CL1-049 was a randomised, double-blind, placebo-controlled, parallel-group study designed to assess the effect of agomelatine on male sexual function compared to placebo and paroxetine. Healthy young males took placebo, agomelatine 25 mg, agomelatine 50 mg or paroxetine 10 mg increasing to 20 mg after 1 week. Agomelatine was taken once daily in the evening (with placebo in the morning), paroxetine was taken once daily in the morning (with placebo in the evening) and placebo was taken twice daily. All study treatments were taken for 8 weeks. Important inclusion criteria were: age 18-30 years; smoked < 10 cigarettes/day; body mass index (BMI) 20-30 kg/m²; stable relationship for at least 6 months with regular (at least 1 per week) and satisfactory sexual activity; Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) total score = 0; International Index of Erectile Function (IIEF) total score > 60. These endpoints were assessed in the 'Sexual Acceptability Set', defined as all volunteers with a sexual function assessment after at least two weeks and ≥70% treatment compliance (based on saliva or urine samples). All volunteers on placebo were considered to be treatment compliant.

The effect of study treatments on sexual function was assessed at baseline, every 2 weeks and the final visit using the PRSexDQ and IEEF, and at baseline and the final visit using the modified Kinsey Questionnaire. The primary criterion was the occurrence of sexual dysfunction based on the PRSexDQ, defined as at least one sexual impairment in one of the 4 following items: decreased libido (item 3), delayed orgasm/ejaculation (item 4), anorgasmia/no ejaculation (item 5), and erectile dysfunction (item 6). Sexual impairment corresponded to a score ≥ 1 for items 4, 5, 6 or a score ≥ 2 for item 3. The effect of study treatments on prolactin, total cortisol and total and free testosterone was also assessed at baseline, every 2 weeks and the final visit.

Ninety four healthy young male volunteers were selected, 92 of whom were randomised (23 per group, age 18-30 years). There were no relevant baseline differences amongst the treatment groups. Four subjects withdrew from the study: one in the agomelatine 25 mg group for protocol deviation, and three in the paroxetine group (one for adverse events, and two for nonmedical reasons). The Sexual Acceptability Set comprised 87 volunteers. The mean ± SD treatment duration was 54.9 ± 9.2 days (median: 57 days). No relevant between-group differences were seen for treatment duration and compliance.

Primary results: Sexual dysfunction assessed by PRSexDQ

Comparison between each dose of agomelatine and paroxetine

In the Sexual Acceptability Set, at the last post-baseline assessment until Week 8 (W8), 22.7% (5/22) of volunteers on agomelatine 25 mg and 4.8% (1/21) on agomelatine 50 mg had sexual dysfunction compared to 85.7% (18/21) on paroxetine. Based on these results, the adjusted risk of having sexual dysfunction on agomelatine compared to paroxetine was significantly reduced by 74% at 25 mg (risk ratio [RR] = 0.26, 95% CI [0.12, 0.58]) and by 94% at 50 mg (RR = 0.06, 95% CI [0.01, 0.38]). These results were confirmed by the unadjusted Cochran-Mantel-Haenszel (CMH) test and Chi-Square test. Similar results were found for the last post-baseline assessment until Week 4 (W4), and at each visit from Week 2 (W2) to W8.

Comparison between paroxetine and placebo

At the last post-baseline assessment until W8, 8.7% (2/23) of volunteers in the placebo group had sexual dysfunction. The adjusted risk of sexual dysfunction on paroxetine compared to placebo was increased 9.4-fold ($p < 0.0001$). These results were confirmed by the unadjusted CMH test and Chi-Square test. Similar results were found for the last post-baseline assessment until W4, and at each visit from W2 to W8.

Comparison between each dose of agomelatine and placebo

There were no statistically significant differences between each agomelatine dose and placebo at the last post-baseline assessment until W4 and until W8, and at each visit from W2 to W8.

Secondary results

Results for the various secondary assessments of sexual dysfunction supported those of the primary endpoint. There were no clinically relevant changes in the mean plasma levels of prolactin, total cortisol, total and free testosterone in the active treatment groups compared to the placebo group.

Evaluator comments

Unlike paroxetine, agomelatine did not adversely affect sexual function in this study in healthy male volunteers. This is consistent with results from depressed patients in the original submission, based on a specific sexual dysfunction study CL3-036 and a pooled analysis of the three short term placebo-controlled studies in which sexual dysfunction was assessed (CL3-022, CL3-023 and CL3-024).[7]

CL3-046

CL3-046 was a multicentre, randomised, double-blind, parallel group study that compared agomelatine 25 to 50 mg daily and sertraline 50 to 100 mg daily in adult male and female outpatients aged 18-60 with single-episode or recurrent MDD according to DSM-IV-TR criteria. The main objective of the study was to demonstrate the time course of the effect of agomelatine on rest/activity circadian rhythms compared to sertraline. Assessment of antidepressant efficacy and the collection of safety data were secondary objectives.

The study consisted of the following periods:

- A 1-week run-in period (Assessment to Week zero [W0]).
- A 6-week double-blind period (W0 to W6) in which patients were randomised to receive agomelatine 25 mg daily or sertraline 50 mg daily from W0 to W2. At W2, in patients who exhibited insufficient improvement according to pre-specified criteria (concealed from patients and investigators), the dosage was increased to 50 mg daily for agomelatine and 100 mg daily for sertraline, under double-blind conditions using a centralised telephone service.
- An optional 18-week double- blind extension period (W6 to Week 24 [W24]) for patients who were 'much improved' at W6 (CGI-global improvement score = 1 or 2).[8] Patients continued the same treatment and dose as they had received during W2-W6.
- A follow- up period of 1 week after treatment discontinuation.

In addition to the DSM-IV-TR diagnosis of MDD, patients had to satisfy all of the following inclusion criteria:

- Requirement for antidepressant treatment in the opinion of the investigator;
- HAM-D total score ≥ 22 at Assessment and inclusion (W0);
- HAM-D item 3 (suicide) ≤ 2 at Assessment and W0;

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[7] Information regarding the assessment of sexual dysfunction in the original submission could not be located in the first or supplementary clinical evaluations of that submission. It is instead taken from the sponsor's *Summary of Clinical Pharmacology Studies*. The studies cited by the sponsor have not been reviewed by the evaluator.

[8] In addition to the Clinical Global Impression – Severity (CGI-S) score, there is a Clinical Global Impression - Global improvement score. This score has an 8 point-ordinal scale. 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse) in comparison with patient's condition at inclusion visit during the open-label phase, in comparison with patient's condition at randomisation during the double-blind phase.

- HAM-D decrease (if any) between Assessment and W0 ≤ 20%;
- Sum of HAM-D item 5 "Insomnia: middle of the night" + item 6 "Insomnia: early hours of the morning" ≥ 3 at Assessment and W0;
- Sum of items H1+H2+H5+H6+H7+H8+H10+H13 (core of depression + 2 items on sleep 5 and 6) of HAM-D ≥ 55% of HAM-D total score;
- CGI severity of illness score ≥ 4 (moderately to severely ill).

Patients with seasonal depression, psychotic features, post partum depression, catatonic features, or a current episode <4 weeks in duration were excluded.

Patients wore electronic activity monitors on the non-dominant wrist, which recorded the intensity and duration of all movements over 0.05 G within each 2 minute time-slot. Continuous actigraphy measurements were recorded between selection and the W6 visit (maximum 7 weeks). Patients were asked to remove the monitor only when showering or bathing. Patients were also asked to press an event marker button on the monitor when they were ready to sleep and immediately on awakening. Actigraphy measurement recordings (actigrams) were centralised and read by a blinded team of three experts.

The primary endpoint was the between-treatment difference in the change from W0 in the 'Relative Amplitude' (RA) of the rest/activity cycle, calculated as the difference between the average activity level during the 10 most active hours (M10) and the average activity level during the five least active hours (L5), divided by the sum of M10 and L5. M10 and L5 values were based on average measurements during the respective time intervals over a 7-day block of time. The RA theoretically ranges from 0 to 1. The primary analysis was conducted in the 'Actigraphy Analysis Set' (AAS, defined as all randomised patients who took at least one dose of study drug and for whom a baseline RA value and at least one post-randomisation RA value could be determined). It used a Mixed-effects Model with Repeated Measures (MMRM) including the factors Treatment, Time and Treatment × Time interaction as fixed effects and relative amplitude at Day 0 (D0) as covariate:

- In terms of the evolution of mean RA (expressed as change from baseline) over time (Day 7 [D7], Day 14 [D14], Day 21 [D21], Day 28 [D28], Day 35 [D35], Day 42 [D42]), using the significance of the Treatment × Time interaction.
- At the three first post-baseline times (D7, D14 and D21) using a test on the adjusted means obtained from the previous model. Since three tests were performed (at D7, D14 and D21), the Hochberg procedure was used to adjust the critical p-value to account for multiplicity.[9]

A range of secondary rest/activity cycle and sleep-related endpoints were investigated. Of these, the most clinically relevant were the Leeds Sleep Evaluation Questionnaire (LSEQ) and the Epworth Sleepiness Scale (ESS).[10,11] The effect of treatment on HAM-D and CGI scores was also examined.

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[9] According to this procedure, the critical p-values for declaring statistical significance were set at 0.017, 0.025 and 0.050 for the D7, D14 and D21 tests, respectively.

[10] The Leeds Sleep Evaluation Questionnaire (LSEQ) is a widely used standardized instrument for the measurement of sleep difficulties in clinical settings and like other standardized questionnaires for the same purpose consists of several well defined components. It comprises ten individual visual analogue scales (100mm) which have been shown by factor analysis to assess four discrete, independent domains of sleep and daytime behaviour: Getting To Sleep (Questions 1-3), Quality Of Sleep (Questions 4,5), Awakening From Sleep (Questions 7,8) and Behaviour Following Wakening (Questions 8-10).

[11] The Epworth Sleepiness Scale (ESS) is a scale intended to measure daytime sleepiness that is measured by use of a very short questionnaire. This can be helpful in diagnosing sleep disorders. The questionnaire asks the subject to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 in eight different situations. The scores for the eight questions are added to obtain a single number. A number in the range 0–9 is considered to be normal while a number in the range 10–24 is considered to indicate that specialist medical advice should be recommended.

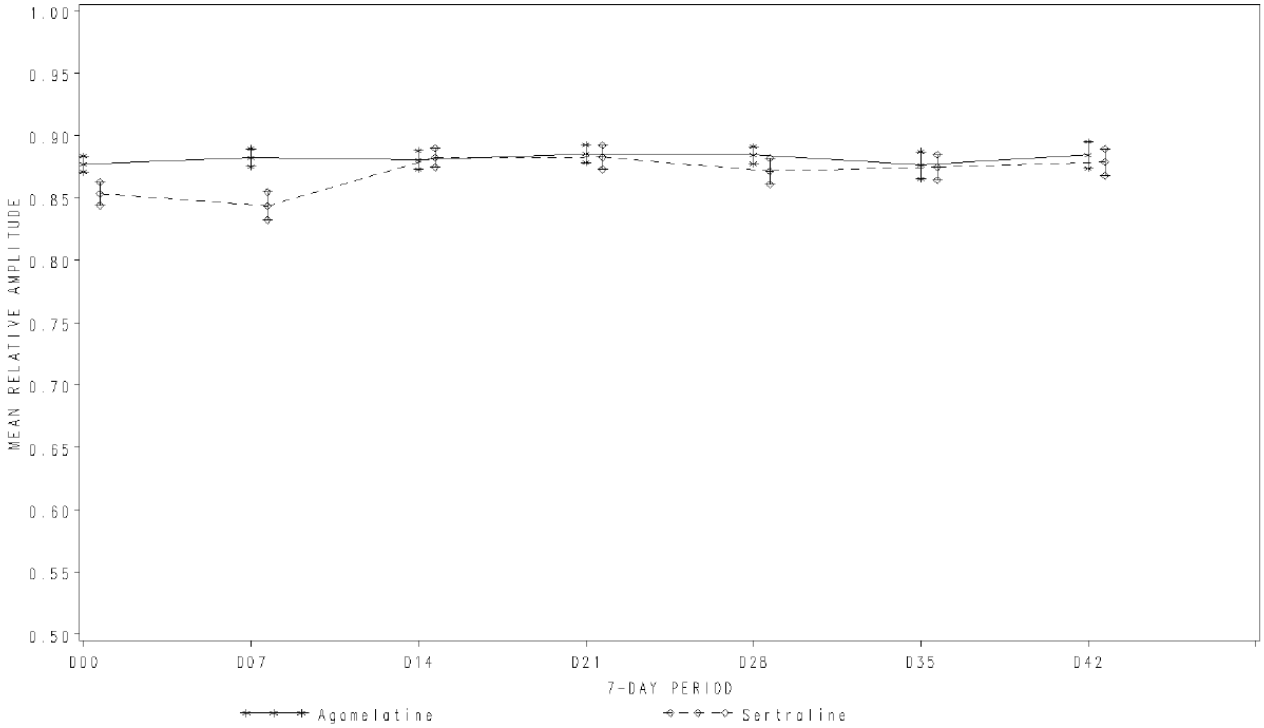
A total of 372 patients were screened and 367 were selected for the study. Of these, 314 patients were included and 313 patients were randomised to agomelatine (N=154) or sertraline (N=159). About 71% of the randomised patients were females and 29% were males. The agomelatine group had a slightly higher percentage of females than the sertraline group (73.4% versus 67.9%) and a slightly lower (better) mean baseline HAM-D total score (26.1 versus 26.5). Otherwise, the baseline characteristics of the two groups were comparable.

The AAS comprised 117 (76%) of the patients randomised to agomelatine and 116 (73%) of those randomised to sertraline. All of the patients excluded from the AAS lacked a reliable baseline and/or post-baseline RA value, and one of them had also failed to take any study treatment. The agomelatine and sertraline groups of the AAS were comparable at baseline in respect of demographics, MDD characteristics and circadian/sleep variables.

Primary results

In the AAS, the evolution of the mean RA over the time was statistically significantly different between the agomelatine group and the sertraline group (Treatment * Time interaction, p = 0.023). The mean RA remained stable over time in the agomelatine group, while in the sertraline group, the mean RA decreased between baseline and D7 (Figure 2). The difference between the 2 groups in the mean change from baseline at D7 was statistically significant in favour of agomelatine (p = 0.010 to be compared to 0.017 [Hochberg procedure]). From D14 onwards, the mean RA in the sertraline group was similar to that of the agomelatine group.

Figure 2: CL3-046: Time course of mean RA in the AAS.



Other results

The evolution of the objective sleep parameters over the W0-W6 period, evaluated by actigraphy data in the AAS, showed a significant difference in favour of agomelatine, with greater sleep efficiency (p < 0.0001), shorter sleep latency (p < 0.0001) and shorter actual wake time (p = 0.018) compared to sertraline. Similar results were observed in the subset of more severely depressed patients.

In addition to this global assessment, the mean sleep efficiency and mean sleep latency, expressed in terms of change from baseline to each post-baseline 7-day period, improved with agomelatine

and worsened with sertraline, leading to a statistically significant between-treatment difference in favour of agomelatine during each period.

In the FAS, the 4 components of the LSEQ (Getting off to sleep, Quality of sleep, Sleep awakening, and Integrity of behaviour) improved in both treatment groups. For each score, the mean last post-baseline value was numerically lower (better) in the agomelatine group than in the sertraline group, but the difference was statistically significant only for the 'Getting off to sleep' and 'Quality of sleep' scores at Week 2 ($p < 0.001$ and $p = 0.025$, respectively).

In the FAS, the mean ESS total score decreased in both treatment groups, indicating a reduction in daytime sleepiness. The mean decrease from baseline to last value over the W0-W6 period was numerically higher in the agomelatine group than in the sertraline group, but not statistically significant.

Evaluator comments

The findings are consistent with previously-evaluated data regarding the relative effects of agomelatine and selective serotonin reuptake inhibitors (SSRIs) on sleep disturbance. However, the observed differences in *objective* circadian and sleep-wake parameters assessed by actigraphy led to only small, and generally non-significant, differences in patients' *subjective* assessments of their quality of sleep and daytime wakefulness assessed by the LSEQ and ESS.

Pharmacokinetics

PKH-066

PKH-066 was an open-label, two period, randomised crossover absolute bioavailability study in 24 healthy, non-smoking males aged 18-36 years. The study treatments were:

- a single agomelatine 25 mg tablet of the formulation proposed for registration, taken orally and
- an intravenous (IV) infusion of agomelatine 1 mg in 40 mL 5% glucose solution given over 1 hour.

The absolute bioavailability of agomelatine was 1.0% (90% CI 0.8-1.3%), based on the dose-adjusted geometric mean AUC ratio. This aspect of the study has been evaluated by the quality evaluator (Section II, Table 1).

Evaluator comments

The absolute bioavailability of about 1% is somewhat lower (in relative, although not absolute terms) than the figure of about 3% obtained from population pharmacokinetic modelling. It is consistent with previous results from Study PKH-012, in which 1% of the radioactive label was recovered as unchanged agomelatine and 99% as metabolites in the urine (81% of the total radioactivity) and faeces (19% of the total radioactivity) after an oral dose of 50 mg.

These data show that the low oral bioavailability of agomelatine is due to extensive first pass metabolism rather than poor absorption. The clinical relevance of this is that a relatively modest reduction in first pass metabolism (for example, due to liver impairment or inhibition of CYP 1A2/CYP2C9) could lead to a substantial increase in systemic exposure to agomelatine.

The other pharmacokinetic parameters in Study PKH-066 are consistent with previous data. Of particular note, given the proposed once daily dose schedule, is the very high clearance, the correspondingly short half life of around 1 hour, and the observation that plasma concentrations of agomelatine had dropped to below the limit of quantification (0.01 ng/mL) within 8 to 10 hours after the dose.

CL1-054

CL1-054 was a randomised, double-blind, 4×4 crossover study of single oral doses of agomelatine 50 mg, agomelatine 400 mg, moxifloxacin 400 mg and placebo in 60 healthy volunteers. The pharmacodynamic aspects of the study were discussed above. The main pharmacokinetic results are summarised in Table 2.

Table 2: CL1-054: Mean pharmacokinetic parameters of agomelatine after single oral doses of 50 mg and 400 mg.

	C_{max} (ng/mL)			T_{max} † (h)			AUC_{∞} (ng.h/mL)			$t_{1/2,z}$ (h)		
	M+F	M	F	M+F	M	F	M+F	M	F	M+F	M	F
50 mg	48	22	74	3.0	2.1	3.1	90	30	151	2.3	2.3	2.4
400 mg	815	436	1208	3.1	3.1	3.1	2868	1072	4728	2.0	2.2	1.8

† median; M = males; F = females; M+F = overall value for all subjects; N (50 mg) = 28M, 28F, 56M+F; N (400 mg) = 29M, 28F, 57M+F); T_{max} = time to maximal plasma concentration; $t_{1/2,z}$ = terminal half-life

The subjects were also genotyped for 5 Single Nucleotide Polymorphisms (SNPs): CYP1A2*1F, CYP2C9*2, CYP2C9*3, CYP2C19*2 and CYP2C19*3. Based on graphs of mean agomelatine plasma concentrations versus time and individual C_{max} and AUC by genotype, these SNPs did not appear to have an impact on agomelatine pharmacokinetics. However, a formal statistical analysis was not performed.

Evaluator comments

The results are consistent with data in the original submission. Agomelatine displayed markedly non-linear pharmacokinetics: an 8-fold increase in dose led to a 17-fold increase in C_{max} and a 32-fold increase in AUC_{∞}, with no change in the time to maximal plasma concentration (t_{max}) and terminal half life. This non-linearity is most likely due to saturation of first pass metabolism.

C_{max} and AUC_{∞} were considerably higher in females (3.4× and 5.0× the male values, respectively at the 50 mg therapeutic dose), but terminal half life did not differ between the sexes. These sex-related differences have been seen in previous studies, although the magnitude of the difference varies considerably (for example, in CLI-028, C_{max} and AUC_{∞} in females were 1.7× and 1.5× the male values after administration of agomelatine 50 mg for 7 days; in CL1-039, C_{max} and AUC_{∞} in females were 12.3× and 6.1× the male values after administration of a single dose of agomelatine 50 mg). The sponsor states that these sex-related differences in C_{max} and AUC are "mainly due to the inhibition effect of oral oestrogens on CYP1A2, the major cytochrome P450 involved in agomelatine metabolism". All of the female subjects in CL1-054 were using oral contraception (oestrogen or oestrogen-progestogen combination), as required by the study protocol. However, a gender effect on bioavailability has not been excluded. As noted in the sponsor's *Summary of Clinical Pharmacology Studies*, oral oestrogens were *not* used by one third of the women in the clinical pharmacology studies, but the overall number of women is too low to statistically separate a possible gender effect from the known oestrogen effect.

Efficacy

Pivotal studies

CL3-041

CL3-041 was a multicentre, randomised, double-blind, placebo-controlled withdrawal study to assess the efficacy of flexible dose agomelatine in the prevention of depressive relapse. The study included non-hospitalised patients, aged 18-65 years, with recurrent depression according to DSM-

IV-TR criteria for Major Depressive Disorder (MDD), of at least moderate severity, based on the following criteria:

- Hamilton 17-item depression scale (HAM-D) total score ≥ 22 at selection and inclusion (a decrease of ≤ 20% between selection and inclusion was permitted); *and*
- Sum of items 1, 2, 5, 6, 7, 8, 10 and 13 of the HAM-D ≥ 55% of the HAM-D total score at inclusion; *and*
- Clinical Global Impression severity of illness score ≥ 4 at selection and inclusion; *and*
- Depression sub-score of the Hospital Anxiety Depression Scale (HAD-D) ≥ 11 at selection.[12]

Details of the assessment scales are provided as footnotes but briefly:

- The HAM-D is a standard depression rating scale that is recommended for the assessment of eligibility and treatment response in antidepressant trials according to the TGA-adopted guideline on products used in the treatment of depression .[4] Patients are asked to respond to a set of questions covering various aspects of depression and a higher score indicates more severe depression.
- The CGI severity of illness score is the physician's assessment of the overall status of the patient's depression. A higher score indicates more severe depression.
- The CGI improvement score is the physician's assessment of the change in the severity of the patient's illness compared to baseline. Scores of 1-3 represent improvement, a score of 4 represents no change and scores of 5-7 represent worsening.
- The HAD-D is the patient's assessment of the severity of his/her depression. A higher score indicates more severe depression.
- The Sheehan Disability Scale measures the degree of disruption to the patient's work, social and family activities. Sheehan Disability score was not an entry criterion, but was measured at baseline and provides relevant information about the study population.

The index depressive episode was to have lasted at least 8 weeks at the time of inclusion. At the beginning of the index episode, patients were to have been free of depressive symptoms of their previous episode for at least 6 months. Of note in relation to the efficacy assessment, the trial excluded patients with any type of depression other than MDD: patients with treatment-resistant depression, patients with marked suicidal intent and/or known suicidal tendencies, and patients with coexisting psychiatric conditions (for example, psychosis, panic disorder, obsessive compulsive disorder [OCD], post-traumatic stress disorder [PTSD], etc).

An overview of the study schedule is shown in Figure 3.

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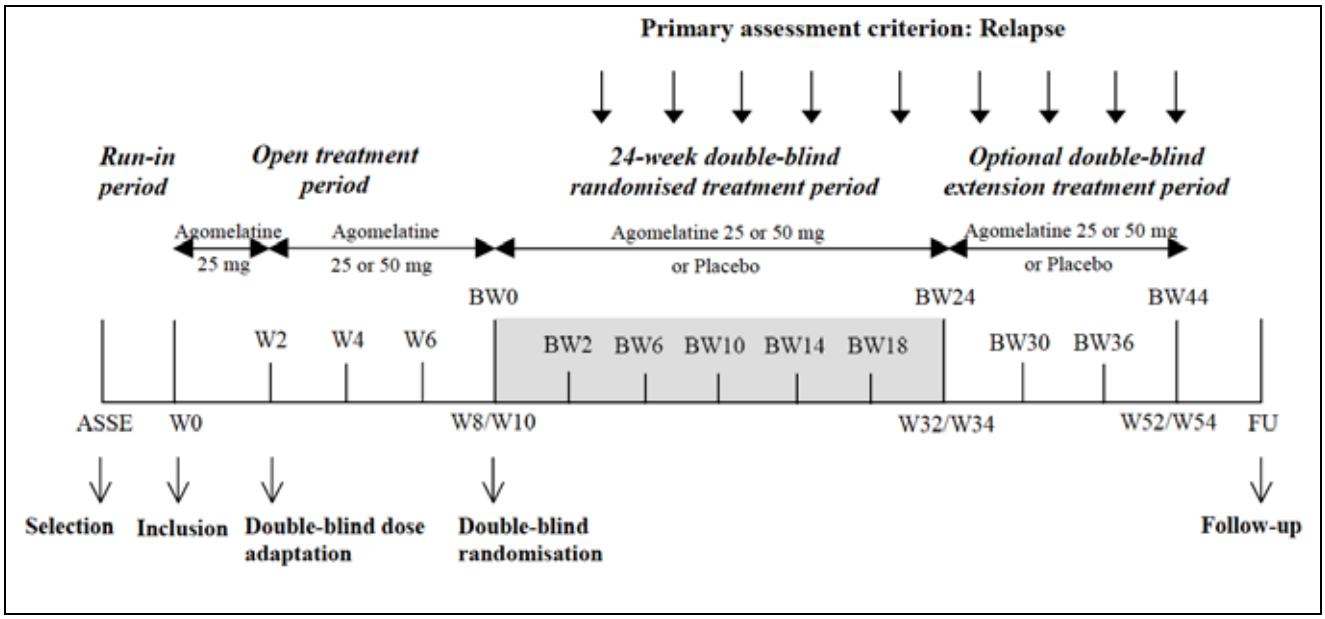
[12] Hospital Anxiety Depression scale (HAD-D): Fourteen questions are asked of the patient, half of them related to anxiety and the other half to depression. The answers are rated using 4-point scales from 0 to 3, 0 corresponding to the patient's best feeling and 3 to the worst one. For both sub-scores, anxiety (HAD-A) or depression (HAD-D), patients were classified in the following categories:
- ≥ 11: presence of anxiety/depression.
- 7 to 10: doubtful anxiety/depression.
- < 7: absence of anxiety/depression.

The HAD was self-assessed by the patient at the selection visit. The requirement of a HAD-D sub-score ≥ 11 at selection was added to the selection criteria by Protocol Amendment No. 3, in order to include patients considered depressed not only by the investigator, but by themselves as well.

Figure 3: CL3-041: Study schedule.



After selection, patients started a one week treatment-free run in. At the end of this period, patients who fulfilled the entry criteria ('included patients') commenced treatment with open-label agomelatine 25 mg once daily in the evening. The dose was increased to 50 mg if improvement after 2 weeks was deemed insufficient based on predefined criteria. The dose increase was performed in a blinded manner via an interactive voice response system (IVRS). The adjustment criteria, and whether or not the dose was adjusted, were not disclosed to the investigator or patient.

After 8 weeks of open-label agomelatine treatment, patients who had responded (defined as HAM-D ≤10 *and* CGI global improvement score = 1 or 2) were randomised to double-blind treatment with either the same dose of agomelatine or placebo. Patients who had not responded at W8 were allowed to continue for a further 2 weeks on open-label agomelatine, at which point they were randomised if they had responded or withdrawn from the study if they had not.

Assessment visits during the first double-blind treatment period were scheduled at 0, 2, 6, 10, 14, 18 and 24 weeks. Double-blind treatment was continued for 24 weeks, or until the occurrence of a depressive relapse, or until the patient withdrew due to other reasons. Patients who completed the 24-week double-blind treatment period were offered an optional 20-week double-blind extension, during which they continued their blinded treatment. Assessments during the extension were performed at Weeks 24, 36 and 44 after the original randomisation. A final follow-up visit was scheduled for 2 weeks after treatment discontinuation regardless of when this occurred.

Evaluator comments

This type of randomised, placebo-controlled withdrawal study is a standard method of assessing the ability of candidate drugs to prevent the relapse of depression during maintenance therapy, as recommended in the TGA-adopted guidance document.[4]

The study used appropriate methods to determine eligibility, corresponding to those used in previously-submitted agomelatine trials. Other noteworthy points regarding the eligibility criteria are:

- The HAM-D, CGI-S and HAD-D inclusion criteria correspond to at least moderate depression.
- The trial excluded patients at the most severe end of the depression spectrum (those needing hospitalisation, with psychotic features, refractory to previous treatments or exhibiting

suicidality), as well as patients whose depression was complicated by other psychiatric conditions. Accordingly, the results should not be generalised to such patients.

- The trial excluded patients with baseline gamma glutamyltransferase (GGT), alanine transaminase (ALT) or aspartate transaminase (AST) >3× the upper limit of normal (ULN). This has implications for the generalisability of the hepatic safety data.

CL3-041 used essentially the same design as Study CL3-021 in the original submission, except that CL3-021 used a fixed dose of agomelatine 25 mg, whereas CL3-041 included a dose titration step at Week 2 of the open-label period. This feature of CL3-041 allowed for dose adjustment in a blinded fashion according to defined criteria, and thus the potential for improved efficacy. A corollary of this is that the results of CL3-041 reflect the efficacy and safety of a treatment schedule that includes dose adjustment using these criteria, rather than the efficacy of a particular dose (25 mg or 50 mg), or the efficacy of a schedule based on *different* dose adjustment criteria. This has implications for the generalisability of the findings.

Efficacy outcomes

Primary efficacy endpoint

The primary efficacy endpoint was the time to depressive relapse during the double-blind treatment period, defined as the time between the date of the first randomised treatment administration and the date of the relapse (or censoring). Depressive relapse was defined as any one of the following events:

- HAM-D total score ≥16; *or*
- Any withdrawal for lack of efficacy during the double-blind period, according to the clinical opinion of the investigator, which was to be based on the evolution of both HAM-D and CGI scores; *or*
- Any suicide or suicide attempt.

All relapse cases were reviewed by a blinded, independent expert committee to confirm or invalidate the diagnosis of relapse.

Secondary efficacy endpoints

Secondary efficacy endpoints during the open-label treatment period were:

- Change in HAM-D total score from inclusion.
- HAM-D treatment response (defined as a ≥50% decrease from HAM-D total score at inclusion).
- Change in CGI severity of illness score from inclusion.
- CGI global improvement score (assessed relative to patient's condition at inclusion).
- CGI response, defined as a CGI global improvement score of 1 or 2.

Secondary efficacy endpoints during the randomised treatment period were:

- Change in HAM-D total score from randomisation.
- CGI global improvement score (assessed relative to the randomisation).

Evaluator comments

The primary efficacy endpoint is acceptable and consistent with primary endpoint definitions in relapse-prevention trials of other antidepressants.

Statistical methods

The primary endpoint of time from randomisation to depressive relapse was compared between agomelatine and placebo groups using a log-rank test stratified for centre type (centres managed by psychiatrists or by GPs) and randomisation visit (W8 or W10), based on the Full Analysis Set (FAS). In order to estimate the hazard ratio of relapse on agomelatine as compared to placebo, a Cox model associated with the likelihood ratio test was performed in the FAS, with adjustment for centre type and randomisation visit. The FAS was defined as all randomised patients who took at least one dose of study randomised treatment and had at least one post-randomisation visit or contact during the double-blind period. Results were presented for the initial 24-week randomised period and for the combined randomised periods (that is, initial 24-week plus optional 20 week extension). In the latter analysis, patients who elected not to continue into the extension were censored at the end of the initial 24-week period.

Sensitivity analyses of the primary endpoint included: (a) estimation of the hazard ratio of relapse on agomelatine compared to placebo using a Cox model with adjustment for HAM-D 17-item total score at inclusion in addition to centre type and randomisation visit, and (b) analysis using a non-stratified log-rank test and an unadjusted Cox model. Two subsets of the FAS were defined to examine questions of clinical interest: The Sub-FAS psychiatrists (defined as patients of the FAS followed by a psychiatrist) and the Sub-FAS with W0 HAM-D total score ≥ 25.

The planned sample size of 316 randomised patients was anticipated to provide 90% power to demonstrate a statistically significant difference between placebo and agomelatine during the initial 24-week randomised treatment period, using a two-sided log-rank test at 5% type I error, assuming relapse rates of 30% and 15% over 24 weeks in the placebo and agomelatine groups, respectively. To provide the requisite number of randomised patients, a sample size of 500 patients was planned for inclusion in the open label phase (assuming 35% withdrawal prior to randomisation, predominantly due to insufficient efficacy).

Evaluator comments

The statistical methods are acceptable. The definition of the FAS is in accordance with the intention-to-treat principle and the TGA-adopted guideline on statistical principles for clinical trials.[13] The log-rank test examines the statistical significance of the treatment effect but does not provide an estimate of the effect size. The Cox model provides an estimate of effect size, but assumes a constant proportional hazard throughout the post-randomisation follow-up period. The study design means that this assumption is expected to have been met during the initial 24-week randomised treatment period and the optional 20-week extension.

Patient disposition and characteristics

A total of 594 patients were screened, 565 were selected, and 492 were included in the open-label period. Among the 471 included patients continuing in the study after the W2 visit, 109 (23.1%) had a dose increase to 50 mg. The most common reason for withdrawal prior to randomisation was lack of efficacy (99 patients [20.1%]). A total of 339 patients (68.9% of the included patients) responded to open-label agomelatine and entered the double-blind period, 251 patients at W8 and 88 at W10; 165 responders were randomised to continue agomelatine and 174 were switched to placebo. Among the agomelatine-treated patients, 141 (85.5%) received the 25 mg dose during the first randomised period and 24 (14.5%) received 50 mg.

A total of 206 patients (60.8%) completed the first 24-week double-blind period and were eligible to enter the optional 20-week extension: 115 patients (69.7%) in the agomelatine group, and 91 patients (52.3%) in the placebo group. 190 patients chose to enter the extension (106 agomelatine,

[13] EMEA, Committee for Proprietary Medicinal Products (CHMP). Note for Guidance on Statistical Principles for Clinical Trials, CPMP/ICH/363/96 . http://www.tga.gov.au/docs/pdf/euguide/ich/036396en.pdf

84 placebo), of whom 159 (95 agomelatine, 64 placebo) completed the full 44 weeks of randomised treatment.

Patients entering the open label phase were predominantly female (71%) with a mean age of 43 years. About half of the patients fulfilled DSM-IV-TR criteria for moderate MDD and half had a diagnosis of severe MDD without psychotic features; 54% had melancholic features. All patients had recurrent depression with a mean duration of 11.4 years, an average of 3.7 depressive episodes per patient and the current episode lasting 1-32 (mean 5.1) months. At inclusion, the mean HAM-D total score was 27.0. About three quarters of the patients (74%) had a total score of 25 or more. The mean CGI severity of illness score at inclusion was 4.9. Mean Sheehan Disability scores were 7.1 (work), 7.6 (social life) and 7.4 (family life).

There were no meaningful baseline differences between patients entering the open-label phase and those who responded to agomelatine and went on to randomisation. In the randomised population, the agomelatine and placebo groups were comparable in respect of demographics and MDD characteristics at inclusion. The two treatment groups were also comparable in respect of Sheehan Disability scores at inclusion, HAM-D scores at inclusion and randomisation, CGI severity of illness scores at inclusion and randomisation, and CGI global improvement scores at Week 2 of open-label treatment (W2) and randomisation. There were some differences between the agomelatine and placebo groups in respect of concomitant treatments that had been used during the open-label period. Patients randomised to agomelatine were more likely than those randomised to placebo to have used psychotropic medication (11% versus 5%, usually a benzodiazepine), and less likely to have used an analgesic (17% versus 28%) or an anti-inflammatory agent (12% versus 21%). These differences did not persist during the double-blind period.

Evaluator comments

The randomised treatment groups were comparable in respect of most characteristics. There were some differences between the agomelatine and placebo groups in respect of the use of benzodiazepines, analgesics and anti-inflammatory agents during the preceding open-label period, but these did not persist after randomisation and are not expected to have affected the efficacy results of the randomised phase.

As is often the case in drug trials, the patients in CL3-041 were not entirely representative of those who are likely to be treated with agomelatine if it is approved for registration. Of note, the study excluded patients with mild and non-recurrent depression as well as the most severely ill patients. It also excluded patients with some depression subtypes that fall under the classic ‘organic’ category, namely bipolar depression and psychotic depression. On the other hand, the study did include patients with melancholic depression. Of relevance to the safety findings, the study also excluded certain patients in whom agomelatine use could present a hazard (notably those with elevated hepatic transaminases). These aspects of the study reduce the generalisability of its findings, but no more so than the studies in the original submission.

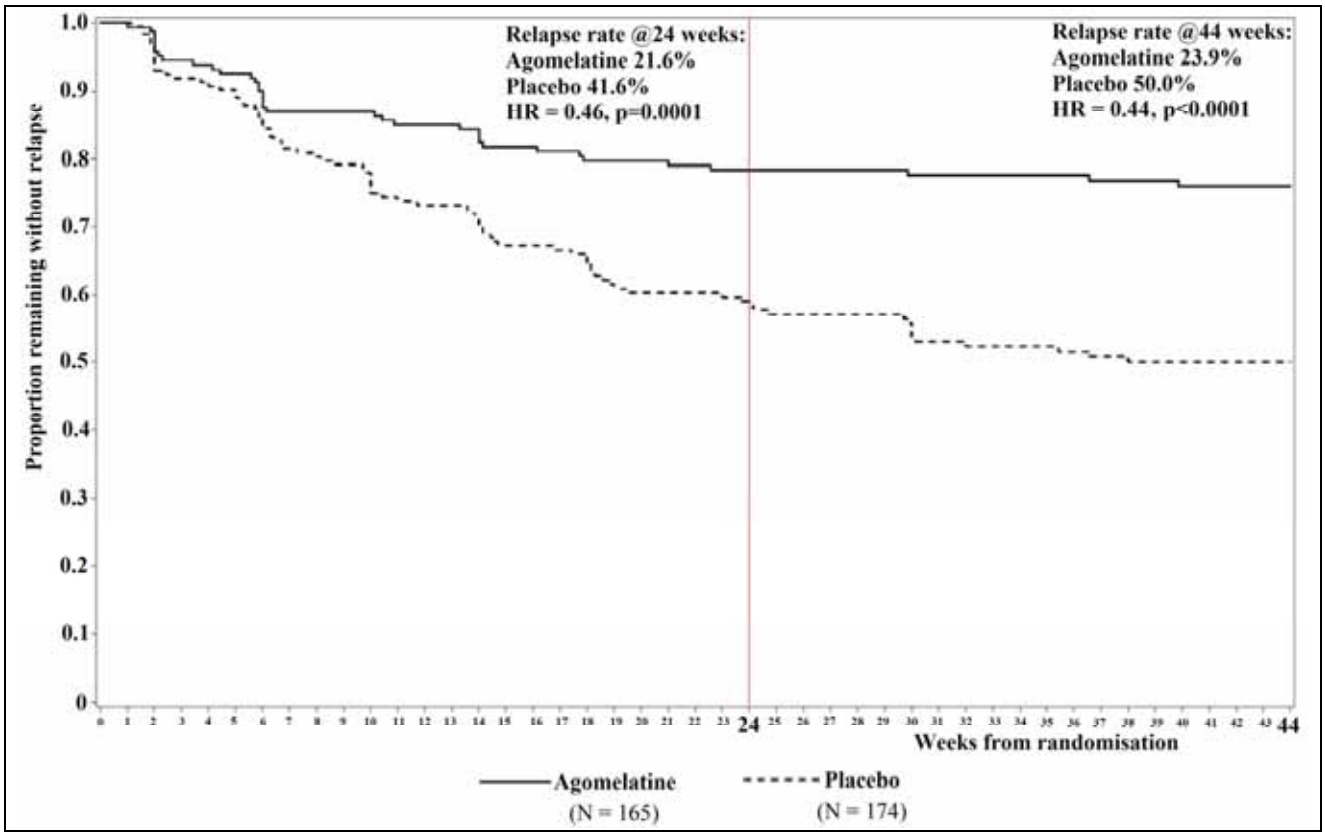
The lack of baseline differences between patients entering the open-label phase and those who responded to agomelatine indicates that patient or disease characteristics are unlikely to aid clinicians in predicting whether or not an individual with MDD will respond to agomelatine. Also noteworthy, in view of the previously-identified inadequacy of long-term safety data for the 50 mg dose, is the finding that about 15% of responders were taking the 50 mg dose.

Primary efficacy results

As shown in Figure 4, the time to depressive relapse was significantly prolonged in the agomelatine group compared to the placebo group (24-week analysis: log-rank p=0.0001, adjusted hazard ratio 0.46 [95% CI 0.31, 0.65], relative hazard reduction 54% [95% CI 35%, 69%]; 44-week analysis: log-rank p<0.0001; adjusted hazard ratio 0.44 [95% CI 0.30, 0.64]; relative hazard reduction 56% [95% CI 36%, 70%]). Over 24 weeks, the Kaplan-Meier (K-M) estimate of the proportion of

patients experiencing a depressive relapse was 21.6% in the agomelatine group, compared to 41.6% in the placebo group. Over 44 weeks, the corresponding proportions were 23.9% and 50.0%.

Figure 4: CL3-041: K-M curves of the proportion of patients with depressive relapse.



The results of the primary statistical analysis were supported by those of the secondary analyses at both 24 and 44 weeks. During the initial 24 week randomised period, the percentage of patients who withdrew due to lack of efficacy was 23% amongst those who were taking agomelatine 25 mg daily, and 17% amongst those who were taking agomelatine 50 mg daily. During the subsequent 20 week optional extension period, the percentage of patients who withdrew due to lack of efficacy was 4% amongst those who were taking agomelatine 25 mg daily, and 7% amongst those who were taking agomelatine 50 mg daily.

The effect of agomelatine on the relapse rate in the subset of patients treated by psychiatrists (62.4% relative reduction at Week 24 and 66.6% relative reduction at Week 44) was larger than in the overall study population. In the subset of patients with HAM-D total score ≥25 at inclusion, the effect of agomelatine on the relapse rate (56.8% relative reduction at Week 24 and 58.6% relative reduction at Week 44) was similar to that that seen in the overall study population.

Evaluator comments

In patients with MDD who responded to an 8 to 10 week course of agomelatine 25 to 50 mg once daily, maintenance treatment at the same dose produced a statistically significant and clinically meaningful reduction in the risk of depressive relapse, with the benefit continuing for at least 44 weeks (1 year after the start of treatment).

The results contrast with those of CL3-021 in the original submission. In that study, a fixed dose of agomelatine 25 mg once daily failed to produce a significant reduction in relapse rates over 26 or 44 weeks in patients who had responded to an initial 8 week course of treatment. The most obvious reason for the differing conclusions of the two studies is an unexpectedly low relapse rate in the placebo group in the negative study. In the positive study (CL3-041) the K-M estimate of the

relapse rate over 24 weeks was 22% for agomelatine and 42% for placebo. These relapse rates are comparable to the rates of 20-28% for duloxetine, fluoxetine, venlafaxine and mirtazapine, and 38-56% for placebo, in published placebo-controlled relapse-prevention studies of other antidepressants, cited in the sponsor's *Clinical Overview*. However, in the negative study (CL3-21) while the K-M estimate of the relapse rate over 26 weeks was in the expected range for agomelatine (26%), it was much lower than expected in the placebo group (23%). The cause of the unexpectedly high placebo effect in CL3-021 is unknown.

Other efficacy results

Results for the secondary efficacy endpoints are shown in

Table 3.

Table 3: CL3-041: Secondary efficacy results in the FAS.

Efficacy endpoint	**Time point**	**Agomelatine** (N=165*)	**Placebo** (N=174)
HAM-D total score	Randomisation (BW0)	6.1 ± 2.6	6.0 ± 2.7
	Last post-randomisation value up to BW24	7.5 ± 7.0	10.6 ± 8.4
	Change from BW0 to last post-rand. value up to BW24	1.4 ± 6.9	4.7 ± 8.4
	Last post-randomisation value up to Week 44	7.8 ± 7.4	11.5 ± 8.6
	Change from BW0 to last post-rand. value up to BW44	1.7 ± 7.4	5.5 ± 8.5
CGI severity of illness score	Randomisation (BW0)	1.8 ± 0.8	1.8 ± 0.7
	Last post-randomisation value up to BW24	2.1 ± 1.2	2.6 ± 1.5
	Last post-randomisation value up to BW44	2.1 ± 1.3	2.7 ± 1.5
CGI global improvement score	Last post-randomisation value up to BW24	3.8 ± 1.6	4.4 ± 1.7
	Last post-randomisation value up to BW44	3.7 ± 1.7	4.5 ± 1.8

* N=163 for post-randomisation values, because 2 agomelatine patients were prematurely withdrawn at week 2 post-randomisation (BW02) without HAM-D assessment.

Evaluator comments

The results for the secondary efficacy endpoints were consistent with those for the primary endpoint. The mean HAM-D total score worsened in both treatment groups between randomisation and the final assessment, but the change was numerically less in the agomelatine group (no statistical test was performed). A corresponding pattern was seen for mean CGI severity of illness CGI improvement scores.

No information was provided regarding changes in the various domains of the HAM-D, either during the open-label phase or the randomised phase. Accordingly, this study does not address the issue, raised in the original evaluation, that agomelatine seems to act primarily to improve the sleep of patients with MDD, with less effect on other aspects of the condition.

In its pre-ADEC submission, however, the sponsor indicated that statistically and clinically significant effects were shown in favour of agomelatine compared to placebo on both the HAM-D total score and the HAM-D score without the sleep items, either over six months or ten months.

Other studies

CL3-046

CL3-046 was a multicentre, randomised, double-blind, parallel group, 6-week study with an optional 18 week extension that compared agomelatine 25 to 50 mg versus sertraline 50 to 100 mg daily in patients with MDD. The study design, subject characteristics and results for the primary circadian-rhythm and sleep-wake-related endpoints have been discussed above. Assessment of antidepressant efficacy was a secondary objective of the study. Antidepressant efficacy was assessed based on changes from inclusion to the final visit in the HAM-D and CGI severity of illness scores, and the CGI improvement score at the final visit. The effect of study treatment on anxiety symptoms was also assessed via the change from inclusion to the final visit in the HAM-A score. The study was designed and analysed as a superiority trial, with no adjustment of p-values for the multiple efficacy endpoints (since they were all secondary endpoints). Formal statistical comparison of the agomelatine and sertraline treatment groups was only performed for the initial 6-week randomised treatment period and not for the 18-week extension.

A total of 372 patients were screened and 367 were selected for the study. Of these, 314 patients were included and 313 patients were randomised to agomelatine (N=154) or sertraline (N=159). 262 patients completed the initial 6 week period (133 agomelatine, 114 sertraline), of whom 230 continued into the 18-week extension (116 agomelatine, 114 sertraline). A total of 188 patients completed the 18 week extension (97 agomelatine, 91 sertraline).

The agomelatine group had a slightly higher percentage of females than the sertraline group (73.4% versus 67.9%) and a slightly lower (better) mean baseline HAM-D total score (26.1 versus 26.5). Otherwise, the baseline characteristics of the two groups were comparable. A similar baseline pattern was seen in the FAS, which included 307 patients (150 agomelatine, 157 sertraline), of whom 224 (114 agomelatine, 110 sertraline) continued into the 18-week extension period.

Efficacy results

Regarding short-term antidepressant efficacy in the FAS (W0 to W6):

- The mean values of the HAM-D total score decreased at each visit in both groups from W0 to W6. The mean decrease of the HAM-D total score from baseline to the last post-baseline value was significantly greater in the agomelatine group than in the sertraline group (-15.8 ± 7.3 and -14.4 ± 8.7, respectively) with an estimated between-group adjusted difference of 1.68 (95% CI [0.15, 3.20], p = 0.031).
- The percentage of responders (HAM-D total score reduction ≥50%) was numerically higher in the agomelatine group at each post-baseline visit, but the difference was not statistically significant at the final visit in the W0-W6 period, nor at any of the intermediate visits except W2.
- The percentage of patients in remission (HAM-D total score <7) increased at each visit from W0 to W6 in both groups. At the last post-baseline visit during W0 to W6, the percentage of patients in remission was slightly higher in the agomelatine group (32.7% of patients) than in the sertraline group (28.8%), but the difference was not statistically significant.
- Agomelatine was statistically significantly superior to sertraline in respect of the last post-baseline value (to W6) of the CGI severity of illness score (2.5 ± 1.1 versus 2.8 ± 1.3, p=0.043), and the CGI global improvement score (1.8 ± 1.0 versus 2.1 ± 1.2, p=0.023).

Regarding medium-term efficacy (up to W24 of the study, that is, W18 of the optional extension):

- In the FAS, the mean decrease in HAM-D total score from baseline to the last post-baseline value was a bit larger in the agomelatine group than in the sertraline group (-17.7 ± 8.4 versus -16.4 ± 10.3). In the subset of the FAS who continued into the extension period, the improvement from baseline was similar in the agomelatine group (-20.5 ± 6.3 versus -21.4 ± 7.2).

- In the FAS, the mean last post-baseline CGI severity score was a little better in the agomelatine group than in the sertraline group (2.1 ± 1.3 versus 2.4 ± 1.6). In the subset of the FAS who continued into the extension period, the last post-baseline value of the CGI severity score did not differ between the two groups. A similar pattern was observed for the CGI improvement score.

Evaluator comments

CL3-46 is regarded as non-pivotal because the assessment of antidepressant efficacy was only a secondary objective of the study. During the first 6 weeks of treatment, the antidepressant effect of agomelatine was statistically superior to that of sertraline in terms of the HAM-D total score, CGI severity of illness score and CGI improvement score. However the mean between-group differences were relatively modest and of uncertain clinical relevance. Furthermore, these were only secondary endpoints in the trial so they should be regarded as exploratory only.

The optional 18-week extension provides limited efficacy information because a formal statistical comparison of the agomelatine and sertraline groups was not performed (nor was the study powered to allow such a comparison). In any case, only those subjects who were much improved after the initial 6 week period were allowed to continue into the extension, which would tend to obscure any differences between the two treatments in respect of efficacy over the full 24-week period. Accordingly, the data and analyses do not allow a conclusion as to whether a possible short-term efficacy advantage of agomelatine over sertraline persists beyond the initial 6 weeks.

It is worth noting that in this trial about 25% of the agomelatine responders were titrated to the 50 mg dose. This supports the previously-expressed TGA view that an adequate demonstration of long-term safety at the 50 mg dose is necessary for the registration of agomelatine. Another corollary of this finding is that if approval of the submission is granted, the sponsor should be encouraged to develop a 50 mg tablet strength to cater for the significant proportion of patients who will need to take that dose. Having to take it as two 25 mg tablets will be inconvenient and may be unnecessarily expensive for those patients.

Conclusions regarding efficacy

In the opinion of the clinical evaluator, the studies in the current submission provided no new placebo-controlled data regarding the short-term efficacy of agomelatine. Accordingly, in regard to the question of whether agomelatine is, or is not, meaningfully superior to placebo in the treatment of MDD, the situation is unchanged from the original submission: the efficacy of agomelatine is statistically significant compared to placebo but of doubtful clinical relevance.

Study CL3-041 shows that in patients who have an initial satisfactory response to agomelatine 25/50 mg, continuation of agomelatine at the same dose significantly prolongs that response. This would be an adequate demonstration of long-term efficacy, provided short-term efficacy had been clearly demonstrated in placebo-controlled trials, but as explained above that is not the case.

Overall, the clinical evaluator considered that the submitted studies still do not clearly show that agomelatine has adequate (clinically meaningful) efficacy in the treatment of MDD.

Safety

Safety analyses incorporating data from multiple studies

Introduction

As regards an overall summary of the safety data, the submission contained five potentially relevant documents. However, none of these provided a detailed, complete overview of the information available to date. The sponsor's five documents are: the *Clinical Overview*, the *Summary of Clinical Safety,* an update to the *Summary of Clinical Safety,* an *Integrated Analysis of Safety* and the *Risk Management Plan*.

Of these, the *Clinical Overview* and the *Summary of Clinical Safety* report the same dataset, based on a cut-off date for completed studies of 31 March 2007. The dataset includes 5260 patients exposed to agomelatine: 522 in Phase I studies, 3956 in Phase II/III MDD studies, and 792 in studies of other indications.[14] It also includes 826 patients exposed to placebo and 1040 exposed to active controls in Phase II/III MDD studies. The *Clinical Overview* and the *Summary of Clinical Safety* provide comprehensive safety overviews that include summaries and analyses of a broad range of safety-related matters covering adverse events (frequency, causality, temporal pattern, necessity of dose reduction or treatment cessation, analysis by organ system or syndrome and events of particular interest), laboratory parameters and vital signs. However, the dataset in the *Clinical Overview* and the *Summary of Clinical Safety* does not include two of the main studies in the current submission - CL3-046 and the 20-week optional extension of CL3-041. The *Integrated Analysis of Safety* contained only supporting information, notably the analytical methods and patient narratives pertinent to the *Summary of Clinical Safety*.

The document titled *2.7.2.B Summary of Clinical Safety* is an update to the *Summary of Clinical Safety* that consists only of a review, requested by the CHMP, of all cases of transaminase elevations >3×ULN in the agomelatine and placebo groups in clinical trials. This review was based on a total of 4033 agomelatine and 969 placebo recipients, which does not correspond to any of the safety datasets in the *Clinical Overview*, *Summary of Clinical Safety* or *Risk Management Plan*, but presumably reflects the number of patients with available data at the time the response to the CHMP request was prepared. Information from this review was included in the *Risk Management Plan.*

The *Risk Management Plan* refers to a later safety dataset, with a cut-off date of 31 December 2007. The dataset comprises 5468 patients exposed to agomelatine: 578 in Phase I studies, 4108 in Phase II/III MDD studies, and 782 in studies of other indications. It includes CL3-046 and the 20-week optional extension of CL3-041. However, the presentation of information in the *Risk Management Plan* is limited to specific areas of risk identified by the sponsor, and does not include the comprehensive information and analyses that are provided in the *Clinical Overview* and the *Summary of Clinical Safety*.

Summary of Data

Safety datasets and duration of exposure

The *Summary of Clinical Safety* (and the *Clinical Overview*) provided summary data for several overlapping datasets:

- The Overall Safety Set included all 6931 patients from completed Phase II/III studies up to the cut-off date, irrespective of indication, agomelatine dose or treatment duration. It included 4783 patients who had taken agomelatine (3089 at 25 mg, 827 at 50 mg and 822 at other doses), 1153 patients who had taken placebo, and 1040 patients who had taken an active comparator (fluoxetine, paroxetine or venlafaxine). In this set, the mean agomelatine treatment duration was 4.2 months, and the total exposure to agomelatine was 20010 patient-months (PM). This set excluded data from the Phase I pharmacology trials (mostly single-dose).
- The All MDD Set included all patients from placebo controlled, active controlled and open-label efficacy/safety studies in MDD. The total exposure duration on agomelatine was 17887 PM, which was respectively 7.2, 14.9, 11.6 and 13.5 times higher than on placebo, fluoxetine, paroxetine and venlafaxine. The mean treatment duration in the 3640 patients who received the proposed therapeutic doses of agomelatine 25 or 50 mg was 4.8 and 4.5 months, respectively

[14]. For comparison, the *Summary of Clinical Safety* in the original Australian submission (which formed the basis for the safety section of the original clinical evaluation report) included 3952 patients exposed to agomelatine, of whom 2757 were in Phase II/III MDD studies. That summary was evidently not updated when the sponsor submitted additional studies as supplementary data in the same submission.

(total 17385.5 PM; 14717 PM at 25 mg; 2669 PM at 50 mg). The breakdown of exposure by duration within the 'All MDD set' is shown in Table 4:

Table 4: Patients included in the Summary of Clinical Safety

	All exposed individuals[1]	All exposed patients (Overall safety set)	All exposed depressed[2] patients (all MDD set)			
	agomelatine	agomelatine		agomelatine	placebo	active control[4]
All periods	5260	4738[3]	all periods	3956	826	1040
			for 5 months	1704	293	565
			for 6 months[5]	1030	68	164
			for 1 year[6]	400	-	-

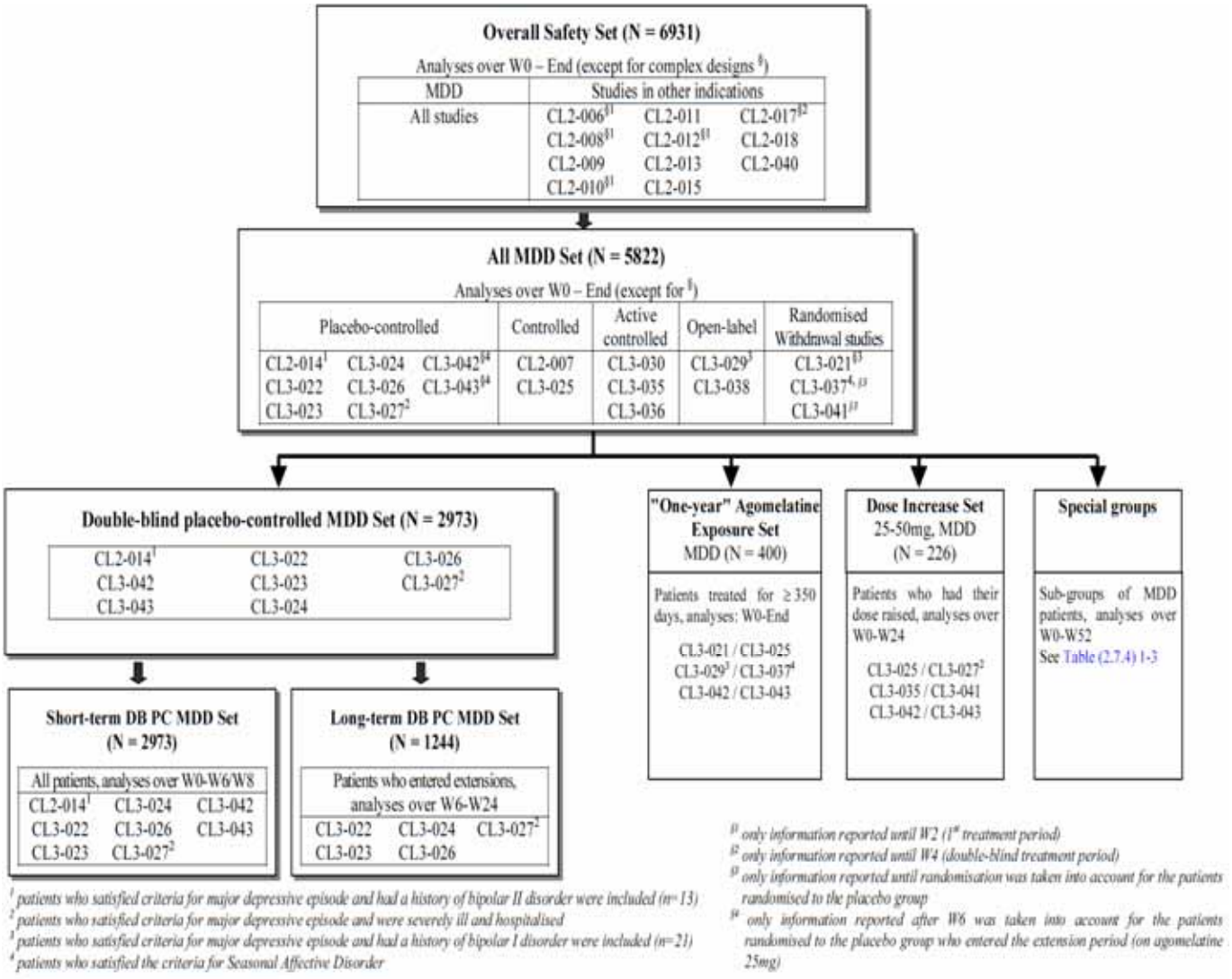
1. Including healthy and patient volunteers in Phase I studies.
2. Patients with MDD in the framework of Unipolar disorder except 13 patients with Bipolar II (CL2-014), 21 patients with Bipolar I (CL3-029) depressive disorders and 355 patients with Seasonal Affective Disorder (CL3-037).
3. 9 children with Smith-Magenis Syndrome exposed to agomelatine and 33 patients in cross-over studies who did not receive agomelatine in the first treatment period were not taken into account.
4. Fluoxetine, paroxetine or venlafaxine.
5. Exposed for at least 175 days.
6. 'One-year Agomelatine Exposure Set', exposed for ≥350 days (to include a number of patients who ceased agomelatine just prior to 12 months due to the study design). Does not include patients from CL3-041.

- The One-year Agomelatine MDD Exposure Set included 400 patients from the 'All MDD Set' who were treated with agomelatine 25 mg (N=368) or 50 mg (N=32) for ≥350 days. The mean exposure duration in this set was 393 days (range 350-583 days; total exposure 4786 PM at 25 mg, 383 PM at 50 mg). This set represents the safety data pertaining to treatment with agomelatine for 12 months, noting that the TGA-adopted guideline on long-term treatment recommends that 300-600 patients should be studied for ≥6 months and at least 100 for ≥12 months.[15] It does not include one-year data from CL3-041.
- The Short-term DB PC MDD Set included data from all double-blind placebo- (±active) controlled trials of 6-8 weeks duration. It is most useful for assessing early-onset EAEs and EADRs in patients taking agomelatine 25/50 mg (N=1120 for a mean of 5.8 weeks) compared to placebo (N=998; 5.8 weeks), and to a lesser extent fluoxetine (N=284; 5.8 weeks) and paroxetine (N=283; 6.5 weeks).
- The Long-term DB PC MDD Set (which really covers only medium-term treatment) includes patients from the Short-term DB PC MDD Set who continued into trial extensions of up to 6 months. This set included 511 patients treated with agomelatine 25/50 mg for a mean 4.9 months (about 21 weeks), 406 treated with placebo, 22 fluoxetine and 105 paroxetine.
- The DB PC MDD Set combines data from the above two sets.

[15] European Commission, pp. 121-125 of Rules 1998 (3C) – 3CC5A, November 1994. The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions. http://www.tga.gov.au/docs/pdf/euguide/vol3c/3cc5aen.pdf

Figure 5: lists the studies from which the above datasets were derived.

Figure 5: *Summary of Clinical Safety*: Studies contributing to the safety datasets.



The updated Overall Safety Set referenced in the *Risk Management Plan* comprised 4890 patients who received agomelatine, 1153 placebo and 1199 active control. The updated All MDD Set in the *Risk Management Plan* included 4108 patients who received agomelatine (number exposed to placebo and active comparators not stated). The updated One-year Agomelatine MDD Exposure Set in the *Risk Management Plan* included 499 patients treated with agomelatine 25 or 50 mg (total 6,368 PM; a breakdown by dose of the number of patients or cumulative exposure was not provided). As previously noted, although these updated safety sets are referred to in the *Risk Management Plan*, no systematic analysis of the safety data in these updated sets was provided.

Demographic and other baseline characteristics in the Overall Safety Set, All MDD Set, DB PC MDD Set and the Short-term DB PC Set were similar in the four sets, and were comparable in the agomelatine, placebo and active treatment groups of the Short-term DB PC Set.

Emergent adverse events (EAEs)

EAEs reported in ≥1% of patients during short-term treatment of MDD with agomelatine 25/50 mg are summarised in Table 5. Overall, 52.8% of patients taking agomelatine 25/50 mg for up to 6-8 weeks had at least one EAE, which was similar to the frequency in the placebo group (51.7%) and the fluoxetine group (49.3%) but lower than in the paroxetine group (67.5%). The most common EAEs in the agomelatine group (incidence ≥2%) were headache (14.1%), nausea (7.7%), dizziness (5.5%), dry mouth (3.5%), diarrhoea (3.1%) and somnolence (2.9%). Dizziness, somnolence,

diarrhoea, fatigue and upper abdominal pain were noticeably more common with agomelatine than placebo. In the agomelatine group, the first report of most EAEs was within the initial 2 weeks of treatment, except for influenza, for which the first report was most commonly made 2 to 4 weeks after the start of treatment (Table 6). During short-term treatment of MDD, there was a clear relationship between agomelatine dose and the incidence of EAEs, which were reported by 49.9% of patients who took agomelatine 25 mg and 63.8% of patients who took agomelatine 50 mg.

Table 5: *Summary of Clinical Safety*: EAEs with incidence ≥1% in the agomelatine 25/50 mg treatment group of the Short-term DB PC MDD Set.

System Organ Class Preferred term	agomelatine 25/50mg N=1120 PM=1486.1			placebo N=998 PM=1337.6			fluoxetine 20mg N=284 PM=377			paroxetine 20mg N=283 PM=422.6		
	n	%	pm	n	%	pm	n	%	pm	n	%	pm
All	**591**	**52.8**	**39.77**	**516**	**51.7**	**38.58**	**140**	**49.3**	**37.14**	**191**	**67.5**	**45.20**
Nervous system disorders	**277**	**24.7**	**18.64**	**215**	**21.5**	**16.07**	**58**	**20.4**	**15.38**	**77**	**27.2**	**18.22**
Headache	158	14.1	10.63	141	14.1	10.54	34	12.0	9.02	38	13.4	8.99
Dizziness	61	5.5	4.10	31	3.1	2.32	8	2.8	2.12	10	3.5	2.37
Somnolence	32	2.9	2.15	23	2.3	1.72	10	3.5	2.65	21	7.4	4.97
Migraine	13	1.2	0.87	4	0.4	0.30	2	0.7	0.53	1	0.4	0.24
Tremor	11	1.0	0.74	8	0.8	0.60	3	1.1	0.80	10	3.5	2.37
Gastrointestinal disorders	**217**	**19.4**	**14.60**	**186**	**18.6**	**13.91**	**67**	**23.6**	**17.77**	**88**	**31.1**	**20.82**
Nausea	86	7.7	5.79	71	7.1	5.31	20	7.0	5.31	45	15.9	10.65
Dry mouth	39	3.5	2.62	33	3.3	2.47	18	6.3	4.77	16	5.7	3.79
Diarrhoea	35	3.1	2.36	26	2.6	1.94	13	4.6	3.45	14	5.0	3.31
Abdominal pain upper	27	2.4	1.82	13	1.3	0.97	3	1.1	0.80	1	0.4	0.24
Constipation	20	1.8	1.35	21	2.1	1.57	4	1.4	1.06	5	1.8	1.18
Dyspepsia	14	1.3	0.94	11	1.1	0.82	4	1.4	1.06	2	0.7	0.47
Infections and infestations	**118**	**10.5**	**7.94**	**97**	**9.7**	**7.25**	**26**	**9.2**	**6.90**	**33**	**11.7**	**7.81**
Influenza	26	2.3	1.75	22	2.2	1.64	7	2.5	1.86	5	1.8	1.18
Nasopharyngitis	24	2.1	1.61	23	2.3	1.72	2	0.7	0.53	5	1.8	1.18
Psychiatric disorders	**117**	**10.5**	**7.87**	**88**	**8.8**	**6.58**	**27**	**9.5**	**7.16**	**44**	**15.6**	**10.41**
Insomnia	27	2.4	1.82	26	2.6	1.94	10	3.5	2.65	12	4.2	2.84
Anxiety	22	2.0	1.48	12	1.2	0.90	6	2.1	1.59	6	2.1	1.42
Depression	15	1.3	1.01	12	1.2	0.90	1	0.4	0.27	3	1.1	0.71
General disorders and administration site conditions	**64**	**5.7**	**4.31**	**56**	**5.6**	**4.19**	**10**	**3.5**	**2.65**	**24**	**8.5**	**5.68**
Fatigue	29	2.6	1.95	20	2.0	1.50	4	1.4	1.06	12	4.2	2.84
Skin and subcutaneous tissue disorders	**57**	**5.1**	**3.84**	**36**	**3.6**	**2.69**	**16**	**5.6**	**4.24**	**17**	**6.0**	**4.02**
Hyperhidrosis	15	1.3	1.01	7	0.7	0.52	8	2.8	2.12	8	2.8	1.89
Musculoskeletal and connective tissue disorders	**56**	**5.0**	**3.77**	**56**	**5.6**	**4.19**	**15**	**5.3**	**3.98**	**10**	**3.5**	**2.37**
Back pain	17	1.5	1.14	13	1.3	0.97	3	1.1	0.80	2	0.7	0.47
Investigations	**33**	**3.0**	**2.22**	**44**	**4.4**	**3.29**	**3**	**1.1**	**0.80**	**12**	**4.2**	**2.84**
Reproductive system and breast disorders	**26**	**2.3**	**1.75**	**17**	**1.7**	**1.27**	**6**	**2.1**	**1.59**	**13**	**4.6**	**3.08**
Metabolism and nutrition disorders	**21**	**1.9**	**1.41**	**23**	**2.3**	**1.72**	**6**	**2.1**	**1.59**	**6**	**2.1**	**1.42**
Eye disorders	**19**	**1.7**	**1.28**	**10**	**1.0**	**0.75**	**6**	**2.1**	**1.59**	**4**	**1.4**	**0.95**
Ear and labyrinth disorders	**17**	**1.5**	**1.14**	**17**	**1.7**	**1.27**	**11**	**3.9**	**2.92**	**4**	**1.4**	**0.95**
Vertigo	12	1.1	0.81	12	1.2	0.90	6	2.1	1.59	3	1.1	0.71
Respiratory, thoracic and mediastinal disorders	**16**	**1.4**	**1.08**	**21**	**2.1**	**1.57**	**7**	**2.5**	**1.86**	**6**	**2.1**	**1.42**
Renal and urinary disorders	**15**	**1.3**	**1.01**	**12**	**1.2**	**0.90**	**6**	**2.1**	**1.59**	**1**	**0.4**	**0.24**
Surgical and medical procedures	**14**	**1.3**	**0.94**	**10**	**1.0**	**0.75**	**3**	**1.1**	**0.80**	**1**	**0.4**	**0.24**
Vascular disorders	**13**	**1.2**	**0.87**	**17**	**1.7**	**1.27**	-	-	-	**10**	**3.5**	**2.37**
Cardiac disorders	**12**	**1.1**	**0.81**	**15**	**1.5**	**1.12**	**2**	**0.7**	**0.53**	**3**	**1.1**	**0.71**
Injury, poisoning and procedural complications	**11**	**1.0**	**0.74**	**16**	**1.6**	**1.20**	**3**	**1.1**	**0.8**	**2**	**0.7**	**0.47**

SOC: System Organ Class PT: Preferred Term
N: number of patients by treatment group
n: number of patients with at least one emergent AE in a given PT or in a given SOC and a given treatment group
%: (n/N) x 100
PM: total number of patient-months in a given treatment group
pm: number of patients with at least one adverse event in a given level and a given treatment group per 100 patient-months = (n/PM) x 100

Table 6: *Summary of Clinical Safety*: Time to onset of the most frequent EAEs in the agomelatine 25/50 mg treatment group of the Short-term DB PC MDD Set. (EAEs with incidence ≥ 2% in the agomelatine group and ≥ incidence than in the placebo group).

Preferred term	N	Time to onset [1]									
		[0-1[week		[1-2[weeks		[2-4[weeks		[4-6[weeks		>=6 weeks	
		n	%	n	%	n	%	n	%	n	%
Headache	158	73	46.2	33	20.9	30	19.0	20	12.7	2	1.3
Nausea	86	47	54.7	19	22.1	14	16.3	5	5.8	1	1.2
Dizziness	61	43	70.5	9	14.8	8	13.1	1	1.6	-	-
Dry mouth	39	20	51.3	6	15.4	8	20.5	3	7.7	2	5.1
Diarrhoea	35	13	37.1	7	20.0	12	34.3	1	2.9	2	5.7
Somnolence	32	19	59.4	4	12.5	6	18.8	1	3.1	2	6.3
Fatigue	29	15	51.7	6	20.7	5	17.2	3	10.3	-	-
Abdominal pain upper	27	11	40.7	6	22.2	5	18.5	4	14.8	1	3.7
Influenza	26	2	7.7	3	11.5	12	46.2	7	26.9	2	7.7
Anxiety	22	9	40.9	5	22.7	5	22.7	3	13.6	-	-

[1] time to onset = duration between first intake of study treatment and onset of the first EAE
N: number of patients with at least one EAE in a given preferred term
n: number of patients with at least one EAE in a given PT and a given class of time to onset
%: (n/N) x 100

Note that for each EAE in the above table the percentage for a particular time period represents the number of patients who had their first report of that EAE during that time period, expressed as a percentage of the total number of patients who had that EAE at any time during the study (not as a percentage of the number of patients exposed to agomelatine during the time period).

EAEs reported in ≥1% of patients during the period from 6 to 24 weeks after the start of MDD treatment are summarised in Table 7. During this period, EAEs were reported by 38.8% of patients taking agomelatine 25/50 mg and 38.4% of those taking placebo. The most common EAEs in agomelatine recipients during this period were headache (8.2%), back pain (2.7%) and insomnia (2.5%). Of these, the first report of headache or back pain within the period from 6 to 24 weeks after the start of treatment was most commonly made within the initial 3 months of that period, whereas no specific temporal pattern was observed for the first report (within the 6-24 period) of insomnia. The *prevalence* of AEs (whether new or continuing) at different time points was not reported. During the period from 6 to 24 weeks after the start of agomelatine treatment of MDD there was a relationship between agomelatine dose and the incidence of EAEs, which were reported in 13.3% of patients who took agomelatine 25 mg and 16.7% of patients who took agomelatine 50 mg.

EAEs reported during the period from 6 months to 1 year after the start of agomelatine therapy in the One-year Agomelatine Exposure Set are summarised in Table 8. The most common EAEs during this period were nasopharyngitis (3.0%), headache (2.8%), back pain (2.3%), gastroenteritis (1.5%) and influenza (1.3%). A meaningful analysis of EAEs according to agomelatine dose was not possible because of the low number of patients who received the 50 mg dose (N=32).

In the All MDD Set, EAEs were reported in 61.3% of the agomelatine 25/50 mg group, compared to 57.4% of the placebo group, 75.9% of the paroxetine group and 57.0% of the fluoxetine group.

Table 7: *Summary of Clinical Safety*: EAEs with incidence ≥1% during the period from 6 to 24 weeks after the start of treatment in the agomelatine 25/50 mg treatment group of the Long-term DB PC MDD Set.

System Organ Class Preferred term	agomelatine 25/50mg N=511 PM=1762.6			placebo N=406 PM=1370.1			fluoxetine 20mg N=222 PM=818.3			paroxetine 20mg N=105 PM=364.7		
	n	%	pm	n	%	pm	n	%	pm	n	%	pm
All	**198**	**38.8**	**11.23**	**156**	**38.4**	**11.39**	**71**	**32.0**	**8.68**	**47**	**44.8**	**12.89**
Nervous system disorders	**61**	**11.9**	**3.46**	**47**	**11.6**	**3.43**	**24**	**10.8**	**2.93**	**12**	**11.4**	**3.29**
Headache	42	8.2	2.38	27	6.7	1.97	18	8.1	2.20	3	2.9	0.82
Dizziness	6	1.2	0.34	4	1.0	0.29	-	-	-	1	1.0	0.27
Infections and infestations	**50**	**9.8**	**2.84**	**55**	**13.6**	**4.01**	**23**	**10.4**	**2.81**	**10**	**9.5**	**2.74**
Influenza	14	2.7	0.79	15	3.7	1.09	6	2.7	0.73	4	3.8	1.10
Nasopharyngitis	11	2.2	0.62	11	2.7	0.80	4	1.8	0.49	1	1.0	0.27
Sinusitis	7	1.4	0.40	-	-	-	-	-	-	1	1.0	0.27
Gastrointestinal disorders	**41**	**8.0**	**2.33**	**31**	**7.6**	**2.26**	**15**	**6.8**	**1.83**	**10**	**9.5**	**2.74**
Diarrhoea	8	1.6	0.45	4	1.0	0.29	2	0.9	0.24	3	2.9	0.82
Nausea	8	1.6	0.45	3	0.7	0.22	4	1.8	0.49	-	-	-
Dyspepsia	6	1.2	0.34	4	1.0	0.29	2	0.9	0.24	2	1.9	0.55
Abdominal pain upper	6	1.2	0.34	2	0.5	0.15	-	-	-	1	1.0	0.27
Constipation	6	1.2	0.34	2	0.5	0.15	-	-	-	-	-	-
Psychiatric disorders	**41**	**8.0**	**2.33**	**22**	**5.4**	**1.61**	**16**	**7.2**	**1.96**	**11**	**10.5**	**3.02**
Insomnia	13	2.5	0.74	3	0.7	0.22	4	1.8	0.49	3	2.9	0.82
Anxiety	9	1.8	0.51	4	1.0	0.29	5	2.3	0.61	2	1.9	0.55
Depression	7	1.4	0.40	4	1.0	0.29	5	2.3	0.61	1	1.0	0.27
Musculoskeletal and connective tissue disorders	**25**	**4.9**	**1.42**	**23**	**5.7**	**1.68**	**10**	**4.5**	**1.22**	**3**	**2.9**	**0.82**
Back pain	14	2.7	0.79	9	2.2	0.66	3	1.4	0.37	1	1.0	0.27
Arthralgia	5	1.0	0.28	4	1.0	0.29	-	-	-	-	-	-
Investigations	**14**	**2.7**	**0.79**	**11**	**2.7**	**0.80**	**2**	**0.9**	**0.24**	**5**	**4.8**	**1.37**
General disorders and administration site conditions	**10**	**2.0**	**0.57**	**15**	**3.7**	**1.09**	**4**	**1.8**	**0.49**	**1**	**1.0**	**0.27**
Injury, poisoning and procedural complications	**9**	**1.8**	**0.51**	**6**	**1.5**	**0.44**	**3**	**1.4**	**0.37**	**2**	**1.9**	**0.55**
Respiratory, thoracic and mediastinal disorders	**6**	**1.2**	**0.34**	**9**	**2.2**	**0.66**	**2**	**0.9**	**0.24**	**3**	**2.9**	**0.82**
Skin and subcutaneous tissue disorders	**9**	**1.8**	**0.51**	**6**	**1.5**	**0.44**	**3**	**1.4**	**0.37**	**1**	**1.0**	**0.27**
Reproductive system and breast disorders	**11**	**2.2**	**0.62**	**3**	**0.7**	**0.22**	-	-	-	**2**	**1.9**	**0.55**
Surgical and medical procedures	**5**	**1.0**	**0.28**	**3**	**0.7**	**0.22**	**1**	**0.5**	**0.12**	**3**	**2.9**	**0.82**

SOC: System Organ Class
N: number of patients by treatment group
n: number of patients with at least one emergent AE in a given preferred term or in a given SOC and a given treatment group
%: (n/N) x 100
PM: total number of patient-months in a given treatment group
pm: number of patients with at least one adverse event in a given level and a given treatment group per 100 patient-months = (n/PM) x 100

Table 8: *Summary of Clinical Safety*: EAEs with incidence ≥ 2 patients during the period from 6 to 12 months after the start of treatment in the One-Year Agomelatine Exposure Set.

Preferred Term	n (%)
Nasopharyngitis	12 (3.0)
Headache	11 (2.8)
Back pain	9 (2.3)
Gastroenteritis	6 (1.5)
Influenza	5 (1.3)
Bronchitis	4 (1.0)
Sinusitis	4 (1.0)
Urinary tract infection	4 (1.0)
Insomnia	4 (1.0)
Weight increased	4 (1.0)
Upper respiratory tract infection	3 (0.8)
Tonsillitis	3 (0.8)
Dizziness	3 (0.8)
Myalgia	3 (0.8)
Rheumatoid arthritis	3 (0.8)
Hypertension	3 (0.8)
Seasonal allergy	3 (0.8)
Respiratory tract infection viral	2 (0.5)
Bronchitis acute	2 (0.5)
Tooth abscess	2 (0.5)
Respiratory tract infection	2 (0.5)
Acute sinusitis	2 (0.5)
Laryngitis	2 (0.5)
Skin infection	2 (0.5)
Nausea	2 (0.5)
Abdominal pain upper	2 (0.5)
Musculoskeletal stiffness	2 (0.5)
Fatigue	2 (0.5)
Asthenia	2 (0.5)
Decreased appetite	2 (0.5)
Hypercholesterolaemia	2 (0.5)
Palpitations	2 (0.5)
Conjunctivitis	2 (0.5)

PT: preferred term %: (n/N) x 100
n: number of patients having had their first emergent adverse event from 6 months of treatment

Emergent adverse drug reactions (EADRs)

In the Short-term DB PC Set, EADRs (EAEs that were considered by the investigator to be related to study treatment) were reported in 32.5% of agomelatine recipients, 29.3% of placebo recipients, 33.8% of fluoxetine recipients and 44.9% of paroxetine recipients. For the individual EAEs with incidence ≥1%, Table 9 shows the number and percentage that were considered by the investigator to be EADRs (that is, treatment-related). There was a clear relationship between agomelatine dose and the incidence of EADRs during short-term treatment of MDD: EADRs were reported by 30.4% of patients who took agomelatine 25 mg and 40.5% of patients who took agomelatine 50 mg.

Table 9: *Summary of Clinical Safety*: Amongst the individual EAEs with incidence ≥1% in the Short-term DB PC MDD Set, the number and percentage that were considered by the investigator to be EADRs (treatment-related).

Treatment-related EAEs Preferred term	**agomelatine 25/50mg N=1120 PM=1486.1**			**placebo N=998 PM=1337.6**		
	n	**%**	**pm**	**n**	**%**	**pm**
headache	103	9.2	6.93	86	8.6	6.43
nausea	66	5.9	4.44	55	5.5	4.11
dizziness	51	4.6	3.43	25	2.5	1.87
dry mouth	35	3.1	2.36	32	3.2	2.39
somnolence	28	2.5	1.88	17	1.7	1.27
fatigue	22	2.0	1.48	13	1.3	0.97
diarrhoea	19	1.7	1.28	15	1.5	1.12
abdominal pain upper	17	1.5	1.14	5	0.5	0.37
anxiety	14	1.3	0.94	5	0.5	0.37
influenza	1	0.1	0.07	-	-	-

[1] *doubtfully, possibly or probably related according to the investigator*
N: number of patients in the treatment group
n: number of patients with at least one treatment-related EAE in a given PT and a given treatment group
%: (n/N) x 100
PM: total number of patient-months in a given treatment group
pm: number of patients with at least one treatment-related adverse event in a given PT and a given treatment group per 100 patient-month = (n/PM) x 100

- Another way of assessing the causality of adverse events in placebo-controlled studies is to examine patterns in the aggregate data instead of the circumstances of the individual event. At the request of the CHMP, Servier did this for EAEs that were reported by at least 1% of patients taking agomelatine 25/50 mg in the Short-term DB PC MDD Set, using criteria in the CIOMS *Guidelines for Preparing Core Clinical Safety Information on Drugs, Second Edition*.[16]

On this basis, the following EAEs were assessed as potentially related to agomelatine during short-term treatment: nausea, dizziness, diarrhoea, somnolence, fatigue, upper abdominal pain, anxiety, hyperhidrosis and migraine.

During the period from 6 to 24 weeks after the start of MDD treatment, EADRs were reported in 14.1% of agomelatine recipients, 13.8% of placebo recipients, 13.5% of fluoxetine recipients and 27.6% of paroxetine recipients. For the individual EAEs with incidence ≥1%, Table 10 shows the number and percentage that were considered by the investigator to be EADRs (treatment-related).

[16] Council for International Organizations of Medical Sciences. Guidelines for preparing Core Clinical Safety Information on Drugs, Second Edition. Report of CIOMS Working Groups III and V including New Proposals for Investigator's Brochures. Geneva 1999.

Table 10: *Summary of Clinical Safety*: Amongst the individual EAEs with incidence ≥1% during the period from 6 to 24 weeks after the start of treatment in the agomelatine 25/50 mg treatment group of the Long-term DB PC MDD Set, the number and percentage that were considered by the investigator to be EADRs (treatment-related).

Treatment-related EAEs Preferred term	agomelatine 25/50mg N=511 PM=1762.6			placebo N=406 PM=1370.1		
	n	%	pm	n	%	pm
headache	19	3.7	1.08	13	3.2	0.95
insomnia	4	0.8	0.23	1	0.3	0.07
back pain	-	-	-	1	0.3	0.07

[1] *doubtfully, possibly or probably related according to the investigator*
N: number of patients in the treatment group
n: number of patients with at least one treatment-related EAE in a given PT and a given treatment group
%: (n/N) x 100
PM: total number of patient-months in a given treatment group
pm: number of patients with at least one treatment-related adverse event in in a given PT and a given treatment group per 100 patient-months = (n/PM) x 100

During the period from 6 to 24 weeks after the start of agomelatine treatment of MDD there was a relationship between agomelatine dose and the incidence of EAEs and EADRs: EADRs were reported in 13.3% of patients who took agomelatine 25 mg and 16.7% of patients who took agomelatine 50 mg.

Summary information regarding EADRs during the period from 6 months to 1 year after the start of agomelatine therapy in the One-year Agomelatine Exposure Set was not provided.

In the All MDD Set, EADRs were reported in 30.6% of the agomelatine 25/50 mg group, compared to 32.3% of the placebo group, 46.8% of the paroxetine group and 38.7% of the fluoxetine group.

EADRs in the Overall Safety Set : In patients taking therapeutic doses of agomelatine (25/50 mg) in the Overall Safety Set, the incidence of EADRs was 30.1% and the most common EADRs (incidence ≥1%, in order of descending frequency) were headache (7.0%), nausea (4.7%), somnolence (3.6%), dizziness (3.4%), dry mouth (2.3%), fatigue (2.3%), diarrhoea (1.4%), constipation (1.2%) and insomnia (1.2%).

Deaths

No deaths occurred in healthy or patient volunteer studies. In the Overall Safety Set there were 26 deaths, of which 9 occurred in MDD trials and 17 in studies in other indications.

Of the 9 deaths in MDD studies, 4 were in the agomelatine group (0.1% of patients), 1 in the placebo group (0.1%), 1 in the fluoxetine group (0.4%) and 3 in the paroxetine group (1.1%). All of the deaths in the agomelatine and placebo groups in MDD studies were cases of suicide, none of which were considered to be treatment-related.

Amongst the 17 deaths in studies of agomelatine for non-MDD indications, 16 were in patients taking agomelatine and 1 in a placebo recipient. All except one of the deaths on agomelatine occurred in a study in elderly patients with Alzheimer's disease (CL2-011).

Serious Emergent Adverse Effects (SEAEs)

In the Overall Safety Set, SEAEs were reported in 4.7% of agomelatine recipients compared to 4.5% of placebo recipients. In MDD studies, SEAEs were reported in 4.2% of agomelatine recipients compared to 4.1% of placebo recipients.

SEAEs reported from 6 months onwards in the One-year Agomelatine Exposure Set were hysterosalpingo-oophorectomy, gastric bypass, suicidal depression, fibrocystic breast disease and uterine disorder (one patient each). None were considered related to study drug by the investigator.

EAEs leading to treatment withdrawal

In short-term placebo controlled studies, slightly more agomelatine recipients discontinued treatment due to an EAE compared to the placebo group (5.5% versus 5.2%). A similar pattern was seen in the Long-term DB PC Set from W6 to W24 visits (agomelatine 6.7%, placebo 5.2%), whereas the reverse was seen in the MDD Set (agomelatine 7.3%, placebo 9.0%) and the Overall Safety Set (agomelatine 6.4%, placebo 6.9%). The main System Organ Classes involved in the agomelatine 25/50 mg group were *Psychiatric Disorders*, *Nervous System Disorders* and *Gastrointestinal Disorders*.

EAEs of particular interest

Suicidality

Suicidality is comprised of suicidal thoughts and suicidal acts, the latter including suicide attempts and completed suicides. Suicidal acts occurring during treatment or within the month following discontinuation of study treatment were counted in the All MDD Set: The incidences of suicide attempts and completed suicides in the agomelatine group (0.8% and 0.1%, respectively) were similar to those in the placebo group (0.6% and 0.1%, respectively). When treatment duration was taken into account (longer for agomelatine than for placebo), the incidence of suicidal acts was 0.19 per 100 PM, compared to 0.24 per 100 PM for placebo.

In order to investigate emerging suicidal thoughts, patients with no or minimal suicidal thoughts at baseline (0 or 1 on the MADRS suicidal thoughts item or the HAM-D suicide item) were analysed in the Short-term DB PC Set.[17] Using both assessment scales, increased or emergent suicidal thoughts tended to be less frequent in patients treated with agomelatine 25/50 mg compared to placebo (7.7% versus 11.0%, respectively for MADRS and 5.2% versus 6.5% for HAM-D).

Emergent mania

Among the MDD patients in double-blind placebo-controlled studies, the incidence of manic/hypomanic episodes on agomelatine 25/50 mg was low (2/1116, 0.2%) and comparable to that on placebo (2/994, 0.2%).

Seizures

The seizure rate in agomelatine recipients in the Overall Safety Set was low (3/4738, 0.06%). The sponsor noted that this is comparable to the incidence of first seizure in the general population (0.07-0.09%). No MDD patient had a seizure during agomelatine treatment.

Sedative and stimulating effects

In the agomelatine group, EAEs representing sedation were about as frequent as those representing stimulation, and only slightly more common than in the placebo group.

Sexual dysfunction

In short-term studies, EAEs indicating sexual dysfunction were slightly more common with agomelatine than placebo, but noticeably less common with agomelatine than fluoxetine or paroxetine.

[17] MADRS = Montgomery-Åsberg Depression Rating Scale. The MADRS is a validated depression rating scale with 10 items that cover the core depressive symptoms (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts). Each item is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptom). The total MADRS score can range from 0 to 60, with higher scores representing more severe depression.

Laboratory abnormalities

Liver function tests

In its summary of changes from baseline to the worst value during treatment in the Overall Safety Set, the sponsor did not report mean values but instead reported the median, range and first and third quartiles, on the grounds that the data were not normally distributed. The sponsor interpreted the data as showing no relevant changes over time and no relevant between-treatment differences. However, in the Overall Safety Set, the median change was lower in the placebo group (0.5 IU/L) than in the agomelatine (1.0 IU/L) and active control groups (1.0 - 3.0 IU/L). The maximal changes for ALT and AST in the agomelatine group were due to a case of acute exacerbation of pre-existing chronic hepatitis in a patient treated with 50 mg; the maximal change for the total bilirubin value in the agomelatine group was due to high values reported in one patient with acute alcohol intoxication.

Emergent out-of-reference-range values and potentially clinically significant abnormal (PCSA) values tended to be more common with agomelatine and the active comparators than with placebo. The incidence and incidence rate of PCSA hepatic laboratory values in agomelatine 25 mg recipients was similar to that in the placebo group, whereas the incidence and incidence rate in agomelatine 50 mg recipients were about 3 times as high (although a statistical analysis did not show a significant difference between either agomelatine dose and placebo). The same pattern was seen in respect of ALT and AST elevations to >5×ULN or >10×ULN.

As previously discussed, in response to a CHMP request, the sponsor reviewed data for all cases of transaminase elevations >3×ULN in the agomelatine and placebo groups in clinical studies (whatever the baseline transaminase value before treatment intake). The review is based on a later dataset than the one covered by the sponsor's *Summary of Clinical Safety*. The resulting information was assessed by a panel of 5 independent clinical experts from France and the UK (4 hepatologists and a specialist in internal medicine).

- A total of 51 cases were identified: 44 with agomelatine (1.1% of 4033 agomelatine recipients) and 7 with placebo (0.7% of 969 placebo recipients).
- All cases had biochemical features characteristic of hepatocellular liver injury[18], except for one case of acute hepatitis that recovered after treatment discontinuation and was considered by the experts to be due to itraconazole.
- There were no 'Hy's Law' cases. Hy's law provides a means to assess a drug's risk of causing serious hepatotoxicity. It is based on the observation of Hyman Zimmerman that the combination of high serum aminotransferase activity and jaundice is an indication of more injury to the liver than elevated transaminases alone.[19] A measurement of elevated bilirubin was later substituted for the qualitative observation of jaundice.[20] In order for a liver toxicity situation to be considered a Hy's Law case, the following two criteria must be met:
    - Evidence that the drug can cause hepatocellular injury as shown by a higher rate than control of patients with transaminase elevations ≥3×ULN;
    - Transaminase elevation to ≥3×ULN and bilirubin elevation to ≥2×ULN in the individual case under review.

[18] Hepatocellular injury pattern = increased ALT alone, or ALT/alkaline phosphatase ratio (R) >5. Cholestatic pattern = increase >2×ULN in alkaline phosphatase alone, or R <2. Mixed pattern = increase >2×ULN in ALT and increase in alkaline phosphatase, and R >2 but <5. Taken from CIOMS, 1999. Reporting adverse drug reactions: definitions of terms and criteria for their use. Available at http://www.cioms.ch/publications/reporting_adverse_drug.pdf

[19] Zimmerman HJ. Drug-induced liver disease. Hepatotoxicity, The adverse effects of drugs and other chemicals on the liver, 1st edition, New York United-States 1978.

[20] Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Safety 2006; 15:241-243

In the context of drug safety evaluation, the FDA has recommended a third criterion, namely that the abnormalities are not explained by another cause such as viral hepatitis, pre-existing liver disease, or another drug.[21]

Retrospective analyses in Sweden and Spain have shown a significant association between Hy's law cases and outcomes of liver transplantation and death.[22,23] The FDA has extended this finding in a proposal to use Hy's Law for assessing whether the premarket data indicate if a drug is likely to display unacceptable hepatic toxicity once marketed. The FDA proposal concludes that "The sensitivity of [Hy's Law] appears very high if at least two cases are seen (for example, dilevalol, bromfenac, troglitazone, ximelagatran). We are not aware of false positive Hy's Law findings. Therefore, the finding of two Hy's Law cases, and probably even one, is a strong predictor of a significant rate of severe liver injury. Failure to find a case, however, does not imply that a drug with AT elevations is free of a risk of severe drug-induced liver injury (DILI). The degree of assurance depends on the population exposed for a long enough time and on the rate of severe DILI that would be of interest".

- 31 (720.5%) of the 44 agomelatine cases were in women, compared to 6/7 (86%) of the placebo cases. This reflects the gender distribution in the studies, consistent with the over-representation of women amongst depressed patients (70%).
- The incidence of ALT and/or AST elevations >3×ULN according to agomelatine dose was 0.6% on agomelatine 1-5-10 mg, 1.0% on agomelatine 25 mg, 1.4% on agomelatine 50 mg, and 3.5% on agomelatine 100 mg, compared to 0.7% in the placebo group. The data for agomelatine 100 mg may not be representative due to the small number of patients (N=57) and confounding factors (1 case was considered not related to agomelatine by the experts; the two other cases were observed in a specific schizophrenic population of patients treated with haloperidol who had abnormal baseline transaminase values). However, even if this dose level is excluded, there is evidence of a relationship between agomelatine dose and the incidence of potentially clinically significant transaminase elevations.
- Out of the 44 cases, 3 cases (7%) were considered to be probably related to agomelatine by the independent experts. These were hepatocellular reactions, with a time to detection between 52 and 73 days, rapid recovery within the month following drug cessation and without obvious alternative cause. 18 cases (41%) were considered to be possibly related to agomelatine and 23 cases (52%) were considered to be unlikely (15 cases) or not (7 cases) related to agomelatine. When cases were considered as unlikely, it was mainly because available information did not allow the complete exclusion of a role for agomelatine.
- Out of the 44 cases, liver function tests returned to baseline in all patients with available information. The outcome was unknown in 2 cases, both of whom were taking agomelatine 25 mg. In those patients with more frequent testing, liver function tests returned to normal within a month.

The consensus conclusions and recommendations of the independent clinical experts were as follows:

Overall it is our view that agomelatine is not associated with a significant risk of liver injury when transaminase elevations ≥3×ULN administered at 25 mg/day and that there does not need to be monitoring of liver function tests at this dose.

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[21] Food and Drug Administration. Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

[22] Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology 2005; 42: 481-489.

[23] Andrade RJ, Lucena MI, Fernandez MC. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005; 129: 512-521.

At the higher dose of 50 mg/day here agomelatine is associated with an increased frequency of transaminase elevation and it is our view that, given the relatively small dataset at this dose, patients should be monitored with liver function tests being carried out at the time of the dose increase, and should be repeated at 6-8 weeks and 12-16 weeks later.

We accept that it is probably prudent to exclude patients with known liver disease, but there are no data to show increased toxicity in patients with high systemic plasma concentrations of agomelatine.

Other biochemistry

Mean changes in non-hepatic laboratory values from baseline to the last value were similar for agomelatine, placebo and active controls. Similar results were obtained for mean changes from baseline to the highest or lowest value on treatment, and in the other safety datasets. Again, no relevant between-group differences were observed and similar results were obtained in other safety datasets. Emergent PCSA values were sparse and there were no relevant differences between treatment groups.

Haematology

No relevant differences were seen between agomelatine and placebo in respect of mean changes in haematology values from baseline to the last value during treatment, mean changes in haematology values from baseline to the highest or lowest value on treatment, emergent out-of-reference range haematology values or PCSA haematology values.

Body weight changes

The mean change in body weight and the percentage of patients whose BMI switched from one class (underweight, normal, overweight, obese) to another were similar in the agomelatine and placebo groups in both the Short-term DB PB MDD set and the Long-term DB PC MDD Set.

Evaluator comments

Duration of exposure

One of the reasons for the proposed rejection of the original submission was the paucity of long-term safety data for the 50 mg agomelatine dose. As previously noted, the relevant TGA-adopted guideline recommends that 300-600 patients should be studied for ≥6 months and at least 100 for ≥12 months. It should also be noted that although the EU guideline states that data on patients treated through 12 months may be submitted after approval, this element of the guideline was expressly not adopted by the TGA, as notified on the TGA web site.[24]

The safety dataset for agomelatine complies with the guideline recommendations, but only for the 25 mg dose or the combined 25/50 mg doses. The number of patients exposed to the 50 mg dose remains low, particularly at 12 months. In the original submission, no patients had received the 50 mg dose for ≥12 months. In the current submission, the One-year Agomelatine MDD Exposure Set in the *Summary of Clinical Safety* included 400 patients, of whom only 32 received agomelatine 50 mg. Adding the 12 patients who took agomelatine 50 mg for 12 months in CL3-041 (but were not included in the *Summary of Clinical Safety*), the total number of patients treated with agomelatine 50 mg for 12 months is still only 44. Furthermore, (a) an overall assessment of safety in these 44 patients is not available, and (b) safety data from the 12 patients in CL3-041 is difficult to interpret because it was reported for either the first 32-34 weeks *or* the last 44 weeks of the study, but was not consolidated over the entire 12 month period.

[24] http://www.tga.gov.au/docs/html/euguide/euad_clin.htm#clinicalsafety

The importance of adequate long-term safety data for the 50 mg dose of agomelatine should be evident when one considers that about 15-25% of responders in the clinical trials were titrated to that dose.

Demographic and other baseline characteristics

The mean age of patients in the summary safety datasets was about 45 years; about 32% were smokers, and about 55% had some past medical history. In the MDD subsets, almost all of the patients had MDD according to DSM-IV criteria; a few patients had Bipolar Disorder. The typical MDD sex distribution was seen (about 70% female) and about 60% had some previous treatment for MDD. In the Short-term DB PC Set, demographics and other baseline characteristics were similar to those in the larger datasets, and were comparable in the agomelatine, placebo and active treatment groups. Of note, the safety datasets contained very few patients over 60 years of age, and the studies excluded children and adolescents, pregnant women, patients with pre-existing liver abnormalities, and patients taking medications likely to interact with agomelatine.

EAEs and EADRs

EAEs and EADRs were consistent with those reported in the original submission. The most common EAEs in agomelatine recipients were headache, nausea, dizziness, dry mouth, diarrhoea and somnolence. The most common EADRs in patients taking agomelatine 25/50 mg were headache, nausea, somnolence, dizziness, dry mouth, fatigue, diarrhoea, constipation and insomnia.

Deaths and non-fatal SEAEs

All of the deaths in MDD studies were due to suicide, but this is a potential complication of MDD. The suicide rate was comparable in the agomelatine and placebo groups, and there was no evidence of an excess of suicidal behaviour or emergent suicidal thoughts with agomelatine compared to placebo.

The deaths in the Alzheimer's disease study were evenly distributed across the three agomelatine dose groups (1, 10 and 50 mg daily) and were due to a variety of causes, often related to the cardiovascular system (not unexpected in a population of this age). The sponsor argued that the mortality rate in the Alzheimer's disease study was consistent with the background rate of death in such patients, as reported in the literature. However, the study included a placebo arm and there were proportionately more deaths in agomelatine recipients compared to placebo: 15/259 (5.5%), compared to 1/87 (1.1%). This imbalance is worrying, and the finding should be documented in the Precautions section of the PI.

Hepatic toxicity

The incidence of potentially clinically significant transaminase elevations (>3×ULN) was higher with agomelatine than placebo. The difference did not reach statistical significance, but there was a clear trend of increased incidence of transaminase elevations with increasing agomelatine dose, which supports a causal role. The apparent distinction between the 25 and 50 mg agomelatine doses in the rate of transaminase elevations contrasts with the overlapping systemic drug exposure achieved at these doses. This raises the possibility that transaminase elevations during agomelatine treatment may be a result of initial liver load rather than systemic exposure, which was further supported by an analysis which found that patients with high plasma agomelatine concentrations did not have a higher frequency of transaminase elevations compared to patients with low plasma concentrations.

None of the 44 cases of transaminase elevation 3×ULN in 4033 agomelatine recipients during clinical trials met the FDA definition of a Hy's Law case. As noted in the FDA draft guideline, this indicates with 95% confidence that the true incidence of Hy's law cases in patients taking agomelatine is no more than 1 in 1344 (4033 ÷ 3). This leads to the further conclusion that we can be 95% confident that the true incidence of severe drug-induced liver injury (DILI) in agomelatine

recipients is lower than 1 in 13,400 (on the basis of published studies showing that the incidence of severe DILI is approximately one-tenth that of Hy's Law cases, and assuming that patients are subject to the selection and monitoring that took place in the clinical trials).

It should be remembered that not all of the patients who took agomelatine in clinical trials had the liver function test (LFT) results needed to assess whether or not they were a Hy's Law case. The agomelatine dataset in the hepatic safety analysis contained 4033 patients. The basis for this number is not clear, but it is certainly less than the total number of patients who had taken agomelatine up to the cut-off date for the analysis (noting that the Overall Safety Set in the *Summary of Clinical Safety*, based on an *earlier* cut-off date, included 4738 agomelatine recipients). The figure of 4033 agomelatine recipients represents the number of patients who had at least one post-baseline LFT result.

It is not clear what percentage this represents of the entire population who had received agomelatine up to that time, but in the Overall Safety Set in the *Summary of Clinical Safety*, only 82% of the 4738 agomelatine recipients had at least one post-baseline liver function test. It is therefore reasonable to assume that the analysis of hepatic toxicity would have similarly excluded about 18% of the patients who had taken agomelatine and it is possible that unidentified Hy's Law cases may have occurred amongst those patients. Whether or not this would affect the estimate of the incidence of severe DILI would depend on whether patients without post-baseline LFTs were more or less likely than other patients to have changes that would have qualified them as a Hy's Law case. This is unknown.

Amongst patients with an elevated ALT or AST at baseline (>ULN but <3×ULN), the percentage who subsequently developed an ALT or AST >3×ULN during treatment was similar in the agomelatine and placebo groups (3.5%, 2.6% and 3.4% of such patients in the agomelatine 25 mg, agomelatine 50 mg and placebo groups, respectively). The sponsor argues that this indicates that there should be no special concern in relation to using agomelatine in patients whose pre-treatment ALT or AST is elevated, provided it is <3×ULN. However, the number of such patients in the clinical trials was relatively small, and does not provide sufficient reassurance in the face of the other findings.

In summary, the clinical data show that agomelatine produces a dose-related increase in hepatic transaminases, but provided that patients are carefully selected and monitored (as per the clinical trials), the risk of severe DILI is likely to be less than about 1 in 13,000. As noted in the FDA draft guidance, most of the drugs withdrawn from the market for hepatotoxicity to date have had rates of death or transplantation of ≤1 per 10,000. The upper 95% confidence boundary for the estimated rate of agomelatine-associated DILI is lower than this (although not greatly so) and the true risk is most probably lower still. Overall, the risk of severe DILI is not sufficient to preclude marketing approval, provided that patients are appropriately selected and monitored, and acknowledging that the estimated risk may change once post-marketing data become available. In regard to the selection and monitoring of patients if the Delegate decides to approve registration, the following precautions are suggested:

- Prescribers and patients should be adequately informed regarding the potential hepatic toxicity of agomelatine and the need to monitor liver function;
- All patients should undergo liver function tests (ALT, AST, alkaline phosphatase and total bilirubin) before commencing agomelatine;
- Agomelatine should be contraindicated in patients with known liver disease or abnormality in the pre-treatment liver function tests;
- Liver function tests should be performed regularly during treatment with agomelatine. The draft PI suggests testing at 6, 12 and 24 weeks after the start of treatment. The evaluator suggested that in addition, testing should be performed before the dose is increased to 50 mg, and at least once yearly.

- If any liver function test result is ≥3×ULN, agomelatine should be suspended, the tests should be repeated as soon as possible, and agomelatine should be permanently ceased if the result remains ≥3×ULN (as was done in the clinical trials).
- If any liver function test result is >ULN but <3×ULN, the tests should be repeated and a decision made as to whether or not to continue agomelatine, based on the clinical circumstances. If agomelatine is continued in a patient with a liver function test result >ULN but <3×ULN, testing should be repeated on a regular basis at intervals determined by the degree of abnormality and the clinical circumstances.
- LFTs should be performed as soon as possible, and agomelatine suspended pending assessment of the results, in any patient who displays symptoms or signs of liver injury;
- Patients should be advised to stop taking agomelatine and tell their doctor immediately if they develop symptoms or signs of liver injury.

To assure this degree of control and monitoring may require a registered prescriber program, under which the sponsor would only be allowed to supply agomelatine on the order of a physician who complies with specific requirements (for example, is a Fellow of the Royal Australian and New Zealand College of Psychiatrists who has completed an acceptable agomelatine education program, and who undertakes to reinforce the importance of hepatic monitoring with patients for whom he/she prescribes agomelatine). The restriction could be reviewed at intervals (on application by the sponsor) and relaxed or removed once there is sufficient post-market evidence to support this.

In its pre-ACPM response, the sponsor noted that as a potent teratogen, prescription of isotretinoin (Roaccutane) is restricted to specialist physicians or dermatologists, a similar restriction to thalidomide. Agomelatine has been classified by the TGA as a 'Use in Pregnancy' Category B1 drug. Additionally the clinical evaluator determined that agomelatine had a "*positive risk:benefit*". The sponsor saw no parallel between this and the proposed need for an isotretinoin or thalidomide-type approach to risk management with agomelatine.

Safety data from individual studies in the current submission

As previously noted, most of the safety data from the studies in the current submission were evidently not included in the overall *Summary of Clinical Safety*. Of the studies in the current submission, the most relevant in relation to the identified deficiency of long-term safety data for the 50 mg agomelatine dose is CL3-041, in which a small number of patients received agomelatine 50 mg for 12 months. CL3-046 also includes safety data relevant to the comparison of agomelatine with sertraline in short- to medium-term treatment of MDD. Accordingly, these two studies will be covered in some detail. Safety data from the remaining studies in the current submission are less relevant, given that the studies were either single dose (CL1-054 and PKH-066) and/or conducted in healthy volunteers rather than patients with MDD (CL1-054, PKH-066 and CL1-049). Only deaths, other serious adverse events and AEs leading to the discontinuation of agomelatine will be considered for those studies.

CL3-041

Introductory comments on the presentation of the safety data

The separate reports for CL3-041 and its extension provided safety data for two overlapping periods. The 24-week report provided safety data for the agomelatine and placebo groups during the initial 24 week-randomised period, and for all agomelatine recipients during open-label treatment plus the first 24 weeks of randomised treatment. These results were presented for the agomelatine groups as a whole and separately for the 25 and 50 mg doses. The assignment to the 25 mg or 50 mg dose groups in the analysis was based on the dose that the patient took for the longest time, rather than the dose that was being taken when the adverse event occurred. This means that some

events ascribed to the 50 mg dose would have actually occurred when the patient was taking 25 mg (during the first two weeks of the open-label period).

The 44-week report for CL3-041 provided safety data for the agomelatine and placebo groups during the entire 44 week-randomised period, but did not include any data from the open-label period (either separately or combined with the data from the agomelatine arm of the randomised period). The 44-week report also did not analyse the safety data according to the agomelatine dose.

There was no overall synthesis of the full 12 months of safety data starting from the first dose of study drug, either for the agomelatine group as a whole or for the separate agomelatine doses.

Patient exposure

During the period for which safety data starting from the beginning of treatment were reported for agomelatine recipients (that is, the open-label period and up to Week 24 of the double-blind period), the mean agomelatine treatment duration was 14.6 weeks with a median of 9.9 weeks. The mean treatment duration was 15.1 (median 10.0) weeks in the 25 mg subgroup, and 12.8 (median 9.7) weeks in the 50 mg subgroup.

In the 44-week double-blind period, the mean treatment duration was 31.7 (median 43.4) weeks in the agomelatine group and 25.8 (median of 24.1) weeks in the placebo group. Treatment duration according to agomelatine dose (25 or 50 mg) was not reported.

The study report did not allow the evaluator to determine how many patients took agomelatine 25 mg or 50 mg for ≥6 months. A total of 115 patients in the agomelatine arm of the study completed the initial 24-week double-blind period and had thus taken agomelatine for about 8 months or more (8-10 weeks in the open-label period plus 24 weeks in the double-bind period). Of these, 98 patients had taken agomelatine 25 mg and 17 patients had taken agomelatine 50 mg. A total of 82 patients took agomelatine 25 mg and 12 patients took agomelatine 50 mg for 12 months (6-8 weeks open-label + 44 weeks randomised). However, the reporting of the safety data for these patients either excluded the last 20 weeks (in the CL3-041 study report) or excluded the first 8-10 weeks and was combined for both agomelatine doses (in the CL3-041 extension study report).

Emergent adverse events and adverse drug reactions

Emergent adverse events (EAEs) in patients treated with agomelatine for up to 34 weeks (8-10 weeks during the open-label period and up to Week 24 of the double-blind period) are summarised in Table 11. EAEs were reported in 61.7% of patients at the 25 mg dose and 75.5% at the 50 mg dose.

Table 11: CL3-041: Number (%) of patients with EAEs during the open-label period and up to Week 24 of the double-blind period in patients taking agomelatine (EAEs with incidence ≥1.5% in either the 25 mg or 50 mg dose subgroup).

Preferred Term	Agomelatine 25 mg (N = 389)			Agomelatine 50 mg (N = 102)			Agomelatine all doses (N = 491)		
	NEAE	n	%	NEAE	n	%	NEAE	n	%
ALL	**594**	**240**	**61.7**	**143**	**74**	**72.5**	**737**	**314**	**64.0**
Headache	76	60	15.4	15	15	14.7	91	75	15.3
Nasopharyngitis	41	35	9.0	8	7	6.9	49	42	8.6
Dizziness	34	33	8.5	7	7	6.9	41	40	8.1
Nausea	25	24	6.2	5	5	4.9	30	29	5.9
Back pain	18	17	4.4	4	4	3.9	22	21	4.3
Fatigue	19	17	4.4	3	3	2.9	22	20	4.1
Somnolence	13	13	3.3	4	3	2.9	17	16	3.3
Influenza	13	13	3.3	1	1	1.0	14	14	2.9
Upper respiratory tract infection	13	13	3.3	1	1	1.0	14	14	2.9
Diarrhoea	11	11	2.8	2	2	2.0	13	13	2.6
Constipation	10	10	2.6	1	1	1.0	11	11	2.2
Gastroenteritis	11	10	2.6	1	1	1.0	12	11	2.2
Dry mouth	9	9	2.3	1	1	1.0	10	10	2.0
Insomnia	5	5	1.3	5	5	4.9	10	10	2.0
Dyspepsia	8	8	2.1	2	2	2.0	10	10	2.0
Sinusitis	4	4	1.0	4	4	3.9	8	8	1.6
Myalgia	6	6	1.5	-	-	-	6	6	1.2
Abdominal pain upper	6	6	1.5	-	-	-	6	6	1.2
Tooth infection	3	3	0.8	2	2	2.0	5	5	1.0
Tinnitus	3	3	0.8	2	2	2.0	5	5	1.0
Conjunctivitis	2	2	0.5	2	2	2.0	4	4	0.8
Gastritis	2	2	0.5	2	2	2.0	4	4	0.8
Neck pain	2	2	0.5	2	2	2.0	4	4	0.8
Weight increased	1	1	0.3	2	2	2.0	3	3	0.6
Nightmare	1	1	0.3	2	2	2.0	3	3	0.6
Otitis media	1	1	0.3	2	2	2.0	3	3	0.6
Osteoarthritis	-	-	-	2	2	2.0	2	2	0.4

NEAE: number of emergent adverse events.
N: total number of exposed patients in the considered agomelatine dose subgroup.
n: number of affected patients.
%: n/N x 100.

EAEs in the agomelatine and placebo groups during the 44-week double-blind period are summarised in Table 12. During this period, EAEs were reported in 59.4% of the agomelatine group and 56.9% of the placebo group.

Table 12: CL3-041: Number (%) of patients with EAEs during the 44-week double-blind period (EAEs reported in at least 2 patients in the agomelatine group).

Preferred term	Agomelatine (N = 165)			Placebo (N = 174)		
	NEAE	n	%	NEAE	n	%
ALL	**209**	**98**	**59.4**	**211**	**99**	**56.9**
Headache	16	16	9.7	16	11	6.3
Nasopharyngitis	15	15	9.1	19	17	9.8
Back pain	11	11	6.7	8	7	4.0
Influenza	7	6	3.6	12	10	5.7
Sinusitis	7	5	3.0	5	5	2.9
Upper respiratory tract infection	5	5	3.0	5	4	2.3
Weight increased	4	4	2.4	3	3	1.7
Gastroenteritis	3	3	1.8	6	6	3.4
Arthralgia	5	3	1.8	2	2	1.1
Dyspepsia	3	3	1.8	2	2	1.1
Constipation	3	3	1.8	1	1	0.6
Gastritis	3	3	1.8	1	1	0.6
Neck pain	3	3	1.8	1	1	0.6
Tonsillitis	3	3	1.8	2	1	0.6
Dizziness	3	3	1.8	1	1	0.6
Initial insomnia	3	3	1.8	-	-	-
Bronchitis acute	2	2	1.2	3	3	1.7
Cystitis	2	2	1.2	5	3	1.7
Pharyngitis	2	2	1.2	3	3	1.7
Cough	2	2	1.2	1	1	0.6
Fall	2	2	1.2	1	1	0.6
Osteoarthritis	2	2	1.2	1	1	0.6
Shoulder pain	2	2	1.2	1	1	0.6
Hepatic enzyme increased	2	2	1.2	1	1	0.6
Alanine aminotransferase increased	2	2	1.2	-	-	-
Arthropod bite	2	2	1.2	-	-	-
Cellulitis	2	2	1.2	-	-	-
Dermatitis contact	2	2	1.2	-	-	-
Gastrointestinal disorder	2	2	1.2	-	-	-
Nausea	2	2	1.2	-	-	-
Rectal prolapse	2	2	1.2	-	-	-
Tooth infection	2	2	1.2	-	-	-
Erectile dysfunction	2	2	1.2	-	-	-

NEAE: number of emergent adverse events.
N: total number of exposed patients in the considered treatment group.
n: number of affected patients.
%: n/N x 100.

Treatment-related EAEs (emergent adverse drug reactions, EADRs) in patients treated with agomelatine for up to 34 weeks were reported in approximately 35% of patients for both agomelatine doses. EADRs in the agomelatine and placebo groups during the 44-week double-blind period were reported in 10.9% of the agomelatine group and 12.6% of the placebo group.

Deaths and other serious adverse events

No deaths were reported during the treatment period. During the whole study, SEAEs were reported in 28 patients as follows:

- 2 patients during the run-in period (both not included).
- 11/491 patients (2.2%) during the open-label period.
- 12/339 patients (3.5%) during the 44-week double-blind period - 6 (3.6%) of the agomelatine group and 6 (3.4%) in the placebo group. Among these patients, 5 (3.0%) in the agomelatine group, and 3 (1.7%) in the placebo group had emergent SEAEs during the initial 24-week double-blind treatment period; 1 (0.6%) in the agomelatine group, and 4 (2.3%) in the placebo group had emergent SEAEs during the 20-week double-blind extension period; 1 patient in the placebo group had an SEAE during each double-blind period.
- 3 patients had SEAEs during the 2-week post-treatment follow-up after ceasing agomelatine (2 after the open period, and 1 after the 24-week double-blind treatment period); 1 patient had an SEAE 36 days after the last dose of open-label agomelatine.

In CL3-041, transaminase increases ≥3×ULN were required by the protocol to be reported as SEAEs and all were regarded as treatment-related. In patients treated with placebo, such transaminase increases accounted for 1 SEAE. In patients treated with agomelatine, they accounted for a total of 7 SEAEs in 6 patients: 2 SEAEs during the open-label period (one each for the 25 mg and 50 mg doses); 3 SEAEs during the 44-week double-blind period (1 at the 25 mg dose and 2 at the 50 mg dose) and 2 SEAEs during the 2-week post-treatment follow-up after ceasing agomelatine 25 mg. In each case, the transaminase elevations resolved, usually after treatment discontinuation, but in one case (agomelatine 25 mg) without discontinuation of treatment.

Withdrawals due to adverse events

During the whole study, 38/491 patients (7.7%) had at least one EAE leading to treatment withdrawal:

- 30/491 patients (6.1%) during the open-label agomelatine period (8 with SEAEs). ;
- 8/339 patients (2.4%) during the 44-week double-blind period - 4 (2.4%) and 4 (2.3%) in the agomelatine and placebo groups, respectively. For 2 patients in the agomelatine group, and 1 patient in the placebo group, treatment withdrawal was due to an SEAE.

EAEs leading to discontinuation of agomelatine were most commonly in the psychiatric, nervous system and gastrointestinal System Organ Classes (SOCs). About two thirds of the discontinuations occurred within the first 16 days of treatment.

Evaluator comments

In CL3-041:

The most common EAEs during up to 34 weeks of agomelatine treatment (overall incidence ≥5%) were headache, nasopharyngitis, dizziness and nausea. The most common EADRs during up to 34 weeks of agomelatine treatment (overall incidence ≥2%) were headache, dizziness, nausea, fatigue and somnolence. This is consistent with the pattern of EAEs and EADRs documented in agomelatine recipients in the original submission and the *Summary of Clinical Safety*.

Meaningful comparisons between the two agomelatine dose levels in CL3-041 are limited by two considerations:

- Firstly, selection of the 25 or 50 mg dose in each patient was not based on randomisation but on treatment response. The overall higher frequency of EAEs in the 50 mg group could, at least in part, reflect more severe underlying MDD (and a higher frequency of EAEs representing effects of the MDD itself rather than the treatment) in those patients whose dose had to be

increased to 50 mg in the attempt to obtain a response. This hypothesis is supported by the lack of difference between the two dose levels in regard to the incidence of EADRs in CL3-041. On the other hand, when safety data were amalgamated across multiple studies in the *Summary of Clinical Safety*, EADRs *were* more common with the 50 mg dose than the 25 mg dose, which suggests that at least some of the difference in EAE incidence may be treatment-related rather than due to the underlying disease.

- Secondly, any comparison is based predominantly on short-term data, since only 24 patients received the 50 mg dose for more than 6-8 weeks.

In the 44-week double-blind period of CL3-041, the most common EAEs in the agomelatine group (incidence ≥5%) were headache and nasopharyngitis; in the placebo group, the most common EAEs were nasopharyngitis, headache and influenza. During the same period, the most common EADRs in both the agomelatine and placebo groups (incidence ≥1.5%) were headache and increased weight.

The pattern of EAEs leading to treatment discontinuation was similar to that seen in previously-evaluated studies and the *Summary of Clinical Safety*.

Agomelatine was associated with increases in mean values of hepatic transaminases (AST and ALT) but not total bilirubin. In a small percentage of patients, transaminases increased to ≥3× ULN. The increases all resolved with treatment discontinuation. There were no reports of overt jaundice, hepatitis or liver failure. The hepatic safety findings in CL3-041 were consistent with data in the original submission and the *Summary of Clinical Safety*.

Agomelatine did not have any clinically relevant effects on other biochemistry or haematology parameters.

CL3-046

In this 6 month comparative study of agomelatine 25/50 mg versus sertraline 50/100 mg in patients with MDD, safety data were collated for the initial 6 week randomised period (short-term safety data) and for the entire 24 week study period including the optional 18 week randomised extension (characterised by the sponsor as 'long-term' safety data, but really only medium-term safety data). Safety data were not reported according to agomelatine or sertraline dose, but were combined across both doses in each group.

Patient exposure

The safety analysis included 311 patients who received at least one dose of study medication (152 agomelatine, 159 sertraline). The median treatment duration in the W0-W6 (short term) dataset was 42 days (6 weeks) for both agomelatine and sertraline. The median treatment duration in the W0-W24 dataset was 168 days for agomelatine and 167 days for sertraline (that is, about 24 weeks for both treatments). Mean treatment durations were somewhat shorter than the medians and shorter for sertraline than agomelatine.

In the Randomised Set, 78/313 patients (24.9%) had a dose increase at W2: 39 patients (25.3%) had an increase of the agomelatine dose to 50 mg and 39 patients (24.5%) had an increase of the sertraline dose to 100 mg. Among the 78 patients with dose increase at W2, 30 patients in the agomelatine group and 27 patients in the sertraline group entered the extension period, but the report did not state how many completed the 6 month study at each dose. The overall treatment duration according to agomelatine or sertraline dose was not reported (except as individual patient data).

Emergent adverse events and adverse drug reactions

During short-term treatment (W0-W6), EAEs were reported by 48.0% and 49.1% of the agomelatine and sertraline groups, respectively. Over the entire study (W0-W24), EAEs were reported by 62.5% and 61.0% of the agomelatine and sertraline groups, respectively).

Over the full study period, the most commonly affected SOCs (>10% in any group) were *Nervous System Disorders* (23.7% in the agomelatine group, and 25.2% in the sertraline group), *Gastrointestinal Disorders* (23.7% and 23.3%, respectively), *Infections and Infestations* (22.4% and 19.5%, respectively) and *Musculoskeletal and Connective Tissue Disorders* (12.5% and 12.6%, respectively). *Psychiatric Disorders* and *Skin and Subcutaneous Tissue Disorders* were more frequently reported in the sertraline group than in the agomelatine group: 15.7% versus 7.9% for *Psychiatric Disorders* and 12.6% versus 7.2% for *Skin and Subcutaneous Tissue Disorders*.

During the initial 6 week period EAEs reported by ≥5.0% of patients in either treatment group were:

- EAEs that were more common with agomelatine: headache (8.6% in the agomelatine group and 10.1% in the sertraline group), dry mouth (5.3% and 5.0%, respectively), fatigue (5.9% and 1.3%, respectively).
- EAEs that were more common with sertraline: diarrhoea (3.9% in the agomelatine group and 5.7% in the sertraline group) and hyperhidrosis (0% and 5.0%, respectively).

During the entire 24 week study EAEs reported by ≥5.0% of patients in either treatment group were:

- EAEs that were more common with agomelatine: nasopharyngitis (8.6% in the agomelatine group and 7.5%, in the sertraline group) and fatigue (6.6% and 2.5%, respectively)
- EAEs that were more common with sertraline: headache (9.2% in the agomelatine group and 11.9% in the sertraline group), diarrhoea (6.6% and 6.9%, respectively) dry mouth (5.3% and 6.3%, respectively) and hyperhidrosis (1.3% and 5.0%, respectively).

During the initial 6 week period, EADRs were reported in 27.6% of the agomelatine group and 26.4% of the sertraline group. The most frequently reported EADRs during this period (>3.0% patients) were:

- Agomelatine: fatigue (5.9%), nausea (4.6%), dry mouth (3.9%) and headache (3.3%).
- Sertraline: hyperhidrosis (4.4%), nausea (3.1%), dry mouth (3.1%), and dizziness (3.1%).

Over the entire 24 week study period, EADRs were reported in 29.6% of the agomelatine group and 28.9% of the sertraline group. The most frequently reported EADRs over the entire study period (>3.0% patients) were:

- Agomelatine: fatigue (6.6%), nausea (4.6%), dry mouth (3.9%) and headache (3.3%).
- Sertraline: hyperhidrosis (4.4%), dry mouth (3.8%), dizziness (3.8%) and nausea (3.1%).

Deaths and other serious adverse events

There were no deaths during the study. SEAEs were reported in 3 agomelatine recipients (2.0%) and 4 sertraline recipients (2.5%). An additional patient assigned to agomelatine had an SEAE but did not take any study drug, and 2 additional sertraline patients had SAEs that were already present prior to treatment and were thus classified as non-emergent. None of the SAEs were considered to be treatment-related.

Withdrawals due to adverse events

10 (6.6%) of the agomelatine patients and 20 (12.6%) sertraline patients had EAEs resulting in treatment discontinuation. The majority were in the *Psychiatric Disorders* and *Gastrointestinal Disorders* SOCs.

Laboratory abnormalities

During short-term treatment (W0-W6), the mean changes in biochemical parameters were small, not clinically relevant, and similar in both groups, except for GGT (8.0 IU/L in the agomelatine group compared to -1.3 IU/L in the sertraline group). The mean GGT increase in the agomelatine group was largely explained by one patient with alcoholism and a large GGT increase that was not considered to be related to study treatment. Over the full 24 weeks of the study, differences between agomelatine and sertraline were observed for AST (respective mean changes 5.0 and 0.0 IU/L), ALT (5.4 and -0.4 IU/L) and GGT (9.9 and 0.8 IU/L). The mean increases in the agomelatine group were due to high values in 2 patients (the previously described patient with alcoholism and another patient), which were classified by the investigators as not related to study treatment.

PCSA values for hepatic laboratory parameters were more common with agomelatine (7 patients, or 4.6%) than sertraline (1 patient, or 0.6%).

Mean values for haematology parameters did not change significantly during short term treatment or over the full 24 week study period. There were no clinically relevant differences between agomelatine and sertraline in respect of mean changes or the proportion of patients with PCSA haematology values.

Vital signs and body weight

There were no clinically relevant differences between agomelatine and sertraline in respect of changes in heart rate, blood pressure, or body weight.

Evaluator comments

In CL3-046:

The most common EAEs in agomelatine recipients were headache, nasopharyngitis, diarrhoea, fatigue and dry mouth. The most common EADRs were fatigue, nausea, dry mouth and headache. The overall proportion of patients with EAEs and EADRs was comparable for agomelatine and sertraline, but treatment withdrawal due to EAEs was less common with agomelatine.

Agomelatine was associated with an increase in mean transaminase levels, although this was exaggerated by the results from one patient in whom the abnormality was not considered to be treatment-related. Nevertheless, agomelatine recipients were more likely than sertraline recipients to have PCSA transaminase elevations. No safety signals were seen in respect of non-hepatic biochemistry and haematology parameters.

These findings are consistent with data in the original submission and the *Summary of Clinical Safety*.

CL1-054, PKH-066 and CL1-049

In studies CL1-054, PKH-066 and CL1-049 there were no deaths, SAEs or AEs leading to the discontinuation of agomelatine.

Post-marketing experience

No post-marketing data were available at the time of submission.

Evaluator comments

The *Risk Management Plan* referred to a post-marketing observational study in the Ukraine, but this was not submitted for review.

Given that agomelatine was approved for marketing in the EU in February 2009, post-marketing data from the EU may be available by the time the submission is considered by ADEC, and if so should be included in the pre-ADEC response.

Conclusions regarding safety

Overall safety conclusions

The safety profile of agomelatine as evidenced in the current submission is essentially unchanged from that described in the original submission.

In regard to hepatic safety, the data show that agomelatine produces a dose-related increase in hepatic enzymes, but (as far as can be determined from the premarketing database) this is probably not associated with a risk of severe DILI that would preclude registration, provided the use of the drug is appropriately controlled.

Importantly, however, the resubmission has failed to address one of the identified deficiencies of the original data, namely inadequate safety information from patients treated long-term with the 50 mg dose. In the original submission, no patients had received the 50 mg dose for ≥12 months. In the current submission, 12-month safety data for the 50 mg dose are now available for 44 patients (32 in the *Summary of Clinical Safety*, plus 12 in CL3-041). However, the data for CL3-041 were not consolidated for the entire 12 month period and there was no overall analysis of safety covering the whole one-year 50 mg patient group. In any case, the number of patients studied for 12 months at the 50 mg dose remains inadequate for a drug that is likely to be taken long term (potentially for years), and for which the 50 mg dose is needed to produce a satisfactory clinical response in about 15-25% of patients. A notional way around this deficiency might be to propose registration at a maximum dose of 25 mg once daily, but the available data do not allow this. Firstly, the existing demonstration of short-term efficacy is based on the combination of the 25 and 50 mg doses, and secondly, agomelatine was only shown to reduce relapse rates when the option of increasing the dose to 50 mg was available.

Also in relation to long-term treatment, there is no information regarding of the *prevalence* of adverse events over time at either the 25 mg dose or the 50 mg dose (as distinct from the emergence of new events).

Clinical Summary and Conclusions

The resubmission has addressed one of the identified deficiencies of the original submission, namely the lack of data regarding the absolute bioavailability of agomelatine. It has also partially addressed the issue of long-term efficacy, in that it demonstrates that if a patient responds to agomelatine 25/50 mg, then continuation of agomelatine at that dose will prolong the duration of the response and thereby reduce the risk of a relapse.

The clinical evaluator considered however, that the resubmission has not adequately addressed two of the main reasons for the recommended rejection of the original submission, namely:

- The efficacy of agomelatine in MDD is statistically superior to placebo but the effect may be due primarily to improvements in sleep rather than mood and the magnitude of the effect is of doubtful clinical relevance; and
- The safety of the 50 mg dose has not been studied for 12 months or more in an adequate number of patients, given the expected proportion of patients who will be titrated to that dose and the expected long-term duration of treatment.

Accordingly, approval of the submission by Servier Laboratories Australia Pty Ltd to register Valdoxan 25 mg tablets for the treatment of major depression in adults including prevention of relapse was not recommended.

Supplementary Data

The clinical data discussed in the previous section was considered by ADEC in August 2009 and ADEC recommended rejection as discussed under *Second Submission (2009)* in Section I. As also noted in Section I under *Second Submission (2090) – supplementary clinical data*, the sponsor submitted further data to address the deficiencies identified by ADEC. The submitted data included one new study to address the proposed indication of the treatment of depression in adults including relapse prevention. This study was performed in accordance with the principles of GCP.

The title and ID of the submitted study was:

"Efficacy and safety of agomelatine (25 mg/d with potential adjustment to 50 mg/d) given orally for 8 weeks in out-patients with Major Depressive Disorder. A randomised double-blind, parallel groups international study versus fluoxetine (20 mg/d with potential adjustment to 40 mg/d) with a double-blind extension period of 16 weeks (**CL3-045**)."

Study CL3-045

The primary objective of this study was to assess the superiority of agomelatine to fluoxetine using the Hamilton Depression Rating Scale 17 items (HAM-D), after an 8-week treatment in out-patients suffering from Major Depressive Disorder (MDD). The secondary objective was to provide additional sleep, anxiety and safety data in this population.

The study was conducted at 41 centres in Argentina, Brazil, Italy, Spain and the UK. The methodology is briefly outlined in Table 13 including details of study participants, diagnosis and selection criteria. Exclusion criteria included all types of depression other than MDD, other psychiatric, neurological or severe medical conditions, alcohol or drug abuse/dependence within 12 months, other psychotropic medications or treatments prone to interfere with the central nervous system or study evaluations. Zolpidem was allowed until week 2 to a maximum dose of 10 mg. Stable treatment with thyroid hormones, HRT and β-blockers was allowed throughout. Study treatments were administered in the morning (fluoxetine/placebo) and evening (agomelatine/placebo) using a double-dummy procedure. Randomisation was balanced and stratified by a centre using a list generated by the sponsor. An interactive voice response system (IVRS) was used to carry out randomisation and dose adjustments at weeks 2 and 4, none of which were disclosed to investigator or patient.

The primary efficacy measure was the 17-item HAM-D, with secondary assessments including the Clinical Global Improvement severity (CGI-S) and improvement (CGI-I) scales, Hamilton Anxiety Rating Scale (HAM-A) and the Leeds Sleep Evaluation Questionnaire (LSEQ). Other secondary assessments included response to treatment (decrease of ≥50% on HAM-D) and remission (total HAM-D ≤6).

Table 13: Details of Study CL3-045

Design	Study posology	Subjects: Randomised (completed, %)	Duration	Gender: M/F (age)	Diagnosis & main selection criteria	Primary endpoint
Phase 3 double-blind, multicentre, randomised, parallel group, comparative study of agomelatine & fluoxetine. Randomisation and dose adjustments using IVRS.	Agomelatine 25 mg/d, increase to 50 mg/d at week 2 allowed. Fluoxetine 20 mg/d, increase to 40 mg/d at week 4 allowed. Increase in dose if insufficient response using *a priori* fixed criteria.	Assessed n=593 W0-W8: Agomelatine 252 (222, 88%), FAS 247; Fluoxetine 263 (214, 81%), FAS 257. W8-W24: Agomelatine 212 (170, 80%), SUB-FAS 208; Fluoxetine 197 (170, 86%), SUB-FAS 191 Safety set: Agomelatine n=250, fluoxetine n=263	3-7 day run-in period, 8 weeks acute study, optional extension of 16 weeks, 1 week follow-up period	Agomelatine: 194 F, 58M 41.8 ± 11.2 years (18-65) Fluoxetine: 206 F, 57M 42.7 ± 11.9 years (18-65)	M/F, aged 18-65 years, outpatients. DSM-IV-TR criteria for MDD, HAMD-17 ≥ 25, CGI-S ≥ 4; & 7 of symptoms A1-A9 of criteria for MDE present and markedly interfering with functioning	W0-W8: 17 item HAM-D total score change from baseline to W8 or last post-baseline value. W0-W24: HAM-D response, HAM-D remission, CGI-scores.

The statistical analysis plan involved initial investigation of the non-inferiority of agomelatine relative to fluoxetine using a non-inferiority margin of 1.5. In the case of a significant non-inferiority test, the superiority of agomelatine versus fluoxetine was to be tested. The two analyses were carried out on the Full Analysis Set (FAS) which was defined as patients of the randomised set who had taken at least one dose of study medication and had both a baseline and at least one post-baseline HAM-D rating. The change in HAM-D total score from baseline to last-post baseline value until W8 was analysed using two-way analysis of covariance (ANCOVA) with baseline as covariate and no interaction. A sensitivity analysis of the last post-baseline value until W8 was performed using a two-sided Student's t-test for independent samples and response to treatment (defined as a HAM-D decrease of ≥ 50%) was examined using a Chi-Square test. The last values of the CGI-scores were also analysed by a two-sided Student's t-test for independent samples and Mann-Whitney test, and response to treatment (last CGI-I value) using a Chi-Square test. For the extension phase, response to treatment, remission and CGI scores were examined in both the FAS and the SUBFAS (those subjects who entered the extension period and had at least one post W8 efficacy assessment) sets. Sample size was estimated from the final 17-item HAM-D total score from a previous 8 week study of agomelatine and fluoxetine.

Results

The number of subjects who were assessed, randomised and completed either the acute (W0-W8) or extension (W8-W24) phases of the study is detailed in Table 13. The major reason for non-inclusion was not meeting the study diagnosis or inclusion criteria. Of those randomised to treatment, more patients were withdrawn during W0-W8 for fluoxetine (17%: adverse event 6.5%, non-medical reason 4.9%, lack of efficacy 4.9%) compared to agomelatine (12%: adverse event 4.0%, non-medical reason 3.6%, lack of efficacy 2.8%). Conversely, more patients were withdrawn during W8-W24 for agomelatine (20%: non-medical reason 9.9%, lack of efficacy 4.7%, adverse event 4.2%) compared to fluoxetine (13%: non-medical reason 8.1%, lack of efficacy 3.0%, adverse event 0.5%). Overall, 68% of agomelatine and 66% of fluoxetine patients completed the study (W0-W24). The number of subjects with protocol deviations was high for both phases of the study: W0-W8 agomelatine (56%), fluoxetine (54%); for W8-W24 agomelatine (72%), fluoxetine (68%). The majority of these were related to study administration, that is, duration of treatment or failure to complete the LSEQ.

There was no relevant difference between the treatment groups for the main demographic measures or for BMI, vital signs, smoking or alcohol habits. The majority of the subjects were diagnosed with recurrent MDD (63.5%) with the rest being single episode MDD and 94 % were diagnosed with severe MDD (DSM-IV-TR). There was no relevant difference between the treatment groups for these and other psychiatric history variables. Baseline ratings were also similar between groups: HAM-D 28.5± 2.7, 28.7 ± 2.5 (agomelatine, fluoxetine); CGI-S both 5.0 ± 0.6; HAM-A 25.9 ± 7.0, 26.3 ±7.0 respectively. Medical and surgical history, previous psychotropic treatment and concomitant treatment at baseline were balanced across groups. Demographic data for the FAS and SUBFAS sets were similar to the randomised set described above.

The majority of subjects remained on the starting dose for the acute phase with only 29% of agomelatine subjects increased to 50 mg/d and 23% of fluoxetine subjects increased to 40 mg/d. During both phases 16% received concomitant treatment (zolpidem, thyroid hormones and β-blockers).

For the primary efficacy analyses, the mean decreases in HAM-D total scores from W0 to last post-baseline visit were -17.3 ± 7.3 and -16.0 ± 8.4 for agomelatine and fluoxetine respectively. This was significantly different for the non-inferiority test based on the non-inferiority margin of -1.5 ($p<0.001$). This allowed for a superiority test which was also statistically significant (estimate of the difference between treatment groups =1.49, 2-sided 95% CI [0.20; 2.77] p= 0.024). Both tests were then confirmed by the sensitivity analysis (non-inferiority $p<0.001$, superiority p=0.030).

The proportion of HAM-D responders for the W0-W8 phase were 71.7% and 63.8% for agomelatine and fluoxetine respectively (p=0.060) whilst for the W0-W24 phase the figures were FAS set 78.9% and 74.3%, SUBFAS 87.5% and 91.6% respectively. The proportion of HAM-D remitters (HAM-D ≤6) for the W0-W8 phase were 32.0% and 28.4% for agomelatine and fluoxetine respectively and for the W0-W24 phase FAS set 51.4% and 50.2%, SUBFAS 59.1% and 64.9% respectively. There were no significant differences between treatments for the final CGI-scores for either the W0-W8 or W0-W24 periods. There was a significant difference in the proportion of CGI-I responders (score of ≤ 2) in favour of agomelatine for the W0-W8 phase (77.7% versus 68.8%, p=0.023) but no difference between groups for the extension phase. There were no significant differences between treatments for CGI remitters (CGI-I =1) for either phases. There were no differences between low and high dose groups for either any of the efficacy measures.

Changes in HAM-A scores from W0 to W8 were similar in both groups for total and both psychic and somatic anxiety scores. Similarly, similar decreases were found from W2 to W8 for the factors of the LSEQ (getting off to sleep, quality of sleep, sleep awakening, integrity of behaviour), however, the HAM-D sleep sub-scale (items 4, 5 and 6) was significantly lower for agomelatine at last visit (p=0.018, independent t-test, complementary analysis).

The primary efficacy analysis was positive for agomelatine. The majority of the secondary assessments showed no differences between treatments either for the acute or extension phases of the study.

Evaluator's overall conclusions on clinical efficacy

The design of the study is in agreement with the current recommendations of the EMEA for guidance on medicinal products in the treatment of depression (CPMP/EWP/518/97, 2002). This includes diagnosis, selection criteria, treatment period and efficacy measures. Dosage selection for both study treatments was appropriate. Statistical procedures were appropriate as was the non-inferiority margin of 1.5. The major criticism of the study is that a placebo-arm was not included, however, given the number of placebo-studies already completed this is acceptable. The primary efficacy variable found that agomelatine was significantly better than fluoxetine. The clinical relevance of this finding is marginal since the changes in HAM-D were similar for each treatment arm and the difference in HAM-D scores between the groups at the final assessment (acute phase) was 1.3 which is less than the non-inferiority margin of 1.5. There were no clinically relevant

differences between the groups for any of the variables over the 24 week study. The study demonstrates that both treatments are effective antidepressants as changes in HAM-D, response and remission rates are similar to other studies in this area. It also shows that agomelatine is at least as effective an antidepressant as fluoxetine and that this effect is maintained over the 6 month extension period. This is particularly of interest since previous studies were criticised for using minimally effective doses (20 mg/d) of SSRIs whereas the dose of fluoxetine in this study was 20 or 40 mg/d.

Safety

The submission included the one new study (**CL3-045**) and the first 6-monthly Periodic Safety Update Report (PSUR) from 19 February to 19 August 2009.

Patient Exposure

The details of subjects included in the safety analysis for **CL3-045** are included in Table 13. Of the subjects included in the safety set and treated with agomelatine, 171 were treated with 25 mg, 70 with 25-50 mg and 9 withdrew before week 2 whilst for fluoxetine 177 were treated with 20 mg, 53 with 20-40 mg and 33 withdrew before week 4. Of the agomelatine subjects, 122 completed the full 24 weeks for the 25 mg dose and 48 in the 25/50 dose group.

Adverse Events

During the W0-W8 period, the proportion of subjects with at least one treatment emergent adverse event (TEAE) was similar in the agomelatine group (57.2%) and the fluoxetine groups (56.3%). The most frequent system organ classes affected were gastrointestinal disorders for both groups (26.4%, 26.6% respectively). In both groups the most frequent TEAEs were headache (16.0%, 11.4%), nausea (8%, 11.4%) and somnolence (6%, 3.4%). The majority of TEAEs were mild or moderate in both groups and the proportion of events considered related to treatment was 38.4% v 41.1% respectively. During the W0-W24 period, the proportion of subjects with at least one TEAE was similar in the agomelatine group (67.2%) and the fluoxetine groups (64.3%) with headache and nausea again the most commonly reported for both groups. The majority of TEAEs were mild or moderate in both groups and the proportion of events considered related to treatment was 42.0% v 44.1% respectively.

Serious adverse events and death

There were no deaths during the study. Over the whole study period, 10 subjects on agomelatine (5 in each dose group) and 4 on fluoxetine (all 20 mg) experienced a serious adverse event. Most of these were not considered related to treatment with the exception of myocardial ischemia (doubtful, agomelatine 25-50 mg) and increased hepatic enzymes (probably, agomelatine 25 mg). All patients were recovered or recovering at the end of the study.

Laboratory findings

Changes from baseline to last observation under treatment were similar for both treatment groups for all biochemical (liver parameters discussed separately) and haematological parameters for both W0-W8 and W0-W24 periods. Percentage of patients with at least one emergent out-of-reference range value for biochemical parameters were similar across both treatment groups with the most frequent being increases in glucose (11.5%, agomelatine, 12.3% fluoxetine), total cholesterol (11.1%, 11.9%) and triglycerides (9.0%, 11.1%) over W0-W24. Overall, potentially clinically significant abnormalities (PCSA) were observed for 15 patients (6.0%) in the agomelatine group and 18 patients (6.8%) in the fluoxetine group, the majority of which were increased triglycerides. Emergent out-of-reference range values for haematological parameters were similar across both treatment groups with the most frequent being decreased lymphocytes (6.6%, 10.2%), increased eosinophils (7.9%, 5.5%), increased WBC (7.8%, 2.1%), and increased basophils (7.0%, 5.1%) from W0-W24. PCSA values were rare for haematological parameters with only 3 subjects in each

treatment group. The most common was high WBC overall. In general there were no relevant differences between treatments or doses for these laboratory parameters.

Over both acute and extension periods, there were increases in mean AST and ALT for agomelatine from baseline to last observation under treatment particularly for the 25 mg group. Emergent out-of-reference range values for liver parameters across the full 24 weeks were similar for AST (5.5% agomelatine, 6.0% fluoxetine) but higher for agomelatine than fluoxetine for both ALT (11.5%, 6.0%) and GGT (7.2%, 5.1%). The higher dose groups for both drugs had higher rates with the exception of ALT in which both agomelatine dose groups had similar rates. PCSA values were observed in 6 agomelatine patients (4 25 mg, 2 25-50 mg) and 1 fluoxetine (20 mg) patient for one or more transaminase. In the agomelatine group, 3 patients had PCSA ALT (x 6.1, x 15.2, x 19.5 ULN) associated with PCSA AST (x 4.3, x 7.9, x 10.9 ULN) and 2 also had PCSA GGT (x 3.1 and x 4.4 ULN). The other 3 had PCSA ALT (x 3.4, x 4.1, x 5.8 ULN) and AST and GGT above the upper normal limit but not at PCSA levels. The last patient had PCSA GGT (x 4 ULN). In the fluoxetine group, one patient had a PSCA AST (x 3 ULN) and one patient had a PSCA GGT (x 3 ULN). Three agomelatine patients recovered following drug withdrawal whilst 2 recovered without drug withdrawal as did one fluoxetine patient.

Changes from baseline to last post-baseline value for vital signs were similar for both treatment groups over the full 24 weeks. Weight gain was similar for both groups (5.6% agomelatine, 6.5% fluoxetine) and the majority of patients remained in the same BMI class as at baseline. The rate of treatment emergent ECG abnormalities was similar across treatments (both (18%) commonly bradycardia and repolarisation disturbances. Clinically significant ECG abnormalities included 3 subjects with prolonged QT intervals, one subject in the 25-50 mg agomelatine and both fluoxetine dose groups.

Discontinuations due to adverse events

Adverse events led to treatment discontinuation in 39 subjects over the 24 week period. Four were serious (hepatic enzymes increased, intentional overdose, congestive cardiomyopathy, suicidal behaviour). All four subjects were treated with agomelatine but only the first event was thought to be treatment related. Of the 35 non-serious events, 16 were treated with agomelatine and 19 fluoxetine. The incidence of treatment withdrawals was not different between the treatment groups (8.0% versus 7.2%).

Post marketing experience

The first PSUR for agomelatine from its marketing authorization date in Europe (19 February 2009) to 19 August 2009 was submitted. The report summarises safety information received by the Pharmacovigilance Department of Institut de Reserches Servier from worldwide sources. All spontaneous reports and all serious adverse drug reactions from clinical trials or post-authorisation studies are presented in this report.

A total of 90 medically confirmed reports are included whilst 33 non-medically confirmed reports were excluded. Three patients died - two were suicides and one a sudden death in a patient with several cardiovascular risk factors. Adverse events of special interest nominated in the agomelatine Risk Management Plan are liver adverse reactions, skin reactions and suicide events. Six patients experienced liver adverse reactions including 4 patients with AST or ALT values >x 3 ULN (25 and 50 mg doses, 2 subjects each). Skin reactions were reported for 15 patients with only 2 being considered serious (angioedema in one patient; generalized erythema, pruritis, facial swelling and urticaria in another). Two completed suicides, one suicide attempt and one intentional self-injury were reported with all 4 patients having a history of previous suicide attempts and 9 reports of suicidal ideation.

The overall safety data base has been updated to include new results from studies **CL3-045, -047, -048, -052, -056** and **-063** to now include 6067 agomelatine-treated patients. The cumulative data on

liver function test abnormalities shows that the incidence of emergent elevation of ALT and/or AST > x 3 ULN was 1.19% (52/4363) compared to 0.71% (8/1128) in the placebo group. No patient experienced an isolated alkaline phosphatase > x 3 ULN. The incidence of isolated elevations of total bilirubin > x 3 ULN was 0.02% (1/4356) for agomelatine and 0.18% (2/1128) for placebo treated patients. New cases from the above listed studies were reviewed by 5 independent hepatologists/internal medicine specialists. A majority of cases had confounding factors mainly overweight/obesity (12/22) or other factors such as alcohol intake, lipid abnormalities, non-alcoholic fatty liver disease, viral gastroenteritis, acute hepatitis E that may have contributed to the elevations. The majority of cases were asymptomatic, detectable within the first months of treatment and all were fully reversible (except for one case with a history of transaminase increases over the previous 18 months, before entering the study). None of the cases were considered to meet the criteria to be a Hy's Law case, that is, to indicate that severe liver damage had been caused by the drug.

From the data presented, there was no added information to indicate a need for amendments to the European Summary of Product Characteristics.

Evaluator's overall conclusions on clinical safety

The methodology used to evaluate the safety and tolerability of agomelatine in study **CL3-045** was appropriate. Assessments were done at least at baseline and end of treatment. Laboratory normal ranges and potentially clinically significant abnormal values were defined in the protocols. The findings are in keeping with the established safety profile of agomelatine. There were no new safety signals from either the acute or extension period. There were a further 48 patients treated with the 25/50 mg dose for 24 weeks. There was no evidence of a dose-effect in this study for any of the adverse events or in particular for the liver abnormalities or for any additional safety concerns.

Conclusion

Currently available antidepressants have limited efficacy – with all antidepressants having similar response rates of only about 50-60 %. But even fewer patients, 30-40%, achieve a full remission of symptoms and remission is necessary to achieve a return to normal psychosocial functioning, such as work or studies. It is now well known that remission of depression is needed to reduce physical morbidity and mortality, suicide risk and adverse effects on the family. A recent large US effectiveness study, STAR*D, found that of 2876 "real world" patients with major depression who received open-label citalopram for 12 weeks, only 28% achieved remission (Warden et al 2007).[25] There is therefore a continuing need for the introduction of novel treatments for depression.

The main mechanism of action of most of the current antidepressant medications, with only a few exceptions, is serotonin and/or noradrenaline reuptake inhibition, making these neurotransmitters more available at the synaptic cleft. The tricyclic antidepressants became available in the 1960's and it was the 1980's that the SSRI's, safer and better tolerated antidepressants, were introduced. These antidepressants have therefore been available for close to three decades and none of the newer antidepressants introduced over recent years are particularly innovative. Venlafaxine was the first of the dual acting antidepressants (SNRIs), which was launched in the mid 90's and mirtazapine at a similar time. The latter is derived from the tetracyclic mianserin with a similar mode of action. Escitalopram is derived from citalopram but is also an SSRI. There has not been a truly novel antidepressant introduced for many years. Duloxetine and desvenlafaxine are both SNRIs.

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[25] Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D project results: A comprehensive review of findings. Current Psychiatry Reports 2007; 9: 449-459.

Over the past decade and longer, several pharmaceutical companies have been pursuing a variety of innovative approaches in an attempt to broaden the repertoire available for antidepressant treatment. These new perspectives have been based on findings from research into the underlying pathophysiology of depression. Sleep-wake cycle abnormalities are almost universal in MDD, as are changes in circadian rhythm with a variety of endocrine abnormalities, such as cortisol, growth hormone, thyroid and melatonin. The antidepressant agomelatine has been developed as a consequence of this line of research in depression.

Is agomelatine a novel antidepressant?

Agomelatine is a melatonergic receptor agonist (MT_1 and MT_2) and therefore its mechanism of action may differ from all other antidepressants. It is hypothesized that its mechanism of action is to correct the abnormalities of circadian rhythm in patients suffering from depression. However it does also have serotonin 5-HT_{2C} receptor antagonist activity and this may confer its antidepressant effect. Therefore the putative mechanism of antidepressant action for agomelatine is not clear. It may be its activity as a melatonin agonist or a 5-HT_{2C} antagonist or both actions. If a standard serotonin reuptake inhibitor or serotonin and noradrenaline reuptake inhibitor is not helping a patient, then theoretically an antidepressant with a unique mode of action would be worthwhile trialling as an alternative. Most clinicians when switching antidepressants because of poor response to treatment will choose one from a different class. Also because of its postulated unique mode of action it has two possible advantages over currently available antidepressants. Its effect on melatonin receptors and circadian rhythm indicates it should improve sleep problems, a very common issue in depression. Secondly, as it does not increase serotonin availability at the receptor, sexual side effects should be avoided. There is in fact evidence available supporting both of these. Sexual problems are present in approximately 50% of patients who receive a standard SSRI or SNRI and are probably by far the most important reason for poor compliance.

Does agomelatine have proven antidepressant efficacy?

Double-blind placebo controlled trials remain the key to proving efficacy for new drugs. They do not tell us how the new drug will perform in everyday clinical settings but nonetheless this information is critical to determining if the medication works. In clinical practice, whether general practice or a general psychiatrist practice, the average patient will have significant co-morbidity such as medical disorder, anxiety disorder or substance abuse, and the medication will perform less well as was demonstrated in STAR*D. To some extent co-morbidity is excluded in clinical trials, but imperfectly, and all of the standard trials are troubled by the broad definition of "Major Depression" which usually subsumes a mix of patients some with a more biological problem but many with depressions that are probably more likely to have a strong psychosocial basis. Unfortunately we still have no biological markers to help us identify those patients with a more biological illness and who are more likely to respond to antidepressants. Hence the disappointing results with antidepressant drug trials. If we were to apply the same strict criteria for efficacy as we do today for the older antidepressants, it is likely there would be very few if any on the market.

There have been 6 double-blind placebo controlled short term trials with three being positive (that is, statistically significant), one negative (no statistical difference) and two failed (lack of assay sensitivity) trials (**CL3-014** Loo et al 2002**,**[26] **CL3-042** Olie & Kasper 2007**,**[27] **CL3-043** Kennedy & Elmsley 2006**,**[28] **CL3-022, CL3-023** and **CL3-024** respectively). In the primary efficacy

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[26] Loo H, Hale A, D'Haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT2C antagonist, in the treatment of major depressive disorder: A placebo-controlled dose range study. International Clinical Psychopharmacology 2002; 17: 239-247.

[27] Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. International J Neuropsychopharmacology 2007*;* 10: 661-673.

[28] Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. J Clinical Psychopharmacology 2008; 28: 329–333.

analyses, mean differences between agomelatine and placebo for final HAM-D score were 2.57, 3.44 and 2.30 for the three positive studies **CL3-014, CL3-042** and **CL3-043.** These drug-placebo differences are clinically relevant and of similar magnitude to those obtained in pivotal studies with fluoxetine, paroxetine, sertraline, venlafaxine, citalopram (Kirsch et al 2002),[29] desvenlafaxine (Yang and Plosker 2008)[30] and duloxetine (MIMS prescribing information). In addition, for a secondary efficacy analysis (CGI-S, a measure of global improvement), mean differences between agomelatine and placebo were also positive for all three studies as were the HAM-D responder differences. Overall, in the opinion of the evaluators, agomelatine has been shown to have efficacy and its degree of efficacy is similar to antidepressants currently on the market. The degree of efficacy of all antidepressants is diluted by the high placebo response rates in numerous trials. There are many complex reasons why this occurs. It is well recognised that patients who receive placebo treatment in all trials receive considerable input – they are made to feel important by research staff and given encouragement for their ongoing involvement in the study. These factors boost the placebo response, however, it is well recognised that many relapses occur soon after study cessation.

The negative study had fluoxetine as the comparator arm which was shown to be significantly superior to placebo (**CL3-022**). The current submission has presented data from a non-inferiority comparison of fluoxetine versus agomelatine (**CL3-045**). In this study which had no placebo arm, agomelatine was shown to be significantly superior to fluoxetine. Thus there are three supportive studies which show that agomelatine has at least the same efficacy as the Australian-registered antidepressants fluoxetine, sertraline and venlafaxine (**CL3-045** Hale et al, **CL3-046** Kasper et al, **CL3-035** Lemoine et al 2007 respectively). [31, 32, 33] In the opinion of the evaluators, this is sufficient evidence supporting agomelatine efficacy in the treatment of acute depressive episodes.

Does agomelatine prevent recurrence/relapse of depression?

In the previous submissions, two relapse prevention studies were presented with one being positive (**CL3-041**) and the second negative (**CL3-021**). The positive study showed highly significant differences in relapse rates at both 24 and 44 weeks for agomelatine compared with placebo. The negative study had an unusually low relapse rate for placebo therefore agomelatine did not separate from placebo. In addition, data from the extension phase of study CL3-022 found both agomelatine and fluoxetine were significantly better than placebo in preventing relapses. The evaluators agreed that there is sufficient evidence that agomelatine does prevent relapse/recurrence of depression. Relapse prevention is further encouraging evidential support that a drug has efficacy – by keeping a person well one would deduce it is preventing recurrences and therefore exerting a positive effect. Furthermore, this submission has presented data which confirm that agomelatine maintains antidepressant activity over a 6 month period with similar efficacy to fluoxetine (**CL3-045**).

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[29] Kirsch I, Moore TJ, Scoboria A. The emperor's new drugs: an analysis of antidepressant medication data submitted to the U.S Food and Drug Administration. Prevention & Treatment 2002; 5: 1-14.

[30] Yang LPH, Plosker GL. Desvenlafaxine extended release. CNS Drugs 2008; 22: 1061-1069.

[31] Hale AS, Corral R-M, Mencacci C, Ruiz JS, Severo CA, Gentil V. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. International Clinical Psychopharmacy 2010; 25: 305-314.

[32] Kasper S, Wulff K, Hajak G, et al. The novel antidepressant agomelatine improves the circadian rest-activity cycle, depressive and anxiety symptoms in patients with Major Depressive Disorders. A randomized, double-blind comparison with sertraline. J Clin Psychiatry, 2010; 71: 109-120.

[33] Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant agomelatine: Randomized double-blind comparison with venlafaxine. J Clin Psychiatry 2007; 68: 1723-1732.

Is agomelatine safe? Does agomelatine have improved tolerability or any other advantages over other antidepressants?

The side effect profile of agomelatine is encouraging. It does not have the anticholinergic side effects of the early tricyclics or cause cardiac arrhythmias or lower blood pressure. Nausea and headache are the most common side effects but these are similar to comparator compounds (nausea less than for paroxetine). Most of the currently available antidepressants, tricyclics, SSRIs and SNRIs, increase serotonin availability at the synaptic cleft, and this is believed to be the cause of the sexual side effects that are common with these drugs – loss of libido, impotence, ejaculatory failure and anorgasmia. There are two published studies that have compared favourably the sexual side effects of agomelatine to other antidepressants, venlafaxine and paroxetine (**CL3-036** Kennedy et al 2008, **CL3-049** Montejo et al 2008).[34,35] Because of its possible unique mode of action, agomelatine has been found to have a significant advantage over both venlafaxine and sertraline for early improvement of sleep quality (**CL3-035** Lemoine et al, **CL3-046** Kasper et al**).** As sleep disturbance is a common symptom in depression, it is likely this property will improve compliance with treatment. Agomelatine has not been associated with weight gain or withdrawal syndrome (**CL3-030** Montgomery et al); this is in contrast to most SSRIs and SNRIs and many antidepressants.

The potential for hepatotoxicity is the major drawback to the use of agomelatine. The data presented in the PSUR indicated that the incidence of emergent elevation of ALT and/or AST > x 3 ULN was 1.19% compared to 0.71% in the placebo group from a data base of over 6000 patients.

Some subjects recovered whilst continuing on agomelatine whilst others were withdrawn, however, the majority of subjects' liver function normalized. Since there are often no obvious clinical symptoms, routine monitoring of liver function is recommended.

Agomelatine has been clearly shown to be more effective than placebo in acute studies and of similar efficacy to other current antidepressants. The longer term studies show evidence of maintenance of effect and relapse prevention that is of considerable clinical benefit. This coupled with the overall favourable tolerability and safety profile including a positive effect on sleep and lack of sexual side-effects leads to a positive risk benefit for agomelatine. The evaluators recommended that it be registered for the proposed indication.

Recommended Conditions for Registration and Product Information

The EU recommendations for monitoring liver function are appropriate and are also recommended in the proposed PI. This should be mandatory.

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[34] Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. European Neuropsychopharmacology 2006; 16: 93-100.

[35] Montejo AL, Prieto N, Terleira A, et al. Better sexual acceptability of agomelatine (25 and 50 mg) compared with paroxetine (20 mg) in healthy male volunteers: An 8-week placebo-controlled study using the PRSEXDQ-SALSEX scale. J Psychopharmacology 2010; 24: 111-20.

V. Pharmacovigilance Findings

Risk Management Plan

The Risk Management Plan (RMP) was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). Safety concerns identified by the sponsor were as follows:

Identified risk	Elevated transaminases leading to a risk of hepatotoxicity
Potential risks	Skin reactions
	Suicide
Missing or limited information	Severe or moderate renal impairment
	Paediatric age group (< 18 years)
	Elderly > 75 years
	Pregnancy
	Lactation
	Hepatic impairment
Drug interactions	Interactions with potent CYP1A2 inhibitors (for example, fluvoxamine, ciprofloxacin) leading to increased serum levels of agomelatine.

The sponsor proposed routine and additional pharmacovigilance activities for the areas of identified and potential risk, and the area of missing or limited information. The routine pharmacovigilance activities proposed by the Sponsor are consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03).* The sponsor also proposed five additional pharmacovigilance activities.

1. Epidemiology study

A 24 week epidemiological, observational (non-interventional), multi-centred study located in Europe. The aim of this study is to collect safety data observed in current medical practice in patients treated with agomelatine. The specific focus will be on patients on agomelatine who develop hepatic disorders, suicide related behaviours and skin events, and the development of ADRs in elderly patients and patients with known renal impairment. The planned number of participants is 10,000 people.

2. Randomised, double-blind, controlled trial

An 8 week, randomised, double-blind, multi-centre study with parallel groups (versus placebo) for elderly patients (aged > 65 years). The aim is to determine the efficacy and safety of agomelatine in the elderly.

3. Hepatic disorder questionnaire

The sponsor proposes to use a specific hepatic disorder questionnaire for all hepatic adverse drug reaction reports. The aim of this activity is to enhance the quality of data collection of spontaneous ADR reports for hepatic events, including collecting information on concomitant hepatotoxic drugs. The information will be presented in a PSUR.

4. Safety Survey

The sponsor has proposed to conduct a retrospective safety survey using the General Practice Research Database in the United Kingdom to document the incidence of hepatobiliary disorders in the general practice setting relative to other anti-depressants and relative to the general population. The sponsor will present this information in a PSUR.

5. DNA analysis

The sponsor will implement specific investigations, including DNA analysis (to determine genetic polymorphism) in clinical trial patients who develop transaminases > 3ULN or bilirubin > 2ULN.

Additionally the sponsor has proposed risk minimisation strategies for the safety issues of raised hepatic transaminases leading to hepatotoxicity and interactions with potent CYP1A2 inhibitors. These strategies are to recommend routine monitoring of LFTs for all individuals on agomelatine, and to provide educational material to prescribers regarding raised hepatic transaminases leading to hepatotoxicity and interactions with potent CYP1A2 inhibitors.

The following safety issues were identified by the OMSM reviewer:

- There is a lack of information regarding proposed milestones for all of the proposed pharmacovigilance activities and risk minimisation strategies.
- Information regarding the use of agomelatine in pregnant females appears to be an area of deficiency. It was suggested that the sponsor make some provisions to gain information regarding the safety profile of agomelatine in this group (for example, by setting up a registry).
- It was suggested that the sponsor provide copies of the educational material they intend to supply to prescribers for evaluation.
- It was suggested that the sponsor clarifies the types of DNA analysis they wish to undertake in patients in clinical trials who suffer from DILI and the reason for this intervention
- It was suggested that the application provide more information on how they intend to monitor the success of the educational materials for prescribers.
- It was suggested the hepatic disorder questionnaire should be used in the data collection for Australian patients who suffer from hepatic ADRs and consequently the sponsor should clarify if this will take place (this was later confirmed).

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

There were no pharmaceutical chemistry objections to registration.

It has previously been noted that food has no significant effect on the extent of absorption of agomelatine but it reduces C_{max} but about 20 – 30%. The low oral bioavailability (1.0% [90% CI 0.8 – 1.3%]) is due to extensive first pass metabolism rather than poor absorption. Thus relatively small reductions in first pass metabolism could lead to a substantial increase in systemic exposure to agomelatine.

Nonclinical

In the previous submission the nonclinical evaluator had no objections to the registration of agomelatine arising from the evaluation of the comprehensive package submitted by the sponsor. With this submission there was no new nonclinical data and the conclusions and recommendations of the original nonclinical evaluation report remain valid.

Agomelatine is an agonist at MT_1 and MT_2 melatonin receptors and an antagonist at $5HT_{2c}$ receptors and is active in animal models of depression, anxiety and desynchronisation of circadian rhythms. Agomelatine induced the hepatic enzymes CYP2B1/2, CYP1A1/2, 3A1/2 and uridine diphosphate glucuronosyltransferases (UGT) (rats), CYP2B (monkeys), CYP2B9/10 (mice).

In the nonclinical studies, the liver was the target organ for toxicity and this was probably related to hepatic enzyme induction. There was some evidence that agomelatine also affects haem metabolism in rats and monkeys. Carcinogenicity studies in mice and rats strongly suggest that agomelatine is a rodent liver carcinogen, at doses associated with high levels of liver enzyme induction (plasma AUC of about 10 fold or greater the anticipated clinical exposure). Exposure at

the no-effect doses was 3-4 fold clinical exposure. The data suggest that the carcinogenic liability of agomelatine in humans is low. The genotoxicity profile of agomelatine was negative.

Clinical

Previous submission

Pharmacology

The absorption of a single 50 mg dose of agomelatine is about 80%. It is not a substrate of P-glycoprotein, suggesting that the drug is absorbed by passive diffusion. The totality of the absorption data suggests that, as the absolute bioavailability is estimated to be 3.4%, the drug undergoes extensive first pass hepatic metabolism.

The drug is ~ 95% bound to human plasma proteins, mainly to albumin and α1-acid glycoprotein and is not concentration dependent. The volume of distribution at steady state (V_{ss}) following an intravenous infusion (1.5 mg, 7.5 mg, 37.5 mg) is ~ 31-37 L which is low suggesting that the drug is not extensively distributed to the extra-vascular tissues.

Agomelatine is metabolised by two major pathways - 7-O-desmethylation and hydroxylation with further metabolism primarily by glucuronidation. About 80% of an oral dose is absorbed and undergoes extensive hepatic metabolism with the metabolites being excreted in the urine. The metabolism of agomelatine is saturable as C_{max} and AUC values increase disproportionately with increasing oral dose, but increases linearly with increasing IV dose. The major metabolites of agomelatine, hydroxylated and demethylated agomelatine, are not pharmacologically active and are rapidly conjugated and eliminated in urine.

The half-life ($t_{1/2}$) of agomelatine is about 1.5 hours, which is unusually short for a drug being proposed for once daily administration. The urinary elimination of unchanged drug is very low and the total plasma clearance is about 1050 to 1200 mL/min which is close to normal hepatic blood flow of ~ 1500 mL/min [CL1-003]. The plasma exposure to agomelatine increased in patients with chronic mild or moderate hepatic impairment (C_{max} increased 61 fold and 111 fold, the AUC increased 71 fold and 140 fold in mild and moderate hepatic impairment, respectively. These results indicate that the agomelatine should be contraindicated in patients with hepatic impairment. In subjects with renal impairment (Clcr < 30 mL/min), the C_{max} was ~ 40% higher than in subjects with normal renal function while the AUC_{∞} ratio was ~ 24% higher. These results were inconclusive due to the large variation in the PK parameters.

CYP 1A2 is the major enzyme involved in agomelatine Phase I metabolism, with CYP2C9 and CYP2C19 involved as minor secondary enzymes. Co-administration of agomelatine and fluvoxamine (a potent CYP1A2 inhibitor and an inhibitor of CYP2C9) increased the plasma C_{max} and AUC of agomelatine by 47-fold and 61-fold, respectively, suggesting that *in vivo* the metabolism of agomelatine is extremely sensitive to CYP1A2 inhibitors.

Supplementary data was separately evaluated and included a review of two PD studies which examined the effect of agomelatine on sleep parameters in patients with MDD and on the extensions of two of the short term efficacy/ safety studies. One of these was a comparative subjective sleep evaluation study in which patients with MDD received either agomelatine or venlafaxine. While sleep onset improved from baseline in patients given drug, agomelatine was superior to venlafaxine at each assessment. The other study was an open, observational polysomnographic study of agomelatine 25 mg daily on sleep parameters in patients with MDD. Only 15 patients were assessed. Small increases in Stage 3 and 4 sleep were seen.

Efficacy

There were six, short-term (6-8 week), placebo-controlled studies which assessed efficacy primarily by the Hamilton Rating Scale for Depression (HAM-D). Two of these (022 and 024) included fluoxetine 20 mg as an active control and another two (014 and 023) included paroxetine 20 mg as

an active control. Three of these 6 studies (014, 042 and 043) reported a statistically significant difference of agomelatine compared with placebo for mean reduction from baseline to end of treatment in total HAM-D score and three (022, 023 and 024) did not. Fluoxetine also did not show a statistically significant difference over placebo in either of its studies. Paroxetine was statistically significantly better than placebo for mean reduction in total HAM-D score in study 014 but not for the 50% responder rate (50% reduction in HAM-D score from baseline to end of treatment). A supportive, placebo-controlled short-term study in patients aged ≥ 60 years also failed to show a statistically significant difference between agomelatine and placebo for improvement in depression as assessed by the Montgomery-Asberg Depression Rating Scale (MDRS).

In a meta-analysis of the six placebo-controlled studies, agomelatine reduced the mean baseline HAM-D score to a statistically significant greater extent than placebo. However, the treatment effect on HAMD total score was 1.71 and of doubtful clinical significance. It is notable that the placebo response rates in the studies which failed to show a statistically significant difference tended to have a very high placebo response rate (in the region of 50%).

The meta-analysis was not prospectively defined suggesting that it was undertaken specifically to address the inconclusive findings in the short-term efficacy studies. In addition, the relapse prevention study (021), which was specifically designed to assess long-term efficacy, failed to establish a statistically significant difference between the drug and placebo on relapse prevention. The ADEC agreed there was no dispute that agomelatine improved the "Getting off to sleep" score but this is not an antidepressant efficacy measure. The ADEC considered that agomelatine may be efficacious in major depressive disease, but the current data (at that time) did not demonstrate this sufficiently to allow a recommendation to register.

In addition to the concerns regarding efficacy there were safety concerns:

- The number of patients with long term exposure to agomelatine was insufficient for a medicine intended for long term use. Only 32 patients had received the 50 mg dose of ≥ 6 months and none had received it for 12 months.
- Hepatic transaminase levels were higher with the 50 mg than the 25 mg dose, suggesting the possibility of dose-related liver toxicity.

In addition to the safety and efficacy concerns, the PSC considered that an absolute bioavailability study on the tablet formulation proposed for registration was required to ensure that the product was optimally formulated. The PSC had noted that agomelatine had low solubility, low bioavailability, possible saturable kinetics and a short half-life. There was also significant intersubject and intrasubject variability observed in the various bioavailability and pharmacokinetic studies presented in the initial submission.

Current submission

Initially 6 studies were submitted:

- 4 pharmacology studies: the absolute bioavailability study previously discussed; a PD study on the effect of agomelatine on QT interval (054); a PD study to assess the effect of agomelatine on male sexual function vs. paroxetine (049) and
- 2 efficacy/ safety studies: a randomised relapse prevention study (041) and an active comparator study with sertraline (046). Study 046 also included PD data comparing agomelatine with sertraline for various circadian/ sleep-wake variables.

Summaries of efficacy and safety which included some, but not all, of the studies performed and a Risk Management Plan were also submitted. These studies were considered by the ADEC at its 265th meeting in August 2009 when ADEC recommended rejection. In summary:

- Agomelatine was not associated with clinically significant QT prolongation.

- Agomelatine did not adversely affect male sexual function in healthy male volunteers.
- After 14 days the effect of agomelatine on sleep parameters in patients with MDD is better to that of sertraline. There was a difference in reduction in day time sleepiness over 6 weeks favouring agomelatine but this did not reach statistical significance.
- Oral contraceptives and oestrogen are known inhibitors of CYP1A2 and in women taking oral contraceptives the mean C_{max} and AUC were 3.4 x and 5.0 x respectively higher than the male values at the 50 mg dose.

Efficacy

Study CL3-041 was a randomised, double-blind, placebo-controlled withdrawal study to assess the efficacy of flexible dose agomelatine in the prevention of depressive relapse. This study enrolled non-hospitalised, adult patients with recurrent depression who had an index episode which had lasted at least 8 weeks at the time of inclusion. At the beginning of the index episode, patients were to have been free of depressive symptoms of their previous episode for at least 6 months. After selection patients started a 1 week treatment-free run in period and eligible patients then commenced open-label treatment with agomelatine 25 mg once daily in the evening, increasing to 50 mg if improvement after 2 weeks was considered insufficient.

After 8 weeks open-label treatment, patients who had responded were randomised to double-blind treatment with either the same dose of agomelatine or placebo. Patients who had not responded at Week 8 were allowed to continue for a further 2 weeks on open treatment with agomelatine and if they had then responded they were randomised, if not, they were withdrawn from the study. Double-blind treatment (agomelatine versus placebo) could continue for 24 weeks with an optional extension for a further 20 weeks or until the occurrence of a depressive relapse or patient withdrawal for other reasons.

The primary efficacy endpoint was time to depressive relapse during the double-blind treatment period. Of the 594 patients screened, 565 were selected and 492 included in the open-label period. Of these, 99 (20.1%) were excluded due to lack of efficacy and 339 (68.9%) responded to open-label agomelatine and were randomised to double-blind treatment (165 to agomelatine and 174 to placebo). 141 (85.5%) of patients randomised to agomelatine received the 25 mg dose. 206 patients (60.8%) completed the first 24 week double-blind period and were eligible to enter the 20 week extension.

Over 24 weeks the K-M estimate of the proportion of patients with depressive relapse was 21.6% in the agomelatine group compared to 41.6% in the placebo group. Over 44 weeks the K-M estimate of the proportion of patients with depressive relapse was 23.9% and 50.0% for agomelatine and placebo respectively. Time to depressive relapse was significantly prolonged in the agomelatine group compared to placebo at 24 weeks (log-rank $p = 0.0001$, adjusted HR 0.46 [95%CI: 0.31, 0.65]) and 44 weeks (log-rank $p < 0.0001$, adjusted HR 0.44 [95%CI: 0.30, 0.64]).

Study CL3-046 was a randomised, double-blind 6 week study with an optional extension for a further 18 weeks to compare agomelatine 25 to 50 mg with sertraline 50 to 100 mg daily in patients with MDD. Assessment of antidepressant efficacy was a secondary objective of this study. The Hamilton Depression (HAM-D) Rating Scale and Clinical Global Improvement (CGI) scores were measured. Mean HAM-D scores decreased at each visit in both groups during the 6 week double-blind period and reductions were statistically significantly greater in the agomelatine group than in the sertraline group (-15.8 and -14.4 for the agomelatine and sertraline groups respectively between group difference 1.68 95%CI 0.15, 3.20). Differences between agomelatine and sertraline in 50% responder rates were statistically significant only for the 2 week visit. Approximately 25% of patients given agomelatine required the 50 mg dose.

Supplementary Data

Study CL3-045

The primary objective of this study was to assess the superiority of agomelatine to fluoxetine using the Hamilton Depression Rating Scale 17 items (HAM-D), after an 8-week treatment in out-patients suffering from Major Depressive Disorder (MDD). The secondary objective was to provide additional sleep, anxiety and safety data in this population.

The primary efficacy measure was the 17-item HAM-D, with secondary assessments including the Clinical Global Improvement severity (CGI-S) and improvement (CGI-I) scales, Hamilton Anxiety Rating Scale (HAM-A) and the Leeds Sleep Evaluation Questionnaire (LSEQ). Other secondary assessments included response to treatment (decrease of ≥50% on HAM-D) and remission (total HAM-D ≤6).

The statistical analysis plan involved initial investigation of the non-inferiority of agomelatine relative to fluoxetine using a non-inferiority margin of 1.5. In the case of a significant non-inferiority test, the superiority of agomelatine versus fluoxetine was to be tested. The two analyses were carried out on the Full Analysis Set (FAS) which was defined as patients of the randomised set who had taken at least one dose of study medication and had both a baseline and at least one post-baseline HAM-D rating. Statistical methods used include ANCOVA, Chi-square test, two-sided Student's t-test, Mann Whitney test etc. The number of subjects completing the acute phase (Week 0-Week 8) were n= 222 for agomelatine and n= 263 for fluoxetine while those completing the extension phase (Week 8 –Week 24) were n= 212 for agomelatine and n= 208 for fluoxetine. Overall, 68% of agomelatine and 66% of fluoxetine subjects completed the Study (WO-W24). Regarding the efficacy outcome, the clinical evaluator stated that:

- For the primary efficacy analyses, the mean decreases in HAM-D total scores from W0 to last post-baseline visit were -17.3 ± 7.3 and -16.0 ± 8.4 for agomelatine and fluoxetine respectively. This was significantly different for the non-inferiority test based on the non-inferiority margin of -1.5 ($p<0.001$). This allowed for a superiority test which was also statistically significant (estimate of the difference between treatment groups =1.49, 2-sided 95% CI [0.20; 2.77] p= 0.024). Both tests were then confirmed by the sensitivity analysis (non-inferiority $p<0.001$, superiority p=0.030).
- The proportion of HAM-D responders for the W0-W8 phase were 71.7% and 63.8% for agomelatine and fluoxetine respectively (p=0.060) whilst for the W0-W24 phase the figures were FAS set 78.9% and 74.3%, SUBFAS 87.5% and 91.6% respectively. The proportion of HAM-D remitters (HAM-D ≤6) for the W0-W8 phase were 32.0% and 28.4% for agomelatine and fluoxetine respectively and for the W0-W24 phase FAS set 51.4% and 50.2%, SUBFAS 59.1% and 64.9% respectively. There were no significant differences between treatments for the final CGI-scores for either the W0-W8 or W0-W24 periods. There was a significant difference in the proportion of CGI-I responders (score of ≤ 2) in favour of agomelatine for the W0-W8 phase (77.7% v 68.8%, p=0.023) but no difference between groups for the extension phase. There were no significant differences between treatments for CGI remitters (CGI-I =1) for either phases. There were no differences between low and high dose groups for either in any of the efficacy measures.
- Changes in HAM-A scores from W0 to W8 were similar in both groups for total and both psychic and somatic anxiety scores. Similarly, similar decreases were found from W2 to W8 for the factors of the LSEQ (getting off to sleep, quality of sleep, sleep awakening, integrity of behaviour), however, the HAM-D sleep sub-scale (items 4, 5 and 6) was significantly lower for agomelatine at last visit (p=0.018, independent t-test, complementary analysis).

- The primary efficacy analysis was positive for agomelatine. The majority of the secondary assessments showed no differences between treatments either for the acute or extension phases of the study.

Safety

The incidence of treatment-emergent adverse events in the short term efficacy/ safety studies was similar for the agomelatine and placebo groups. The most frequent treatment-emergent adverse events associated with agomelatine were headache (14.1%), nausea (7.7%), dizziness (5.5%), dry mouth (3.5%, diarrhoea (3.1%) and somnolence (2.9%). Dizziness, somnolence, diarrhoea, fatigue and upper abdominal pain were more frequently reported with agomelatine than placebo. The incidence of emergent AEs was higher in patients given 50 mg agomelatine (63.8%) compared with those given 25 mg (49.9%).

Serious treatment emergent adverse events were reported in 4.7% of patients given agomelatine compared with 4.5% given placebo. None of the serious emergent adverse events reported in the one year agomelatine exposure set were considered related to treatment.

Adverse events of special interest are suicidality and hepatic adverse events. The incidence of suicidality and of completed suicide was similar in the agomelatine and placebo groups for the MDD population. The incidence of suicide attempts and completed suicides were 0.8% and 0.1% for agomelatine and 0.6% and 0.1% for placebo. When treatment duration was considered the incidence of suicidal acts was 0.19 per 100 patient-months for agomelatine compared with 0.24 per patient-month for placebo.

In terms of laboratory values, of particular note is that while the incidence and incidence rate of potentially clinically significant abnormal hepatic laboratory values is similar for agomelatine 25 mg and placebo, the incidence and incidence rate for agomelatine 50 mg is about two times higher, suggesting a dose-related hepatic effect

The observation in the clinical development programme on which the RMP is based was that transaminase rises >3x ULN were seen in 1.1% of agomelatine-treated versus 0.7% of placebo-treated patients. These changes were usually fully reversible on cessation of treatment. For additional context the sponsor noted that the incidence of transaminase elevations observed with agomelatine 50mg remains in the range observed with venlafaxine which was used as active reference in studies CL3-035 and CL3-036 (1.39% for agomelatine 50mg versus 1.53% for venlafaxine 75-150mg in the pool of these two studies). Indirect comparison with published data provided by the sponsor concerning the commonly prescribed antidepressants duloxetine and mirtazapine also contributes useful context to the agomelatine data as shown in Table 14.

Table 14: Comparison of incidence of liver enzyme increases

Antidepressant	**Placebo-adjusted incidence of uncomplicated liver enzyme increases**	**Reference**
Mirtazapine	1 in 58 (1.7%)	US PI/Labelling (Remeron)[36]
Duloxetine	1 in 138 (0.72%)	EPAR, p31/35[37]
Agomelatine	1 in 250 (0.4%)	Australian PI (attached to this AusPAR)

[36] US FDA, Label information for Remeron. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020415s023s024,021208s013s014lbl.pdf

[37] EMA. Cymbalta EPAR. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000572/WC500036776.pdf.

An independent review of 51 cases (44 agomelatine and 7 placebo) of hepatic abnormality was performed in response to a CHMP request. The independent reviewer panel considered that agomelatine 25 mg daily is not associated with a significant risk of liver injury and that the 50 mg dose is associated with an increased frequency of transaminase elevation and that, given the small dataset at this dose, such patients should have liver function tests from the time of dose increase which should be repeated at 6- 8 weeks and 12 to 16 weeks. There are no data to show increased toxicity in patients with existing hepatic impairment.

Mania, seizures, marked sedation/ stimulation and body weight changes do not appear to be associated with agomelatine. Sexual dysfunction was less frequent with agomelatine than with fluoxetine or paroxetine.

Post Marketing experience

Regarding post marketing experience, the clinical evaluator stated that:

- The first PSUR for agomelatine from its marketing authorization date in Europe to 19 August 2009 was submitted. The report summarises safety information received by the Pharmacovigilance Department of Institut de Reserches Servier from worldwide sources. All spontaneous reports and all serious adverse drug reactions from clinical trials or post-authorisation studies are presented in this report.
- A total of 90 medically confirmed reports are included whilst 33 non-medically confirmed reports were excluded. Three patients died, two were suicides and one sudden death in a patient with several cardiovascular risk factors. Adverse events of special interest in the agomelatine Risk Management Plan are liver adverse reactions, skin reactions and suicide events. Six patients experienced liver adverse reactions including 4 patients with AST or ALT values >x 3 ULN (25 and 50 mg doses, 2 subjects each). Skin reactions were reported for 15 patients with only two being considered serious (angioedema; generalized erythema, pruritis, facial swelling and urticaria). Two completed suicides, one suicide attempt and one intentional self-injury were reported with all 4 patients having a history of previous suicide attempts and 9 reports of suicidal ideation.

On the overall safety analysis, the clinical evaluator commented that:

- The side effect profile of agomelatine is encouraging. It does not have the anticholinergic side effects of the early tricyclics or cause cardiac arrhythmias or lower blood pressure. In the studies presented its side effect profile is generally similar to placebo. Nausea and headache are the most common side effects but these are similar to comparator compounds (nausea less than for paroxetine). Most of the currently available antidepressants, tricyclics, SSRIs and SNRIs, increase serotonin availability at the synaptic cleft, and this is believed to be the cause of the sexual side effects that are common with these drugs – loss of libido, impotence, ejaculatory failure and anorgasmia. There are 2 published studies that have compared favourably the sexual side effects of agomelatine to other antidepressants, venlafaxine and paroxetine (CL3-036 Kennedy et al 2008, CL3-049 Montejo et al 2008).[34,35] Agomelatine has been found to have a significant advantage over both venlafaxine and sertraline for early improvement of sleep quality (CL3-035 Lemoine et al, CL3-046).[33] As sleep disturbance is a common symptom in depression, it is likely this property will improve compliance with treatment. Agomelatine has not been associated with weight gain or withdrawal syndrome (CL3-030); this is in contrast to most SSRIs and SNRIs and many antidepressants.

  The potential for hepatotoxicity is the major drawback to the use of agomelatine. The data presented in the PSUR indicated that the incidence of emergent elevation of ALT and/or AST > x 3 ULN was 1.19% compared to 0.71% in the placebo group from a database of over 6000 patients. Some subjects recovered whilst continuing on agomelatine whilst others were

withdrawn, however, the majority of subjects' liver function normalized. Since there are no obvious clinical symptoms, routine monitoring of liver function is recommended.

The clinical evaluator stated that agomelatine has been clearly shown to be more effective than placebo in acute studies and of similar efficacy to other current antidepressants. The longer term studies show evidence of maintenance of effect and relapse prevention that is of considerable clinical benefit. This coupled with the overall favourable tolerability and safety profile including a positive effect on sleep and lack of sexual side-effects leads to a positive risk benefit for agomelatine. The evaluators recommended that it be registered for the proposed indication on the condition that the monitoring of liver functions be made mandatory in the Product Information.

Risk-Benefit Analysis

Delegate Consideration

The Delegate agreed with the clinical evaluator that there is sufficient efficacy evidence to support the application bearing in mind, the issue of agomelatine's possible hepatotoxicity especially with the higher 50mg daily dose. The recommended initiating dose is 25 mg daily and the requirement for liver function tests to be performed is documented in the proposed PI. Agomelatine is currently on the Special Access Scheme (SAS) and is usually requested infrequently by consultant psychiatrists after the failure of most other anti-depressants. It might therefore be worthwhile to consider qualified registration, that is, treatment of major depression in adults including prevention of relapse (when other antidepressants have failed or not tolerated and to be prescribed by either consultant psychiatrists or general practitioners in consultation with the former). Consideration should also be given to limiting the duration of use to < 48 weeks which apparently represents the available overall duration of drug exposure. All these restrictions could be accommodated under the Medicare's Authority Prescription Code.

In its pre-ACPM response, the sponsor noted that as a potent teratogen, prescription of isotretinoin (Roaccutane) is restricted to specialist physicians or dermatologists, a similar restriction to thalidomide. Agomelatine has been classified by the TGA as a 'Use in Pregnancy' Category B1 drug. Additionally the clinical evaluator determined that agomelatine had a "*positive risk:benefit*". The sponsor saw no parallel between this and the proposed need for an isotretinoin or thalidomide-type approach to risk management with agomelatine.

The Delegate proposed to approve Valdoxan for:

Treatment of major depression in adults including prevention of relapse (when other antidepressants have failed or not tolerated)

Consideration should be given to both restricted prescription and duration of use as stated above. In particular, the advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) is required as to whether or not:

- The proposed Product Information is sufficiently reinforced to highlight the mandatory requirement to carry out regular liver function tests
- Restricted prescription by consultant psychiatrists should apply to registration
- Limited duration of use should apply.

Sponsor Response

The sponsor also did not agree with the Delegate's proposal to limit duration of use to "*<48 weeks*" as this time does not represent best or current clinical practice. The current Australian Psychotropic Therapeutic Guidelines (2008) reflect this, recommending that "*….antidepressants should be continued for at least six months, and preferably up to 12 months, after a single episode of major depression as there is a high risk of relapse in this period……. If there is a history of two episodes*

within the last two years, treatment for at least two years is recommended."[38] These guidelines are endorsed by organisations such as RACGP, RACP, SHPA, and Royal College of Nursing Australia and the National Prescribing Service, whilst other Australian publications recommend even longer treatment duration (up to 3 years) for recurrent depression (Malhi et al, 2009).[39] The Delegate's proposal to limit duration of use to "<48 weeks" is therefore not consistent with recommended best clinical practice in the management of depression.

Advisory Committee Consideration

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal to recommend approval but for the indication:

Treatment of major depression in adults including prevention of relapse

In making this recommendation, the ACPM advised that while the new study has confirmed efficacy, safety issues remained a concern, particularly in the context of anticipated use by a large and diverse population group. The ACPM considered the adequacy of the RMP to appropriately manage the significant safety risks associated with hepatic function, the anticipated dose escalation and the concomitant SSRI therapy in the target population.

The specific conditions of registration should include development of a more rigorous RMP to manage and monitor the significant safety risks in relation to hepatic function and dose escalation in the target population. Consistent with what was proposed by the sponsor, the ACPM recommended that the RMP include a major prescriber and consumer education activity that is independently developed and evaluated.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Valdoxan containing agomelatine 25mg for the indication:

The treatment of major depression in adults including prevention of relapse.

Included among the conditions of registration was that the sponsor is required to forward to the TGA a copy of the education material(s) which will be provided to the prescribers at the launch of this product.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

[38] Pharmacological treatment of depression: general considerations, Therapeutic Guidelines Limited (etg29, November 2009).

[39] Malhi GS, Adams D, Porter R, et al. Clinical practice recommendations for depression. Acta Pychiatrica Scandinavica 2009; 119: 8-26.

VALDOXAN®
Product Information

NAME OF THE MEDICINE

VALDOXAN
Agomelatine 25mg

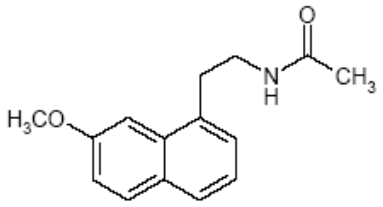
DESCRIPTION

The active component of VALDOXAN is agomelatine which has the chemical name: N-[2-(7-methoxy-1-naphthyl)ethyl] acetamide. Agomelatine is practically insoluble in purified water (<0.1 mg/mL) but freely soluble (>100 mg/mL) in various organic solvents (96% ethanol, methanol, methylene chloride). Agomelatine has no asymmetric carbon atom.

CAS Registry Number*: 138112-76-2*

Molecular formula: $C_{15}H_{17}NO_2$ (MW = 243.3).

Chemical structure:



Excipients: Lactose, starch - maize, povidone, sodium starch glycollate, stearic acid, magnesium stearate, silica - colloidal anhydrous, hypromellose, iron oxide yellow (CI77492), glycerol, macrogol 6000, and titanium dioxide (CI77891), shellac, indigo carmine (CI73015), propylene glycol.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Other antidepressants (ATC-code: NO6AX22)

VALDOXAN (agomelatine) is a melatonin receptor (MT_1 and MT_2) agonist and 5-HT_{2C} receptor antagonist. VALDOXAN (agomelatine) has shown an antidepressant-like effect in animal models of depression (learned helplessness test, despair test, chronic mild stress), in models with circadian rhythm desynchronisation and in models related to stress and anxiety.

In vitro studies indicate that VALDOXAN (agomelatine) has no effect on monoamine uptake and no affinity for α or β adrenergic, histaminergic, cholinergic, dopaminergic, or benzodiazepine receptors. VALDOXAN (agomelatine) has no influence on the extracellular levels of serotonin and increases dopamine and noradrenaline release specifically in the prefrontal cortex. These properties may explain why, compared with other antidepressants, it has less gastrointestinal (e.g.

vomiting, constipation) and sexual function (e.g. libido decrease) side effects, and no cardiovascular side effects in clinical trials.

In humans, VALDOXAN (agomelatine) has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset.

VALDOXAN (agomelatine) resynchronises circadian rhythms in animal models of circadian rhythm disruption.

In depressed patients, treatment with VALDOXAN (agomelatine) 25mg increased slow wave sleep without modification of REM (Rapid Eye Movement) sleep amount or REM latency. VALDOXAN (agomelatine) 25mg also induced an advance of the time of sleep onset and of minimum heart rate. From the first week of treatment, onset of sleep and the quality of sleep were significantly improved without daytime clumsiness as assessed by patients.

At therapeutic doses, in healthy volunteers, VALDOXAN (agomelatine) preserves vigilance and memory, with no sedation in the morning following drug intake.

Cardiovascular

In clinical studies, VALDOXAN had no affect on QT interval and no clinically-significant affect on heart rate, blood pressure and ECG tracings

Body weight

VALDOXAN (agomelatine) had no affect on body weight in clinical and non-clinical studies.

Withdrawal / Discontinuation

The abrupt discontinuation of VALDOXAN (agomelatine) was evaluated in a specific active control study (CL3-030) using the Discontinuation Emergent Signs and Symptoms (DESS) check-list. Patients with major depression were treated under double-blind conditions with VALDOXAN (agomelatine) 25mg or paroxetine 20mg over a twelve week period. Only those who remitted at week 8 and sustained that remission until week 12 were randomised to placebo or the initial active treatment for a two-week double-blind period. Patients discontinued from VALDOXAN (agomelatine) to placebo were compared to those who continued treatment on VALDOXAN (agomelatine) and, likewise for the active control paroxetine.

The abrupt discontinuation of VALDOXAN (agomelatine) was not associated with discontinuation symptoms [p=0.250 for difference between the VALDOXAN (agomelatine) and placebo groups]. The sensitivity of the study was demonstrated by the presence of significant emergent discontinuation symptoms following the abrupt discontinuation of treatment with the active control paroxetine [p<0.001 for difference between the paroxetine and placebo groups].

Sexual function

No deleterious affect on sexual function (SEX-FX total score and SEX-FX sub-scores and items) was observed during VALDOXAN (agomelatine) 50mg treatment over 12 or 24 week treatment periods in a specific sexual dysfunction comparative study in remitted depressed patients. There was a numerical trend towards less sexual emergent dysfunction on VALDOXAN (agomelatine) 50mg than venlafaxine 150mg for SEX-FX drive arousal or orgasm scores but statistical separation was not achieved.

A separate pooled analysis of studies using the Arizona Sexual Experience Scale (ASEX) showed that VALDOXAN (agomelatine) was not associated with sexual dysfunction. In healthy volunteers VALDOXAN (agomelatine) did not affect sexual function, in contrast to paroxetine.

Pharmacokinetics

Absorption and bioavailability

VALDOXAN (agomelatine) is rapidly and well (≥80%) absorbed after oral administration. The peak plasma concentration is reached within 1 to 2 hours after administration of VALDOXAN (agomelatine). Absolute bioavailability is low (approximately 1% at the therapeutic oral dose), and is highly variable due to the first pass effect and the inter-individual differences of CYP1A2 activity. The bioavailability is increased in women compared to men. Although not clinically relevant, the bioavailability is increased by intake of oral contraceptives and reduced by smoking. In the therapeutic dose-range, VALDOXAN (agomelatine) exposure appears to increase proportionally with dose with saturation of the first pass effect occurring at supra-therapeutic doses (from 200 to 1200mg).

Food intake (standard meal or high fat meal) reduced the peak concentration (Cmax) by approximately 20 – 30% but did not modify overall absorption or bioavailability. The variability is increased with high fat food.

Distribution

Steady state volume of distribution is about 35L. Plasma protein binding is 95% irrespective of concentration and is not modified with age and in patients with renal impairment but the free fraction is doubled in patients with hepatic impairment.

Biotransformation

Following oral administration, VALDOXAN (agomelatine) is rapidly oxidized mainly by the hepatic cytochromes CYP1A2 (90%) and CYP2C9/CYP2C19 (10%). The major metabolites, hydroxylated and demethylated agomelatine, are not pharmacologically active and are rapidly conjugated and eliminated in the urine.

Elimination

Elimination is rapid. The mean plasma half-life is between 1 and 2 hours. Clearance is high (about 1100mL/min) and essentially metabolic. Excretion is mainly urinary (80%) and corresponds to metabolites. Urinary excretion of the unchanged compound is negligible. Pharmacokinetics remained unchanged following repeated administration.

Special Populations

Severe renal impairment: In subjects with severe renal impairment the pharmacokinetic parameters Cmax and AUC were slightly higher than in healthy subjects. However, due to the high inter-individual variability of VALDOXAN (agomelatine) pharmacokinetics, this result was not clinically relevant. Renal impairment did not affect the protein binding of VALDOXAN (agomelatine).

Hepatic Impairment: Following a single oral dose of 25mg VALDOXAN (agomelatine) in patients with hepatic impairment, Cmax increased by a factor of ~60 and ~110, while AUC increased by ~70-times and ~140-times, in mild (Child-Pugh score of 5 or 6) and moderate (Child-Pugh score of 7 to 9) hepatic impairment, respectively compared to healthy subjects. Both mild and moderate liver impairment increased the half-life of VALDOXAN (agomelatine) by a factor of ~3. The unbound fraction of VALDOXAN (agomelatine) was also increased in subjects with hepatic insufficiency. The inter-individual variability decreased with mild hepatic impairment, with a further decrease in moderate hepatic impairment, suggesting a progressive saturation of the hepatic first-pass effect. VALDOXAN (agomelatine) is therefore contraindicated in patients with hepatic impairment (see *CONTRAINDICATIONS* section).

Gender, smoking and age: No significant difference in exposure was shown between the young and the elderly as well as between males and females. Although not clinically relevant:

- a 3.7-fold decrease in mean exposure was observed in volunteers without depression who were heavy smokers (≥15 cigarettes per day);
- a decrease of 33% of agomelatine exposure has been shown in the smoker population (healthy volunteers and depressed patients smoking >5 cigarettes per day) compared to non smoker population, suggesting that cigarette smoking could induce CYP1A2 which is involved in the metabolism of VALDOXAN (agomelatine).

CLINICAL TRIALS

Clinical trials for acute treatment of Major Depression

The efficacy and safety of agomelatine in the treatment of major depression have been studied in a clinical development programme including more than 5,800 patients of whom over 3,900 were treated with VALDOXAN (agomelatine) for between six weeks and one year.

Six placebo-controlled trials have been performed to investigate the short-term efficacy of agomelatine in major depressive disorder: two flexible dose studies and four fixed dose studies. At the end of treatment (over 6 or 8 weeks), both flexible dose studies and one of the fixed dose studies showed statistically the superiority of VALDOXAN (agomelatine) over placebo on the primary outcome criterion HAM-D total score and consistent results across secondary criteria (see Table 1). The superiority of VALDOXAN (agomelatine) over placebo was shown after two weeks of treatment.

VALDOXAN (agomelatine) did not differentiate from placebo in one study (CL3-022) where the active control fluoxetine showed assay sensitivity. In two other studies (CL3-023, 024), it was not possible to draw any conclusions because the active controls, paroxetine and fluoxetine, failed to differentiate from placebo.

Table 1 - Efficacy results in the pivotal short-term placebo-controlled studies

Study (duration) Treatment group	**HAM-D total score**			**HAM-D responder[#]**	**CGI[##] Severity**		
	n	**Baseline** mean	**Final** mean	**Final** mean	**n**	**Baseline** mean	**Final** mean
CL2-014 (8 weeks)							
agomelatine 25mg	135	27.4	12.8*	61.5%*	135	4.7	2.8*
placebo	136	27.4	15.3	46.3%	136	5.0	3.3
paroxetine 20mg	144	27.3	13.1*	56.3%	-	-	-
CL3-042 (6 weeks)							
agomelatine 25-50mg	116	27.4	13.9*	54.3%*	116	4.9	3.1*
placebo	119	27.2	17.0	35.3%	119	4.9	3.6
CL3-043 (6 weeks)							
agomelatine 25-50mg	106	26.5	14.1*	49.1%*	106	4.8	3.2*
placebo	105	26.7	16.5	34.3%	105	4.8	3.6

Notes: [#] *Percentage of patients with a decrease in baseline HAM-D total score ≥ 50%*
[##] *CGI: Clinical Global Impression;*
** Statistically significant difference from placebo.*

The short term efficacy of 25-50mg/day of VALDOXAN (agomelatine) was also demonstrated in study CL3-046 which assessed the antidepressant efficacy of VALDOXAN (agomelatine) as a

secondary objective compared to sertraline (50-100 mg/day) over a double-blind treatment period of 6 weeks where male or female patients, aged between 18-60 years fulfilling DSM-IV criteria for major depressive disorder, received VALDOXAN (agomelatine) 25-50mg daily or sertraline 50-100mg daily (see Table 2).

Table 2 - Efficacy results in short-term study CL3-046 versus sertraline

Study (duration) Treatment group	**HAM-D total score**			**HAM-D responder#**	**CGI-Severity**		
	n	**Baseline** mean	**Final** mean	**Final** mean	**n**	**Baseline** mean	**Final** mean
CL3-046 (6 weeks)							
agomelatine 25-50mg	150	26.1	10.3*	70.0%	150	4.7	2.5*
sertraline 50-100mg	156	26.5	12.1	61.5%	157	4.7	2.8

Notes: *# Percentage of patients with a decrease in baseline HAM-D total score ≥ 50%*
** Statistically significant difference in favour of VALDOXAN*

The short term efficacy of VALDOXAN (agomelatine) was also shown in study CL3-045 which demonstrated the antidepressant efficacy of VALDOXAN (agomelatine) vs fluoxetine after a double-blind treatment period of 8 weeks where male or female patients, aged between 18-65 years fulfilling DSM-IV criteria for major depressive disorder, received VALDOXAN (agomelatine) 25-50mg daily or fluoxetine 20-40mg daily (see Table 3).

Table 3 – Primary efficacy criterion results in short-term study CL3-045 versus fluoxetine

Study (duration) Treatment group	**HAM-D total score**				**Superiority test^**
	n	**Baseline** W0 mean	**Final** W8 mean	**Difference W8-W0** E [95% CI]	p-value
agomelatine 25-50mg	247	28.5	11.1	1.49*	0.024
fluoxetine 20-40mg	257	28.7	12.7	[0.20; 2.77]	

Notes: ** Statistically significant difference in favour of VALDOXAN*
^ a priori superiority test: two sided p-value to be compared to 0.05 following a non-inferiority test centred on a non-inferiority margin of –1.5: one-sided p-value of <0.001 compared to 0.025

Prevention of Relapse of Depression

The primary objective of study CL3-041 was to assess the efficacy of VALDOXAN (agomelatine) at flexible dose in the prevention of depressive relapse compared to placebo. In this study, 492 patients received open label treatment with VALDOXAN (agomelatine) 25mg/day for eight to ten weeks, with an increase to 50mg/day in patients who were not sufficiently improved after two weeks. Thereafter, the patients who responded to therapy (HAM-D total score ≤10) were randomised to receive treatment with VALDOXAN (agomelatine) or placebo until relapse occurred for up to 44 weeks. 338 patients participated in the double blind, long-term portion of the study: 165 were treated with VALDOXAN (agomelatine) and 174 were treated with placebo. The primary efficacy criterion was the relapse, defined as HAM-D 17-item total score ≥16, or any withdrawal for lack of efficacy during the 44-week double-blind period.

The risk over time of relapse was significantly reduced by 54.2% in the VALDOXAN (agomelatine) group compared to the placebo group in study CL3-20098-041 (see Figure 1). As is indicated in Table 4, the percentage of patients with a relapse during the 24-week double-blind period was more than two times lower in the VALDOXAN (agomelatine) group than in the placebo group.

Figure 1 – Time to relapse over the 24 week double blind study period

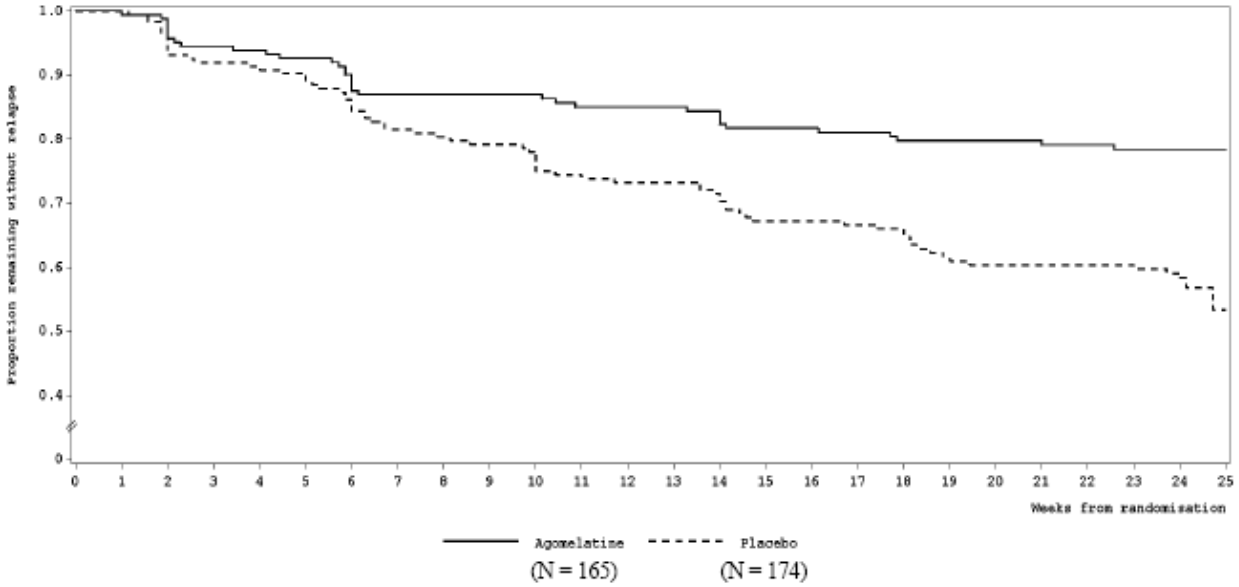


Table 4– Time to relapse analysis over 24 weeks

Group	No. of patients	Relapses		Cumulative incidence of relapse at 175 days	Cox model HR	Logrank
		N	%	E [95%CI]	E [95%CI]	p-value
Agomelatine 25-50mg	165	34	20.6	21.7 [15.19; 28.10]	0.458 [0.305; 0.690]	<0.0001
Placebo	174	72	41.4	46.6 [36.84; 56.41]		

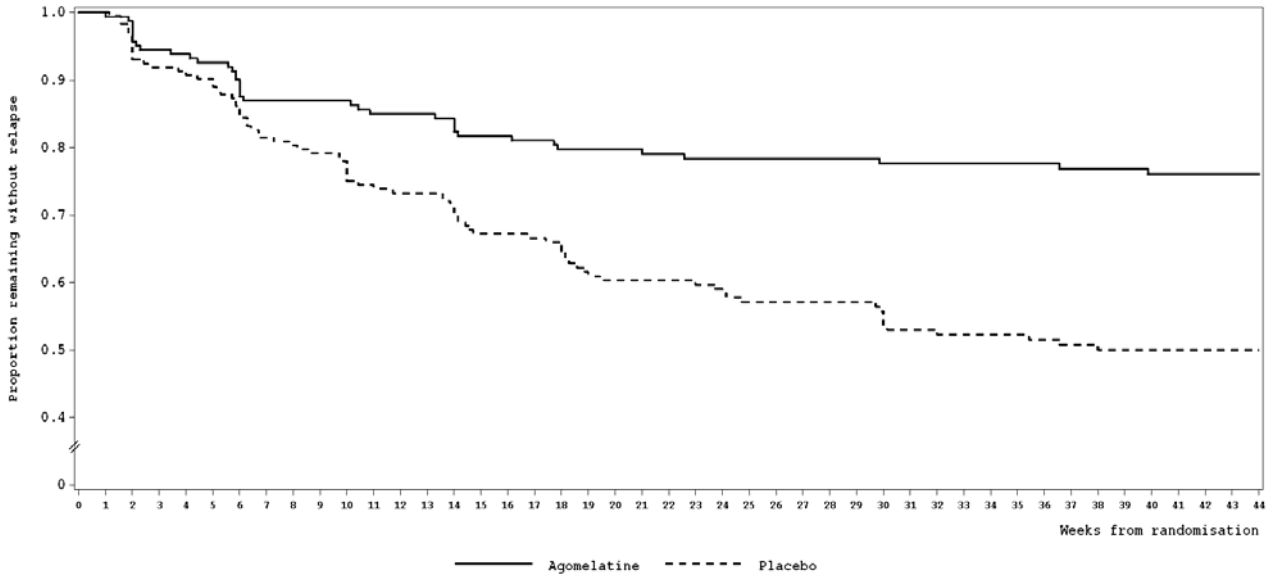
Results over the 44-week double-blind treatment period confirm the efficacy of VALDOXAN (agomelatine) 25-50 mg to prevent depressive relapse in patients with major depressive disorder and showed the maintenance of long-term efficacy. The percentage of patients with a relapse over the whole 44-week double-blind period remained more than two times lower in the VALDOXAN (agomelatine) group than in the placebo group (see Table 5).

Table 5 – Time to relapse analysis over 44 weeks

Group	No. of patients	Relapses		Cumulative incidence of relapse at 308 days	Cox model HR	Logrank
		N	%	E [95%CI]	E [95%CI]	p-value
Agomelatine 25-50mg	165	39	23.6	23.9 [17.16; 30.70]	0.437 [0.298; 0.640]	<0.0001
Placebo	174	83	50.0	50.0 [42.20; 57.75]		

As shown in Figure 2, the risk over time of relapse was significantly reduced by more than half, 56.3% in the VALDOXAN (agomelatine) group compared to the placebo group.

Figure 2 - Time to relapse over the 44 week double blind study period



In another relapse-prevention study (CL3-021), VALDOXAN (agomelatine) did not separate from placebo as a result of an unexplained low relapse rate in the placebo group which was unexpected and markedly lower than the mean placebo relapse rate reported in the literature.

INDICATIONS

Treatment of major depression in adults including prevention of relapse.

CONTRAINDICATIONS

VALDOXAN (agomelatine) is contraindicated in patients:

- with a history of previous hypersensitivity to the active ingredient or any of the excipients;
- with hepatic impairment (i.e. cirrhosis or active liver disease); or
- taking potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

PRECAUTIONS

Suicide Ideation / Suicidality

In clinical trials, VALDOXAN (agomelatine) is not associated with an increased risk of suicide ideation / suicidality.

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking

antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/ behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials) or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied.

The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medications in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

A further pooled analysis of short-term placebo controlled trials of antidepressant medicines (SSRIs and others) showed the increased risk of suicidal thinking and behaviour (suicidality) during the initial treatment period (generally the first one to two months) extends to young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. These studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

When treatment duration was considered the incidence of suicidal acts was 0.19 per 100 patient-months for VALDOXAN (agomelatine) compared with 0.24 per 100 patient-months for placebo.

Mania / Hypomania

As with other antidepressants, VALDOXAN (agomelatine) should be used with caution in patients with history of mania or hypomania and should be discontinued if a patient develops manic symptoms.

Increased serum transaminases:

In clinical studies, elevations of serum transaminases (>3 times the upper limit of the normal range) have been observed in patients treated with VALDOXAN (agomelatine) more commonly on a 50mg dose. When VALDOXAN (agomelatine) was discontinued in these patients, the serum transaminases usually returned to normal levels.

Liver function tests should be performed in all patients: at initiation of treatment and then periodically after around six weeks (end of acute phase), after around twelve and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated.

Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours. Therapy should be discontinued if the increase in serum transaminases exceeds three times the upper limit of normal and liver function tests should continue to be performed regularly until serum transaminases return to normal.

If any patient develops symptoms suggesting hepatic dysfunction, liver function tests should be performed. The decision whether to continue the patient on therapy with VALDOXAN (agomelatine) should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed therapy should be discontinued.

Caution should be exercised when VALDOXAN (agomelatine) is administered to patients who consume substantial quantities of alcohol or who are treated with medicinal products associated with risk of hepatic injury.

Lactose intolerance

VALDOXAN (agomelatine) tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Alcohol

As with all antidepressants, patients should be advised to avoid alcohol consumption.

Electroconvulsive therapy (ECT)

There is no experience of concurrent use of VALDOXAN (agomelatine) with ECT. In animals VALDOXAN (agomelatine) is devoid of proconvulsant properties. Therefore, clinical consequences of concomitant ECT treatment with VALDOXAN (agomelatine) are considered to be unlikely.

Abuse potential

VALDOXAN (agomelatine) has no abuse potential. This was assessed in healthy volunteer studies on a specific visual analogue scale or the Addiction Research Centre Inventory 49 (ARCI) check-list.

Use in Pregnancy (Category B1)

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofoetal development, parturition or postnatal development at systemic exposures (plasma AUC) of 100-fold or greater the human exposure at the maximal recommended clinical dose. Agomelatine and/or its metabolites passes into the placenta and foetuses of pregnant rats. No clinical data on exposed pregnancies are available. Caution should be exercised when prescribing to pregnant women.

Use in Lactation

It is not known whether agomelatine is excreted into human milk. Agomelatine and/or its metabolites were excreted in the milk of lactating rats. There were no adverse effects on offspring following oral administration of agomelatine to rats from prior to mating until weaning, with systemic exposures (plasma AUC) of 100-fold human exposure at the maximal recommended clinical dose. The effects of VALDOXAN (agomelatine) on the nursing infant have not been established. If treatment with VALDOXAN (agomelatine) is considered necessary, breastfeeding should be discontinued.

Paediatric Use

Use of VALDOXAN (agomelatine) in children and adolescents (under 18 years of age) is not recommended as safety and efficacy have not been established in this age group.

In clinical trials among children and adolescents treated with other antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed compared to those treated with placebo.

Use in Elderly Patients

No adjustment in the usual dose is recommended for elderly patients solely because of their age.

VALDOXAN (agomelatine) should not be used for the treatment of major depressive episodes in elderly patients with dementia since the safety and efficacy of VALDOXAN (agomelatine) have not been established in these patients.

Carcinogenicity

Oral lifetime carcinogenicity studies with agomelatine were conducted in mice and rats. Male and female mice showed increased incidences of hepatocellular adenomas and hepatocellular carcinomas at systemic exposures (plasma AUC) about 15-fold human exposure at the maximal recommended clinical dose; the no-effect exposure was about 4-fold clinical exposure. Male rats showed an increased incidence of hepatocellular carcinomas at systemic exposures (plasma AUC) about 45-fold human exposure at the maximal recommended clinical dose; the no-effect exposure was about 8-fold clinical exposure. These effects were associated with liver enzyme induction in these species and are unlikely to be relevant to humans. In male and female rats, the frequency of benign mammary fibroadenomas was increased at high systemic exposures (30-fold or greater the exposure at the maximal recommended clinical dose) but remained within the historical control range. Malignant mammary tumours were not observed.

Genotoxicity

Based on results from a standard battery of *in vitro* and *in vivo* assays, agomelatine is not considered to have genotoxic potential in humans receiving the maximum proposed clinical dose.

Effects on fertility

Oral reproductive toxicity studies with agomelatine in rats showed no effect on fertility at plasma exposures of 60-100 fold human exposure at the maximal recommended clinical dose.

Interactions with other medicines

Potential interactions affecting VALDOXAN (agomelatine)

VALDOXAN (agomelatine) is metabolised mainly by cytochromes CYP1A2 (90%) and CYP2C9/19 (10%). Drugs that interact with these isoenzymes may decrease or increase the bioavailability of VALDOXAN (agomelatine).

Co-administration of VALDOXAN (agomelatine) with potent CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin is contraindicated. Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor, has been shown to markedly inhibit the metabolism of VALDOXAN (agomelatine) resulting in a large increase in agomelatine exposure.

Combination of VALDOXAN (agomelatine) with oestrogens (moderate CYP1A2 inhibitors) results in a several fold increased exposure of VALDOXAN (agomelatine). While there was no specific safety signal in the 800 patients treated in combination with oestrogens, caution should be exercised when prescribing VALDOXAN (agomelatine) with other moderate CYP1A2 inhibitors (*e.g.* propranolol) until more experience has been gained.

Fluconazole, a potent CYP2C9 and CYP2C19 inhibitor, has been shown not to affect the pharmacokinetics of VALDOXAN (agomelatine).

Table 6 - Summary of CYP1A2 and CYP2C9/C19 interactions from agomelatine clinical studies

Contraindicated:	Caution should be taken until more experience has been gained:	No interaction:
Potent CYP1A2 inhibitors (e.g. fluvoxamine and ciprofloxacin)	***Moderate CYP1A2 inhibitors*** (e.g. propranolol)	***Potent CYP2C9/CYP2C19inhibitors*** (e.g. fluconazole)

As the decrease in VALDOXAN (agomelatine) exposure in cigarette smokers due to induction of CYP1A2 is not clinically relevant, no dosage adjustment is necessary because a patient is a cigarette smoker (see *Pharmacokinetics* section).

Use with other antidepressants

VALDOXAN (agomelatine) should not be combined with fluvoxamine as fluvoxamine is a potent inhibitor of the metabolism of VALDOXAN (agomelatine) (see *CONTRAINDICATIONS* section). Caution should be taken when administering VALDOXAN (agomelatine) with other antidepressants as the safety and efficacy of VALDOXAN (agomelatine) in combination with other antidepressants has not been examined.

There is no pharmacokinetic or pharmacodynamic interaction between VALDOXAN (agomelatine) and paroxetine.

Lithium

There is no pharmacokinetic or pharmacodynamic interaction between VALDOXAN (agomelatine) and lithium.

Benzodiazepines (lorazepam)

There is no pharmacokinetic or pharmacodynamic interaction between VALDOXAN (agomelatine) and lorazepam.

Potential for VALDOXAN (agomelatine) to affect other medicinal products

VALDOXAN (agomelatine) inhibits neither CYP1A2 *in vivo* nor the other CYP450 *in vitro* and does not induce CYP450 isoenzymes *in vivo*. Therefore, VALDOXAN (agomelatine) will not modify exposure to drugs metabolised by CYP450.

In healthy volunteers VALDOXAN (agomelatine) did not modify the kinetics of theophylline, a CYP1A2 substrate.

Drugs highly bound to plasma protein

VALDOXAN (agomelatine) does not modify free concentrations of drugs highly bound to plasma proteins (eg. zolpidem, diazepam, sertraline, warfarin, oestrogen and salicylic acid) or *vice versa*.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. While clinical pharmacodynamic studies have shown that VALDOXAN (agomelatine) treatment does not impair cognitive or psychomotor function in healthy volunteers, dizziness and somnolence were reported during clinical trials. As with all psychoactive drugs, patients should be cautioned about their ability to drive a car or operate machinery.

ADVERSE EFFECTS

In clinical trials, over 3,900 depressed patients have received VALDOXAN (agomelatine).

In clinical trials dose escalation was associated with an increase in liver function abnormalities. The incidence of ALT and/or AST elevations >3xULN according to agomelatine dose in clinical trials was: 0.6% on agomelatine 1-10mg (4/679 patients), 1.0% on agomelatine 25mg (26/2506 patients), 1.4% on agomelatine 50mg (11/791 patients) and 3.5% on agomelatine 100mg (2/57 patients), compared to 0.7% in the placebo group (7/969 patients) – (see *PRECAUTIONS* section). Whilst 1-10mg and 100mg dosages were included in dose ranging studies, these are not within the approved therapeutic dose range of 25mg to 50mg (see *DOSAGE AND ADMINISTRATION* section).

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with VALDOXAN (agomelatine).

Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were nausea, dizziness and headache, which were also commonly reported in the placebo treatment group. These adverse reactions were usually transient and did not generally lead to cessation of therapy (see Table 7 where all adverse events >1% are listed including adverse reactions identified with an asterix *).

Table7: Emergent Adverse Events with incidence >1% in the agomelatine 25/50mg treatment group of the Short-term double blind placebo controlled MDD Set

Preferred term	Agomelatine 25/50mg N=1120 PM=1486.1 (%)	Placebo N=998 PM=1337.6 (%)
Nervous system disorders		
Headache*	14.1	14.1
Dizziness*	5.5	3.1
Somnolence*	2.9	2.3
Migraine*	1.2	0.4
Tremor	1.0	0.8
Gastrointestinal disorders		
Nausea*	7.7	7.1
Dry mouth	3.5	3.3
Diarrhoea*	3.1	2.6
Abdominal pain upper*	2.4	1.3
Constipation*	1.8	2.1
Dyspepsia	1.3	1.1
Infections and infestations		
Influenza	2.3	2.2
Nasopharyngitis	2.1	2.3
Psychiatric disorders		
Insomnia*	2.4	2.6
Anxiety*	2.0	1.2
Depression	1.3	1.2
General disorders and administration site conditions		
Fatigue*	2.6	2.0
Skin and subcutaneous tissue disorders		
Hyperhidrosis*	1.3	0.7
Musculoskeletal and connective tissue disorders		
Back pain*	1.5	1.3
Ear and labyrinth disorders		
Vertigo	1.1	1.2

Notes: PM = total number of patient-months in a given treatment group, N = number of patients,
** = adverse reactions*

The following additional adverse reactions were reported during clinical trials of agomelatine in depressed patients:

Adverse reactions are listed below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data) and have not been corrected for placebo. The frequencies are shown as: (*agomelatine vs placebo*).

Nervous system disorders:
Uncommon: paraesthesia (0.9% *vs* 0.1%).

Eye disorders:
Uncommon: blurred vision (0.6% *vs* 0%).

Skin and subcutaneous tissue disorders:
Uncommon: eczema (0.2% *vs* 0.1%)
Rare: erythematous rash (0.1% *vs* 0%)

Hepato-biliary disorders (in the overall safety database; N=3,297):
Common: increases (>3 times the upper limit of the normal range) in ALT and/or AST (1.1% vs. 0.7%)
Rare: hepatitis (0.03% *vs* 0%)

There were no differences in the nature and frequency of adverse events between treatment groups regardless of gender or age.

The percentage of patients who spontaneously reported sexual side effects in the short-term placebo-controlled studies in depression was similar for VALDOXAN (agomelatine) and placebo (1.2% and 1.1% respectively).

VALDOXAN (agomelatine) had no effect on body weight in clinical and non-clinical studies.

The following reactions have been reported in post-marketing experience (frequency not known):

Psychiatric disorders:
suicidal thoughts or behaviour, agitation

DOSAGE AND ADMINISTRATION

The recommended daily dose is one 25mg tablet taken orally at bedtime. After two weeks of treatment, if there is no improvement in symptoms, the dose may be increased to 50mg once daily, taken as a single dose of two tablets at bedtime. The maximum recommended dose should not be exceeded.

Liver function tests should be performed in all patients: at initiation of treatment, and then periodically after around six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated (see *PRECAUTIONS* section).

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.

VALDOXAN (agomelatine) tablets may be taken with or without food.

Children and adolescents:

VALDOXAN (agomelatine) is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy (see *PRECAUTIONS* section).

Elderly Patients

No adjustment in the usual dose is recommended for elderly patients solely because of their age.

Only limited clinical data is available on the use of VALDOXAN (agomelatine) in elderly patients ≥65 years old with major depressive episodes. Therefore, caution should be exercised when prescribing VALDOXAN (agomelatine) to these patients (see *PRECAUTIONS* section.)

Patients with renal impairment

No relevant modification in agomelatine pharmacokinetic parameters in patients with severe renal impairment has been observed. However, as only limited clinical data on the use of VALDOXAN (agomelatine) in depressed patients with severe or moderate renal impairment with major depressive episodes is available, caution should be exercised when prescribing VALDOXAN (agomelatine) to these patients.

Patients with hepatic impairment

VALDOXAN (agomelatine) is contraindicated in patients with hepatic impairment (see *CONTRAINDICATIONS* section).

Treatment discontinuation

No dosage tapering is needed on treatment discontinuation, as VALDOXAN (agomelatine) does not induce discontinuation symptoms after abrupt treatment cessation.

OVERDOSAGE

There is limited experience with agomelatine overdose.

During the clinical development, there were a few reports of agomelatine overdose, taken alone (up to 450mg) or in combination (up to 525mg) with other psychotropic medicinal products. Signs and symptoms of overdose were limited and included drowsiness and epigastralgia.

No specific antidotes for agomelatine are known. Management of overdose should consist of treatment of clinical symptoms and routine monitoring. Medical follow-up in a specialised environment is recommended.

PRESENTATION AND STORAGE CONDITIONS

Orange-yellow, oblong, film-coated tablet with a blue imprint of  on one face. Supplied in blister packs of 28 and 56[1] tablets.

Store in a dry place below 30°C.

NAME AND ADDRESS OF SPONSOR

SERVIER LABORATORIES (AUST) PTY LTD
8 Cato Street, Hawthorn,
Victoria 3122, Australia
ABN 54 004 838 500

POISONS SCHEDULE

S4

Date of TGA approval: 05 August, 2010

Date of last amendment: 12 October, 2010

[1] The 56 tablets pack size is not distributed in Australia