PRODUCT INFORMATION

NAME OF THE MEDICINE

VALDOXAN®
Agomelatine 25mg

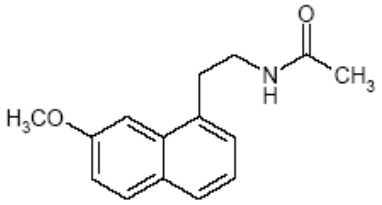
DESCRIPTION

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 monohydrate, maize starch, povidone, sodium starch glycollate, stearic acid, magnesium stearate, colloidal anhydrous silica, 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)

Agomelatine is a melatonin receptor (MT_1 and MT_2) agonist and 5-HT_{2C} receptor antagonist. 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 agomelatine has no effect on monoamine uptake and no affinity for α or β adrenergic, histaminergic, cholinergic, dopaminergic, or benzodiazepine receptors. 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, agomelatine has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset.

Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption.

In patients with depression, treatment with agomelatine 25 mg increased slow wave sleep without modification of REM (Rapid Eye Movement) sleep amount or REM latency. Agomelatine 25 mg 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, agomelatine preserves daytime alertness and memory, with no sedation in the morning following drug intake.

Cardiovascular

In clinical trials, agomelatine had no effect on QT interval and no clinically-significant effect on heart rate, blood pressure and ECG tracings

Withdrawal / Discontinuation

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

The abrupt discontinuation of agomelatine was not associated with discontinuation symptoms [$p=0.250$ for difference between the agomelatine and placebo groups]. The sensitivity of the trial 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 effect on sexual function (SEX-FX total score and SEX-FX sub-scores and items) was observed during agomelatine 50 mg treatment over 12 or 24-week treatment periods in a specific sexual dysfunction comparative trial in remitted depressed patients. There was a numerical trend towards less sexual emergent dysfunction on agomelatine 50 mg than venlafaxine 150 mg for SEX-FX drive arousal or orgasm scores but statistical separation was not achieved.

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

Pharmacokinetics

Absorption

Agomelatine is rapidly and well absorbed ($\geq$ 80%) after oral administration. The peak plasma concentration is reached within one to two hours after administration of 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, agomelatine exposure appears to increase proportionally with dose with saturation of the first pass effect occurring at supra-therapeutic doses (from 200 to 1200 mg).

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 35 L. 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.

Metabolism

Following oral administration, 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.

Excretion

Elimination is rapid. The mean plasma half-life is between one and two hours. Clearance is high (about 1100 mL/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 agomelatine pharmacokinetics, this result was not clinically relevant. Renal impairment did not affect the protein binding of agomelatine.

Hepatic Impairment: Following a single oral dose of 25 mg 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 agomelatine by a factor of ~3. The unbound fraction of 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. 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 patients with depression smoking > 5 cigarettes per day) compared to non-smoker population, suggesting that cigarette smoking could induce CYP1A2 which is involved in the metabolism of agomelatine.

CLINICAL TRIALS

Acute treatment of Major Depressive Disorder (MDD)

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 agomelatine for between six weeks and one year.

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

Agomelatine did not differentiate from placebo in one trial (CL3-022) where the active control fluoxetine showed assay sensitivity. In two other trials (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 trials

Trial (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 25-50 mg/day of agomelatine was also demonstrated in trial CL3-046 which assessed the antidepressant efficacy of agomelatine as a secondary objective compared to sertraline (50-100 mg/day) over a double-blind treatment period of six weeks where male or female patients, aged 18-60 years fulfilling DSM-IV criteria for MDD, received agomelatine 25-50 mg/day or sertraline 50-100 mg/day (see Table 2).

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

Trial (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 agomelatine

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

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

Trial (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^ [0.20; 2.77]	0.024
fluoxetine 20-40mg	257	28.7	12.7		

Notes: *^ Statistically significant difference in favour of agomelatine*
^^ 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 trial CL3-041 was to assess the efficacy of agomelatine at flexible dose in the prevention of depressive relapse compared to placebo. In this trial, 492 patients received open label treatment with agomelatine 25 mg/day for eight to ten weeks, with an increase to 50 mg/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 agomelatine or placebo until relapse occurred for up to 44 weeks. 338 patients participated in the double blind, long-term portion of the trial: 165 were treated with 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 agomelatine group compared to the placebo group in trial CL3-041 (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 agomelatine group than in the placebo group.

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

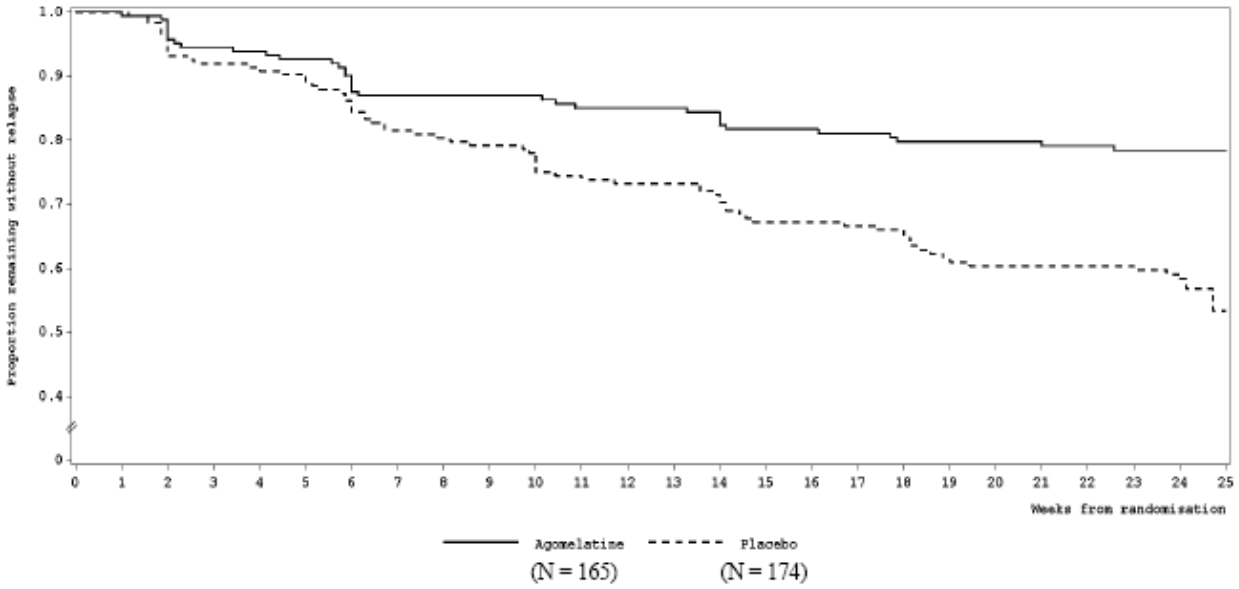


Table 4– Time to relapse analysis over 24 weeks

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]		

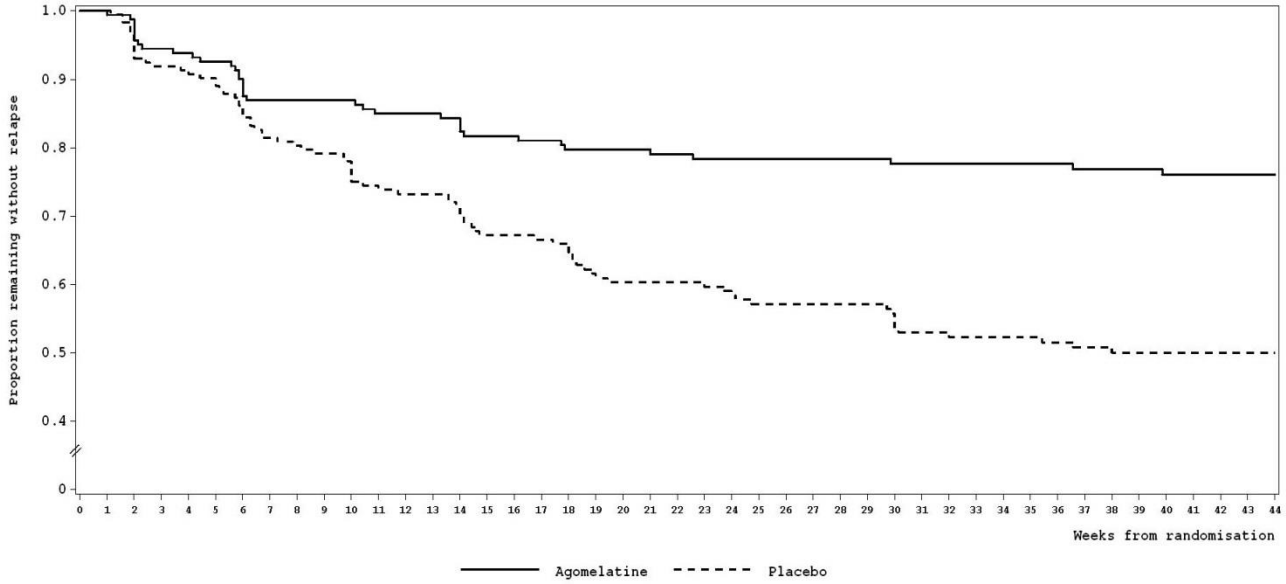
Results over the 44-week double-blind treatment period confirm the efficacy of agomelatine 25-50 mg to prevent depressive relapse in patients with MDD and showed the maintenance of long-term efficacy. The percentage of patients with a relapse over the whole 44-week double-blind period remained more than two times lower in the 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	47.7	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 agomelatine group compared to the placebo group.

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



In another relapse-prevention trial (CL3-021), 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 transaminases exceeding 3 times the upper limit of normal (see *PRECAUTIONS* and *DOSAGE AND ADMINISTRATION* sections)
- taking potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

PRECAUTIONS

Monitoring of liver function:

Caution should be exercised before initiation of treatment and close surveillance should be performed during continuing treatment, especially during combined use with medicines associated with risk of hepatic injury or where risk factors for hepatic injury are present.

In post-marketing experience cases of liver injury, including elevations of liver enzymes (> 10 times upper limit of the normal range), hepatic failure, hepatitis and jaundice have been reported in patients treated with agomelatine, most often during the first months of treatment (see *ADVERSE EFFECTS* section).

Isolated cases of transplantation or death in patients with hepatic failure have been reported following the use of agomelatine. Some patients had hepatic risk factors. This highlights the importance of performing liver function tests in all patients.

The pattern of liver damage is predominantly hepatocellular with serum transaminases usually returning to normal levels following discontinuation of agomelatine. In clinical trials, elevations of serum transaminases (> 3 times the upper limit of the normal range) have been observed in patients treated with agomelatine more commonly on a 50 mg dose.

Before initiation of treatment:

Treatment with agomelatine should only be initiated after careful consideration of the benefits and risk in patients with hepatic injury risk factors e.g.:

- overweight, obesity, non-alcoholic fatty liver disease, diabetes or use with medicines associated with risk of hepatic injury
- alcohol use disorder and /or substantial alcohol intake.

Baseline liver function tests should be performed in all patients before initiation of treatment. Treatment with agomelatine should not be initiated if serum transaminase levels are > 3 times the upper limit of the normal range (see *CONTRAINDICATIONS* section). Caution should be exercised when agomelatine is administered to patients with pre-treatment elevated transaminases (i.e. between the upper limit of the normal ranges and up to ≤ 3 times the upper limit of the normal range).

Frequency of liver function tests:

Before starting treatment and then:

- around 3 weeks
- around 6 weeks (end of acute phase)
- around 12 weeks
- around 24 weeks (end of maintenance phase)
- thereafter when clinically indicated.

When increasing the dosage, liver function tests should again be performed at the same frequency as when starting treatment.

Patients who develop any increased serum transaminases should have their liver function tests repeated within 48 hours.

During treatment:

Therapy should be discontinued immediately if any of the following are observed:

- an increase in serum transaminases > 3 times the upper limit of normal (see *CONTRAINDICATIONS* section
- signs or symptoms of potential liver injury (such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right abdomen, new-onset and unexplained fatigue).

Liver function tests should continue to be performed regularly following discontinuation of therapy until serum transaminases return to normal.

Suicide Ideation / Suicidality

In clinical trials, 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 patients with depression.

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. Patients with a history of suicide-related events or those exhibiting suicidality prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should be monitored during treatment.

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 MDD (16 trials), obsessive compulsive disorder (four trials) or other psychiatric disorders (four trials) have revealed a greater risk of adverse events representing 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 MDD 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 suicidality during the initial treatment period (generally the first one to two months) extends to young adults (aged 18-24 years) with MDD and other psychiatric disorders. These trials 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 years 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 MDD 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 MDD 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 events was 0.28 per 100 patient-months for agomelatine compared with 0.50 per 100 patient-months for placebo.

Bipolar disorder / Mania / Hypomania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

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

Lactose intolerance

VALDOXAN (agomelatine) tablets contain lactose monohydrate. 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.

Combination with CYP1A2 inhibitors (see *PHARMACOLOGY-Pharmacokinetics*, *CONTRAINDICATIONS* and *INTERACTIONS WITH OTHER MEDICINES* sections)

Use caution when combining agomelatine with moderate CYP1A2 inhibitors (e.g. propranolol) as these medicines may result in increased exposure to agomelatine.

Electroconvulsive therapy (ECT)

There is no experience with the combined use of agomelatine and ECT. In animals agomelatine has no proconvulsant properties. Therefore, adverse consequences of combined ECT and agomelatine treatment are considered to be unlikely.

Abuse potential

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

Use in Pregnancy (Category B1)

Animal trials 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. As a precautionary measure, it is recommended to avoid the use of agomelatine during pregnancy.

Use in Lactation

It is not known whether agomelatine and/or its metabolites are excreted into human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of agomelatine/metabolites in milk. 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 agomelatine on the nursing infant have not been established. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from agomelatine therapy following consideration of the relative benefits of breast feeding for the child and of therapy for the woman.

Paediatric Use

Use of agomelatine in children and adolescents (aged < 18 years) 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

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

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

The efficacy and safety of agomelatine (25 to 50 mg/day) have been established in elderly patients with MDD (aged < 75 years).

As efficacy has not been demonstrated in elderly patients aged ≥ 75 years, agomelatine should not be used in this patient group (see *DOSAGE AND ADMINISTRATION* section).

Carcinogenicity

Oral lifetime carcinogenicity trials 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 trials 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 %). Medicines 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.

Rifampicin an inducer of all three cytochromes involved in the metabolism of agomelatine may decrease the bioavailability of agomelatine.

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

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

Contraindicated:	Caution recommended:	No interaction:
Potent CYP1A2 inhibitors (e.g. fluvoxamine and ciprofloxacin)	***Moderate CYP1A2 inhibitors*** (e.g. propranolol) ***CYP1A2/CYP2C9/CYP2C19 inducers*** (e.g. rifampicin)	***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 dose 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 medicines 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 (e.g. zolpidem, diazepam, sertraline, warfarin, oestrogen and salicylic acid) or *vice versa*.

Effects on ability to drive and use machines

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

ADVERSE EFFECTS

In clinical trials, over 7,200 patients with depression have received agomelatine.

In clinical trials dose escalation was associated with an increase in liver function abnormalities. The incidence of ALT and/or AST elevations > 3x ULN according to agomelatine dose in clinical trials was: 0.6 % on agomelatine 1-10 mg (4/679 patients), 1.4 % on agomelatine 25 mg (62/4,543 patients), 2.5 % on agomelatine 50 mg (63/2,543 patients) and 3.5 % on agomelatine 100 mg (2/57 patients), compared to 0.6 % in the placebo group (8/1,464 patients) – see *PRECAUTIONS* section. Whilst 1-10 mg and 100 mg doses were included in dose ranging trials, these are not within the approved therapeutic dose range of 25 mg to 50 mg (see *DOSAGE AND ADMINISTRATION* section).

Patients with depression 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 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 a § symbol).

Table7: Emergent Adverse Events with incidence > 1 % in patients with MDD treated with agomelatine 25/50 mg short-term double blind placebo controlled trials (in the MDD set at the time of registration)

Preferred term	Agomelatine 25/50mg N=1,120 PM=1,486.1 (%)	Placebo N=998 PM=1,337.6 (%)
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§	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 patients with MDD:

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 %).

Psychiatric disorders:
Uncommon: suicidal thoughts or behaviour (see *PRECAUTIONS* section)

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:
Common: increases (> 3 times the upper limit of the normal range) in ALT and/or AST (1.4 % of patients on agomelatine 25 mg/day and 2.5 % on agomelatine 50 mg/day *vs* 0.6 % on placebo)
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.

Investigations:
Common: weight increased in patients on agomelatine 25/50 mg daily (1.4 % *vs* 1.4 %)
Uncommon: weight decreased in patients on agomelatine 25/50 mg daily (0.7 % *vs* 0.9 %)

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

The following reactions have been reported in post-marketing experience:

Skin and subcutaneous tissue disorders:
Uncommon[#]: pruritus, urticaria
Rare[#]: face oedema and angioedema

Gastrointestinal disorders:
Common[#]: vomiting

Psychiatric disorders:
Common[#]: abnormal dreams
Uncommon[#]: agitation and related symptoms (such as irritability and restlessness), aggression, nightmares, mania/hypomania (these symptoms may also be due to the underlying disease) (see *PRECAUTIONS* section), confusional state
Rare[#]: hallucinations

Hepato-biliary disorders:
Uncommon[#]: increased gamma-glutamyltransferase (GGT) (> 3 times the upper limit of the normal range)
Rare[#]: increased alkaline phosphatase (> 3 times the upper limit of the normal range), hepatic failure (see *PRECAUTIONS* section), jaundice

Nervous system disorders:
Uncommon[#]: restless leg syndrome
Rare[#]: akathisia

Ear and vestibular system disorders:
Uncommon[#]: tinnitus

Musculoskeletal and connective tissue disorders
Uncommon[#]: myalgia

Renal and urinary disorders
Rare[#]: urinary retention

[#] Frequency estimated from clinical trials for adverse events detected from spontaneous reports

DOSAGE AND ADMINISTRATION

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

Dose escalation has been associated with an increased incidence of serum transaminase elevations. Dose increases to 50 mg should only occur following an assessment of the benefits and risk and assessment of liver function.

Liver function tests should be performed in all patients before initiation of treatment and before a dose increase to 50 mg. Treatment with VALDOXAN (agomelatine) should not be initiated if serum transaminase levels are > 3 times the upper limit of normal range (see *CONTRAINDICATIONS* and *PRECAUTIONS* sections).

During treatment transaminases should be monitored periodically after around 3, 6 (end of acute phase), 12, and 24 (end of maintenance phase) weeks with regimen to be repeated following dose increase to 50 mg and thereafter when clinically indicated (see *PRECAUTIONS* section). Treatment should be discontinued if serum transaminase levels are > 3 times the upper limit of the normal range (see *CONTRAINDICATIONS* and *PRECAUTIONS* sections).

Treatment duration

Patients with depression should be treated for a sufficient period of at least six 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 aged < 18 years due to a lack of data on safety and efficacy (see *PRECAUTIONS* section).

Elderly Patients

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.

The efficacy and safety of agomelatine (25 to 50 mg/day) have been established in elderly patients with MDD (aged < 75 years). No adjustment in the usual dose is recommended for elderly patients with MDD (aged < 75 years) solely because of their age.

As efficacy has not been established in very elderly patients aged ≥ 75 years VALDOXAN (agomelatine) should not be used in this patient group (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 agomelatine in patients with depression and 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 dose 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.

Experience with agomelatine in overdose has indicated that epigastralgia, somnolence, fatigue, agitation, anxiety, tension, dizziness, cyanosis or malaise have been reported. One person having ingested 2,450 mg of agomelatine, recovered spontaneously without cardiovascular and biological abnormalities.

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

VALDOXAN (agomelatine) 25 mg is an orange-yellow, oblong, 9.5 mm long, 5.1 mm wide film-coated tablet with a blue imprint of the Servier company logo on one face. Supplied in a PVC/Alu blister pack of 28 tablets.

Store in a dry place below 30 ^{o}C.

NAME AND ADDRESS OF SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

S4 - Prescription only medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

09 August, 2010

DATE OF MOST RECENT AMENDMENT

04 September 2017