PACKAGE INSERT

VALDOXAN 25 MG

1. NAME OF THE MEDICINAL PRODUCT

Valdoxan 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg of agomelatine.

Excipient with known effect
Each film-coated tablet contains 61.8 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Orange-yellow, oblong, 9.5 mm long, 5.1 mm wide film-coated tablet with blue imprint of Servier logo on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Valdoxan is indicated for the treatment of:
- major depressive episodes (MDE);
- generalised anxiety disorder (GAD).

4.2. Posology and method of administration

Posology
The recommended dose is 25 mg once daily taken orally at bedtime.
If there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets, taken together at bedtime
- 2 weeks after treatment initiation in major depressive episode;
- 4 weeks after treatment initiation in generalized anxiety disorder.

Decision of dose increase has to be balanced with a higher risk of transaminases elevation. Any dose increase to 50 mg should be made on an individual patient benefit/risk basis and with strict respect of Liver Function Test monitoring.

Liver function tests should be performed in all patients before starting treatment. Treatment should not be initiated if transaminases exceed 3 X upper limit of normal (see sections 4.3 and 4.4).

During treatment transaminases should be monitored periodically after around three weeks, six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated (see also section 4.4). Treatment should be discontinued if transaminases exceed 3 X upper limit of normal (see sections 4.3 and 4.4).
When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment.

Treatment duration
Patients should be treated for a sufficient period of at least 6 months following response to ensure that they are free of symptoms.

Switching therapy from SSRI/SNRI antidepressant to agomelatine
Patients may experience discontinuation symptoms after cessation from an SSRI/ SNRI antidepressant.
The package insert of the actual SSRI/SNRI should be consulted on how to withdraw the treatment to avoid this. Agomelatine can be started immediately while tapering the dosage of a SSRI/SNRI (see section 5.1).

Treatment discontinuation
No dosage tapering is needed on treatment discontinuation.

Special populations
Elderly
The efficacy and safety of agomelatine (25 to 50mg/day) have been established in elderly patients with MDE (< 75years). No dose adjustment in the usual dose is recommended for elderly patients with MDE (aged < 75 years) solely because of their age. As efficacy has not been established in elderly patients aged ≥ 75 years with MDE, agomelatine should not be used in this patient group (see sections 4.4 and 5.1).

Data on the use of agomelatine in elderly patients with GAD are limited. Therefore, agomelatine is not recommended to treat GAD in the elderly aged ≥65 years (see sections 4.2 and 5.1).

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

Hepatic impairment
Agomelatine is contraindicated in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of agomelatine in children from 2 years onwards have not been established. No data are available (see section 4.4).
There is no relevant use of agomelatine in children from birth to 2 years.

Method of administration:
For oral use.
Valdoxan film-coated tablets may be taken with or without food.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 X upper limit of normal (see sections 4.2 and 4.4).

Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) (see section 4.5).

4.4. Special warnings and precautions for use

Monitoring of liver function

Cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors), elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in patients treated with agomelatine in the post-marketing setting (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with increased serum transaminases which usually return to normal levels on cessation of agomelatine.

Caution should be exercised before starting treatment and close surveillance should be performed throughout the treatment period in all patients, especially if hepatic injury risk factors or concomitant medicinal products associated with risk of hepatic injury are present.

Before starting treatment

Treatment with Valdoxan should only be prescribed after careful consideration of benefit and risk in patients with hepatic injury risk factors e.g.

- obesity/overweight/non-alcoholic fatty liver disease, diabetes;
- alcohol use disorder and/or substantial alcohol intake

and in patients receiving concomitant medicinal products associated with risk of hepatic injury.

Baseline liver function tests should be undertaken in all patients and treatment should not be initiated in patients with baseline values of ALT and/or AST >3 X upper limit of normal (see section 4.3). Caution should be exercised when Valdoxan is administered to patients with pretreatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range).

- *Frequency of liver function tests*

- before starting treatment
- and then:
    - after around 3 weeks,
    - after around 6 weeks (end of acute phase),
    - after around 12 and 24 weeks (end of maintenance phase)
    - and thereafter when clinically indicated.
- When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment

Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours.

During treatment period

Valdoxan treatment should be discontinued immediately if:

- patient develops symptoms or signs of potential liver injury (such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue).
- the increase in serum transaminases exceeds 3 X upper limit of normal.

Following discontinuation of Valdoxan therapy liver function tests should be repeated until serum transaminases return to normal.

Use in paediatric population
Valdoxan is not recommended in patients under 18 years of age since safety and efficacy of Valdoxan 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 (see section 4.2).

Elderly
As efficacy has not been demonstrated in elderly patients aged ≥75 years, agomelatine should not be used in this patient group (see also sections 4.2 and 5.1).

Data on the use of agomelatine in elderly patients with GAD are limited. Therefore, agomelatine is not recommended to treat GAD in the elderly aged ≥65 years (see sections 4.2 and 5.1).

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

Bipolar disorder/mania/hypomania
Valdoxan should be used with caution in patients with a history of bipolar disorder, mania or hypomania and should be discontinued if a patient develops manic symptoms (see section 4.8).

Suicide/suicidal thoughts
Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Generalized anxiety disorder for which Valdoxan is prescribed can also be associated with an increased risk of suicide-related events. The same precautions observed when treating depressed patients should therefore be observed when treating patients with generalized anxiety disorder.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo, in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany treatment especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Combination with CYP1A2 inhibitors (see sections 4.3 and 4.5)
Combination with potent CYP1A2 inhibitors is contraindicated. Caution should be exercised when prescribing Valdoxan with moderate CYP1A2 inhibitors (*e.g.* propranolol, enoxacin) which may result in increased exposure of agomelatine.

Lactose intolerance
Valdoxan contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Level of sodium
Valdoxan contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

Potential interactions affecting agomelatine
Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Medicinal products that interact with these isoenzymes may decrease or increase the bioavailability of agomelatine.

Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor markedly inhibits the metabolism of agomelatine resulting in a 60-fold (range 12-412) increase of agomelatine exposure.
Consequently, co-administration of Valdoxan with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.

Combination of agomelatine with oestrogens (moderate CYP1A2 inhibitors) results in a several fold increased exposure of agomelatine. While there was no specific safety signal in the 800 patients treated in combination with oestrogens, caution should be exercised when prescribing agomelatine with other moderate CYP1A2 inhibitors (e.g. propranolol, enoxacin) until more experience has been gained (see section 4.4).

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

Smoking induces CYP1A2 and has been shown to decrease the bioavailability of agomelatine, especially in heavy smokers ($\geq$ 15 cigarettes/day) (see section 5.2).

Potential for agomelatine to affect other medicinal products
In vivo, agomelatine does not induce CYP450 isoenzymes. Agomelatine inhibits neither CYP1A2 *in vivo* nor the other CYP450 *in vitro*. Therefore, agomelatine will not modify exposure to medicinal products metabolised by CYP 450.

Other medicinal products
No evidence of pharmacokinetic or pharmacodynamic interaction with medicinal products which could be prescribed concomitantly with Valdoxan in the target populations was found in phase I clinical trials: benzodiazepines, lithium, paroxetine, fluconazole and theophylline.

Alcohol
The combination of agomelatine and alcohol is not advisable.

Electroconvulsive therapy (ECT)
There is no experience of concurrent use of agomelatine with ECT. Animal studies have not shown proconvulsant properties (see section 5.3). Therefore, clinical consequences of ECT performed concomitantly with agomelatine treatment are considered to be unlikely.

Paediatric population
Interaction studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

Fertility
Reproduction studies in the rat and the rabbit showed no effect of agomelatine on fertility. (see section 5.3).

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of agomelatine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Valdoxan during pregnancy.

Breast-feeding
It is not known whether agomelatine/metabolites are excreted into human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of agomelatine/metabolites in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Valdoxan therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7. Effects on ability to drive and use machines

Agomelatine has minor influence on the ability to drive and use machines
Considering that dizziness and somnolence are common adverse reactions patients should be cautioned about their ability to drive a car or operate machines.

4.8. Undesirable effects

Summary of the safety profile
Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were headache, nausea and dizziness.
These adverse reactions were usually transient and did not generally lead to cessation of therapy.

Tabulated list of adverse reactions
The below table gives the adverse reactions observed from clinical trials and post marketing spontaneous reports.
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). The frequencies have not been corrected for placebo.

System organ class	Frequency	Preferred Term
Psychiatric disorders	Common	Anxiety
		Abnormal dreams*
	Uncommon	Suicidal thoughts or behaviour (see section 4.4)
		Agitation and related symptoms* (such as irritability and restlessness)
		Aggression*
		Nightmares*
		Mania/hypomania* These symptoms may also be due to the underlying disease (see section 4.4).
		Confusional state*
	Rare	Hallucinations*
Nervous system disorders	Very common	Headache
	Common	Dizziness
		Somnolence

		Insomnia
	Uncommon	Migraine
		Paraesthesia
		Restless leg syndrome*
	Rare	Akathisia*
Eye disorders	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Tinnitus*
Gastrointestinal Disorders	Common	Nausea
		Diarrhoea
		Constipation
		Abdominal pain
		Vomiting*
Hepato-biliary disorders	Common	Increased ALT and/or AST (in clinical trials, increases >3 times the upper limit of the normal range for ALT and/or AST were seen in 1.3% of patients on agomelatine 25 mg daily and 2.6 % on agomelatine 50 mg daily vs. 0.4% on placebo).
	Uncommon	Increased gamma-glutamyltransferase* (GGT) (>3 times the upper limit of the normal range
	Rare	Hepatitis
		Increased alkaline phosphatase* (>3 times the upper limit of the normal range)
		Hepatic failure*(1)
		Jaundice*
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis
		Eczema
		Pruritus*
		Urticaria*
	Rare	Erythematous rash
		Face oedema and angioedema*
Musculoskeletal and connective tissue disorders	Common	Back pain
	Uncommon	Myalgia*
Renal and urinary disorders	Rare	Urinary retention*
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Weight increased *
	Uncommon	Weight decreased*

* Frequency estimated from clinical trials for adverse reactions detected from spontaneous report

(1) Few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

Symptoms
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 agomelatine, recovered spontaneously without cardiovascular and biological abnormalities. No specific antidotes for agomelatine are known.
Management
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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics, Other antidepressants, ATC-code: NO6AX22

Mechanism of action
Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist. Binding studies indicate that agomelatine has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors.
Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption.
Agomelatine increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin.

Pharmacodynamic effects
Agomelatine has shown an antidepressant-like effect in animal models of depression (learned helplessness test, despair test, chronic mild stress) as well as in models with circadian rhythm desynchronisation and in models related to stress and anxiety.
In humans, agomelatine has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset.

Clinical efficacy and safety
Major depressive episodes:
The efficacy and safety of agomelatine in major depressive episodes have been studied in a clinical programme including 7,900 patients treated with agomelatine.

Ten placebo controlled trials have been performed to investigate the short term efficacy of agomelatine in major depressive disorder in adults, with fixed dose and/or dose up-titration. At the end of treatment (over 6 or 8 weeks), significant efficacy of agomelatine 25-50 mg was demonstrated in 6 out of the ten short-term double-blind placebo-controlled trials. Primary endpoint was changed in HAMD-17 score from baseline. Agomelatine failed to differentiate from placebo in two trials where the active control, paroxetine or fluoxetine showed assay sensitivity. Agomelatine was not compared directly with paroxetine and fluoxetine as these comparators were added to ensure assay sensitivity of the trials. In two other trials, it was not possible to draw any conclusions because the active controls, paroxetine or fluoxetine, failed to differentiate from placebo. However, in these studies it was not allowed to increase the starting dose of either agomelatine, paroxetine or fluoxetine even if the response was not adequate.

Efficacy was also observed in more severely depressed patients (baseline HAM-D ≥ 25) in all positive placebo-controlled trials.

Response rates were statistically significantly higher with agomelatine compared with placebo.
Superiority (2 trials) or non-inferiority (4 trials) has been shown in six out of seven efficacy trials in heterogeneous populations of depressed adult patients versus SSRI/SNRI (sertraline, escitalopram, fluoxetine, venlafaxine or duloxetine) The anti-depressive effect was assessed with the HAMD-17 score either as primary or secondary endpoint.

The maintenance of antidepressant efficacy was demonstrated in a relapse prevention trial. Patients responding to 8/10-weeks of acute treatment with open-label agomelatine 25-50 mg once daily were randomised to either Valdoxan 25-50 mg once daily or placebo for further 6-months. agomelatine 25-50 mg once daily demonstrated a statistically significant superiority compared to placebo (p=0.0001) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow up period was 22% and 47% for agomelatine and placebo, respectively.

A placebo-controlled 8-week trial of agomelatine 25-50mg/day in elderly depressed patients (≥ 65 years, N=222, of which 151 on agomelatine) demonstrated a statistically significant difference of 2.67 points on HAM-D total score, the primary outcome. Responder rate analysis favoured agomelatine. No improvement was observed in very elderly patients (≥75 years, N= 69, of which 48 on agomelatine). Tolerability of agomelatine in elderly patients was comparable to that seen in the younger adults.

A specific controlled, 3-week trial has been conducted in patients suffering from major depressive disorder and insufficiently improved with paroxetine (a SSRI) or venlafaxine (a SNRI). When treatment was switched from these antidepressants to agomelatine, discontinuation symptoms arose after cessation of the SSRI or SNRI treatment, either after abrupt cessation or gradual cessation of the previous treatment. These discontinuation symptoms may be confounded with a lack of early benefit of agomelatine.
The percentage of patients with at least one discontinuation symptom one week after the SSRI/SNRI treatment stop, was lower in the long tapering group (gradual cessation of the previous SSRI/SNRI within 2 weeks) than in the short tapering group (gradual cessation of the previous SSRI/SNRI within 1 week) and in the abrupt substitution group (abrupt cessation): 56.1%, 62.6 % and 79.8% respectively.

In a trial designed to assess discontinuation symptoms by the Discontinuation Emergent Signs and Symptoms (DESS) check-list in patients with remitted depression, agomelatine did not induce discontinuation syndrome after abrupt treatment cessation.

Generalized anxiety disorder:
Acute Treatment of Generalised Anxiety Disorder (GAD)

The efficacy and safety of agomelatine (25 mg & 50 mg/day) in generalised anxiety disorder have been studied in a clinical programme including more than 1,100 patients with GAD treated with agomelatine. On the primary endpoint of (HAM-A) total score in all three placebo-controlled short-term trials (12-week treatment) agomelatine demonstrated a statistically significant superiority compared to placebo. In addition, response and remission rates were superior with agomelatine vs placebo (see Table 1). Assay sensitivity was shown in the trial including escitalopram as a validator.

Table 1 - HAM-A total score (expressed as change from baseline) and response rates to treatment for the last value over 12 weeks for study

		Difference placebo – Agomelatine or Escitalopram			
		N	**E**	**SE**	**95% CI**	**p-value**
CL2-040						
HAM-A total score (mean±SD)						
Placebo	-13.2 ± 9.5	58				
Agomelatine	-16.6 ± 8.9	63	3.28	1.58	[0.15;6.41]	0.040[1]
HAM-A response rate (%)						
Placebo	46.6	58				
Agomelatine	66.7	63	-20.11	8.84	[-37.44; -2.79]	0.026[2]
CL3-071						
HAM-A total score (mean±SD)						
Placebo	-10.6 ± 9.5	131				
Agomelatine 25-50mg	-15.6 ± 9.4	139	4.71	1.03	[2.69;6.73]	<0.0001[3]
Escitalopram 10-20mg	-15.6 ± 8.2	139	4.77	1.03	[2.74;6.79]	<0.0001[3]
HAM-A response rate (%)						
Placebo	36.6	131				
Agomelatine 25-50mg	64.0	139	-27.39	5.86	[-38.86;-15.91]	<0.0001[2]
Escitalopram 10-20mg	66.2	139	-29.55	5.82	[-40.94;-18.15]	<0.0001[2]
CL3-087						
HAM-A total score (mean±SD)						
Placebo	-6.9 ± 9.2	140				
Agomelatine 10mg	-13.7 ± 8.7	130	7.16	1.00	[5.19;9.13]	<0.0001[3]
Agomelatine 25mg	-18.0 ± 7.7	138	11.08	0.98	[9.14;13.01]	<0.0001[3]
HAM-A response rate (%)						
Placebo	22.86	140				
Agomelatine 10mg	51.54	130	-28.68	5.64	[-39.74; -17.63]	<0.0001[2]
Agomelatine 25mg	70.29	138	-47.43	5.27	[-57.75; -37.11]	<0.0001[2]

Notes: *SD: Standard Deviation; E: estimate of the difference between treatment groups; SE: Standard Error*

1: general linear model with baseline as covariate, previous psychotropic treatment intake as fixed effect, centre as random effect

2: Chi-Square test

3: Covariance analysis with adjustment for baseline and centre as random effect

The results for meta-analyses performed on the change from baseline to W12 in HAM-A total score (primary criterion) and response to treatment at W12 in the pool of studies summarising the efficacy of agomelatine versus placebo are detailed in Table 2.

Table 2 - HAM-A total score - Change from baseline to W12 and responder rates at W12 - meta-analysis of short-term placebo-controlled studies (CL2-040, CL3-071 and CL3-087)

	Agomelatine 25 & 25-50 mg (N = 340)	**Placebo (N = 329)**
HAM-A total score (mean ± SD)		
Baseline	28.8 ± 3.9	28.5 ± 3.6
Change to W12 (LOCF)	-16.8 ± 8.7	-9.5 ± 9.6
Diff. from placebo (change to W12 LOCF)		
E (SE)(1)	6.43 (2.50)	
95% CI(2)	[1.53; 11.32]	
p-value(3)	0.010	
HAM-A Responders (%)*		
% at W12 (LOCF)	67.06	32.52
Diff. from placebo (at W12 LOCF)		
E (SE)(1)	32.55 (8.40)	
95% CI(2)	[16.09; 49.02]	
p-value(3)	< 0.001	

Notes: *N: Number of patients with value; SD: Standard Deviation; E: estimate of the difference between treatment groups; SE: Standard Error; LOCF: Last observation carried forward*

Meta-Analysis: Overall Treatment Effect Using A Random Effect Model

(1) Overall estimate (standard error) of the difference between treatments:
Weighted mean of effects of treatment (adjusted on baseline and centre for the HAM-A total score [primary criterion]) estimated in the studies (Placebo minus Agomelatine 25 & 25-50 mg for score) (respectively Agomelatine 25 & 25-50 mg minus Placebo for responders). A positive estimate indicates greater improvement in Agomelatine 25 & 25-50 mg as compared to Placebo.

(2) 95% Confidence interval of the estimate

(3) Overall treatment effect: Meta-analytic methods

**A responder to treatment was defined as a patient with a decrease in baseline HAM-A total score > 50%*

Efficacy was also observed in more severely anxious patients in the three placebo-controlled trials. The meta-analyses of HAM-A total score in GAD patients in the three short-term placebo-controlled studies (CL2-040, CL3-071, CL3-087) showed a significant treatment effect of agomelatine 25 and 25-50 mg in severely ill patients (defined successively by a HAM-A total score ≥ 25 at baseline or, a HAM-A total score ≥ 25 and CGI-S ≥ 5 at baseline) (See Table 3).

Table 3 - HAM-A total score - Change from baseline to W12 (LOCF) in more severe patients - Meta-analysis of placebo-controlled studies (CL2-040, CL3-071 and CL3-087) - W0-W12 period

Subsets of the FAS Treatment group		**Difference *vs* placebo** *(change from baseline to W12 LOCF)*		
	N	E (SE)[1]	95% CI[2]	p-value[3]
All				
Agomelatine 25 & 25-50 mg	340	6.43 (2.50)	[1.53; 11.32]	0.010
Placebo	329			
HAM-A > 25				
Agomelatine 25 & 25-50 mg	296	6.69 (2.76)	[1.28; 12.11]	0.015
Placebo	291			
HAM-A > 25 & CGI-S > 5				
Agomelatine 25 & 25-50 mg	193	7.69 (2.84)	[2.13; 13.26]	0.007
Placebo	172			

Notes: *N: Number of patients with value; SD: Standard Deviation; E: estimate of the difference between treatment groups; SE: Standard Error; LOCF: Last observation carried forward; FAS: Full Analysis Set*
Meta-Analysis: Overall Treatment Effect Using A Random Effect Model
(1) Overall estimate (standard error) of the difference between treatments:
Weighted mean of effects of treatment (adjusted on baseline and centre) estimated in the studies (Placebo minus Agomelatine 25 & 25-50 mg). A positive estimate indicates greater improvement in Agomelatine 25 & 25-50 mg as compared to Placebo
(2) 95% Confidence interval of the estimate
(3) Overall treatment effect: Meta-analytic methods

Agomelatine efficacy was compared directly with escitalopram in one study [CL3-089] in patients suffering from severe generalised anxiety disorder (W0 HAM-A > 25), using the HAM-A as the primary endpoint. Patients were randomised in double blind, parallel-group, flexible-dose study with a main duration of evaluation of 12 weeks, followed by a possible extension period up to 9 months. The non-inferiority of agomelatine compared to escitalopram in terms of short-term efficacy was assessed after a 12-week treatment period. In this study, agomelatine showed similar efficacy results to escitalopram in terms of improvements on the HAM-A total score and response rates without reaching non inferiority at week 12. (See Table 4).

Table 4 - HAM-A total score (expressed as change from baseline) and response rates to treatment for the last value over 12 weeks for study CL3-089

			Difference vs comparator			
		N	**E[1]**	**SE**	**95% CI[2]**	**p-value**
Study CL3-089 - HAM-A total score (mean±SD) in FAS (LOCF)						
Agomelatine 25-50mg	-16.0 ± 9.1	258				
Escitalopram 10-20mg	-16.9 ± 8.4	261	-0.91	0.69	[-2.26;0.44]	0.195[3]
HAM-A response rate (%) in FAS (LOCF)						
Agomelatine 25-50mg	60.9	258				
Escitalopram 10-20mg	64.8	261	-3.90	4.24	[-12.21;4.41]	0.358[4]

Notes: *SD: Standard Deviation; E: estimate of the difference between treatment groups; SE: Standard Error; LOCF: Last observation carried forward*

1: Covariance analysis with adjustment for baseline and centre (as random effect) with baseline HAM-A total score as covariate

2: 95% Confidence interval of the estimate

3: Non inferiority test centred on a non-inferiority margin of 1.5; one sided p-value to be compared to 0.025

4: Chi-Square test

Prevention of Relapse of GAD

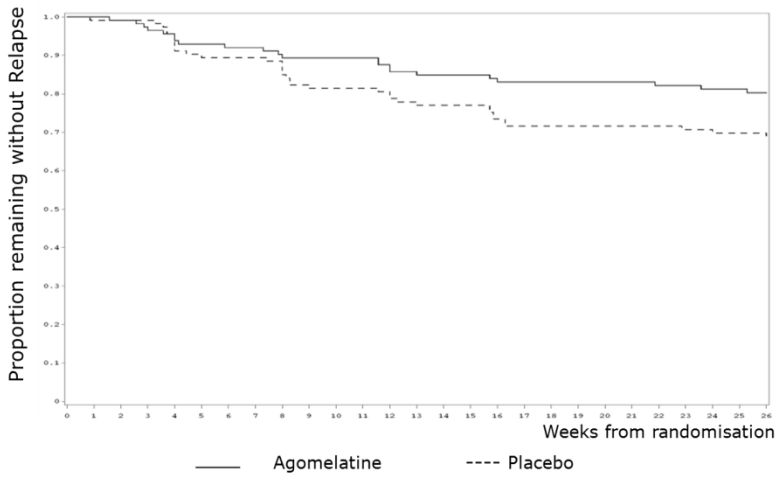
The maintenance of efficacy in generalised anxiety disorder was demonstrated in a relapse prevention trial [CL3-050]. The primary efficacy criterion was relapse during the double-blind treatment period defined as a HAM-A total score ≥ 15, or a lack of efficacy as judged by the clinician among patients who responded to the open-label treatment. Patients responding to 16-weeks of acute treatment with open-label agomelatine 25 mg once daily, with a possible up titration to 50 mg once daily after four weeks, were randomised to either agomelatine 25-50 mg or placebo for further six months (26 weeks). Agomelatine 25-50 mg once daily demonstrated a statistically significant superiority compared to placebo (p=0.046) on the primary outcome measure, the prevention of anxious relapse, as measured by time to relapse. The incidence of relapse during the 6-month double-blind follow up period was 19.5 % and 30.7 % [95% CI: 0.641;0.995) for agomelatine and placebo, respectively. In patients treated with agomelatine, the risk of relapse over time was significantly reduced by 41.8% compared to placebo (p = 0.045) (see Table 5).

Table 5 - Number of patients with relapse during the 26-week double-blind period, incidence over time and risk of relapse over 26 weeks

Group	No. of patients	Relapses[1]		Logrank	Incidence of relapse at 182 days	Logrank
		N	%	p-value[2]	E [95% CI]	p-value[2]
Agomelatine 25-50mg	113	22	19.5	0.046	0.582[3]	0.045
Placebo	114	35	30.7		[0.341; 0.995][4]	

Notes: *1: Total number and percentage of patients having a relapse during the double-blind period*
2: Stratified or adjusted for country
3: Estimate (Standard Error) of the Hazard Ratio (adjusted) of relapse between treatment groups: agomelatine vs placebo.
4: 95% confidence interval of the estimate.

Figure 1 – Time to anxious relapses over 26 weeks survival curves (CL3-050)



Discontinuation symptoms in study CL3-050 were assessed by the Discontinuation Emergent Signs and Symptoms (DESS) checklist in patients having completed the study up to week 42 and re-randomised either on placebo or agomelatine. Absence of discontinuation syndrome after abrupt agomelatine treatment cessation was confirmed in this population.

General properties
Agomelatine does not alter daytime vigilance and memory in healthy volunteers. In depressed patients, 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.

In healthy volunteers agomelatine preserved sexual function in comparison with paroxetine. In a specific sexual dysfunction comparative trial with remitted depressed patients, there was a numerical trend (not statistically significant) towards less sexual emergent dysfunction than venlafaxine for Sex Effects Scale (SEXFX) drive arousal or orgasm scores on agomelatine. The pooled analysis of trials using the Arizona Sexual Experience Scale (ASEX) showed that agomelatine was not associated with sexual dysfunction.

Agomelatine had neutral effect on heart rate and blood pressure in clinical trials.

Agomelatine has no abuse potential as measured in healthy volunteer studies on a specific visual analogue scale or the Addiction Research Center Inventory (ARCI) 49 check-list.

5.2. Pharmacokinetic properties

Absorption and bioavailability
Agomelatine is rapidly and well (≥ 80%) absorbed after oral administration. Absolute bioavailability is low (< 5% at the therapeutic oral dose) and the inter-individual variability is substantial. The bioavailability is increased in women compared to men. The bioavailability is increased by intake of oral contraceptives and reduced by smoking. The peak plasma concentration is reached within 1 to 2 hours.

In the therapeutic dose-range, agomelatine systemic exposure increases proportionally with dose. At higher doses, a saturation of the first-pass effect occurs.
Food intake (standard meal or high fat meal) does not modify the bioavailability or the absorption rate. The variability is increased with high fat food.

Distribution
Steady state volume of distribution is about 35 l and plasma protein binding is 95% irrespective of the 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, agomelatine is rapidly metabolised mainly via hepatic CYP1A2; CYP2C9 and CYP2C19 isoenzymes are also involved but with a low contribution.
The major metabolites, hydroxylated and demethylated agomelatine, are not 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 and the clearance is high (about 1,100 ml/min) and essentially metabolic.
Excretion is mainly (80%) urinary and in the form of metabolites, whereas unchanged compound recovery in urine is negligible.
Kinetics are not modified after repeated administration.

Renal impairment
No relevant modification of pharmacokinetic parameters in patients with severe renal impairment has been observed (n=8, single dose of 25 mg), but caution should be exercised in patients with severe or moderate renal impairment as only limited clinical data are available in these patients (see section 4.2).

Elderly
In a pharmacokinetic study in elderly patients (≥ 65 years), it was shown that at a dose of 25 mg the mean AUC and mean Cmax were about 4-fold and 13-fold higher for patients ≥ 75 years old compared to patients < 75 years old. The total number of patients receiving 50 mg was too low to draw any conclusions. No dose adaptation is required in elderly patients.

Hepatic impairment
In a specific study involving cirrhotic patients with chronic mild (Child-Pugh type A) or moderate (Child-Pugh type B) liver impairment, exposure to agomelatine 25 mg was substantially increased (70-times and

140-times, respectively), compared to matched volunteers (age, weight and smoking habit) with no liver failure (see section 4.2, 4.3 and 4.4).

Ethnic groups
There is no data on the influence of race on agomelatine pharmacokinetics.

5.3. Preclinical safety data

In mice, rats and monkeys sedative effects were observed after single and repeated administration at high doses.
In rodents, a marked induction of CYP2B and a moderate induction of CYP1A and CYP3A were seen from 125 mg/kg/day whereas in monkeys the induction was slight for CYP2B and CYP3A at 375 mg/kg/day. No hepatotoxicity was observed in rodents and monkeys in the repeat dose toxicity studies.
Agomelatine passes into the placenta and foetuses of pregnant rats.
Reproduction studies in the rat and the rabbit showed no effect of agomelatine on fertility, embryofoetal development and pre- and post natal development.
A battery of *in vitro* and *in vivo* standard genotoxicity assays concludes to no mutagenic or clastogenic potential of agomelatine.

In carcinogenicity studies agomelatine induced an increase in the incidence of liver tumours in the rat and the mouse**,** at a dose at least 110-fold higher than the therapeutic dose. Liver tumours are most likely related to enzyme induction specific to rodents. The frequency of benign mammary fibroadenomas observed in the rat was increased with high exposures (60-fold the exposure at the therapeutic dose) but remains in the range of that of controls.

Safety pharmacology studies showed no effect of agomelatine on hERG (human Ether à-go-go Related Gene) current or on dog Purkinje cells action potential. Agomelatine did not show proconvulsive properties at ip doses up to 128 mg/kg in mice and rats.

No effect of agomelatine on juvenile animals behavioural performances, visual and reproductive function were observed. There were mild non dose dependent decreases in body weight related to the pharmacological properties and some minor effects on male reproductive tract without any impairment on reproductive performances.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:
- Lactose monohydrate
- Maize starch
- Povidone (K30)
- Sodium starch glycolate type A
- Stearic acid
- Magnesium stearate
- Silica, colloidal anhydrous

Film-coating:
- Hypromellose
- Yellow iron oxide (E172)
- Glycerol
- Macrogol 6000
- Magnesium stearate

- Titanium dioxide (E171)

Printing ink containing shellac, propylene glycol and indigo carmine aluminium lake(E132)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

Aluminium/PVC blister packed in cardboard boxes (calendar).
Packs containing 14 and 28 film-coated tablets. Not all pack sizes may be marketed.

Date of last revision of package insert: March 2023

Les Laboratoires Servier – France

Manufacturers:
Les Laboratoires Servier Industrie
45520 Gidy – France
Or
Servier (Ireland) Industries Ltd
Gorey Road – Arklow
Co. Wicklow – Ireland