ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 company logo on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Valdoxan is indicated for the treatment of major depressive episodes in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 25 mg once daily taken orally at bedtime.
After two weeks of treatment, 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.

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 with depression should be treated for a sufficient period of at least 6 months 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 SmPC 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 depressed patients (< 75years). No effect is documented in patients ≥75 years. Therefore, agomelatine should not be used by patients in this age group (see sections 4.4 and 5.1). No dose adjustment is required in relation to age (see section 5.2).

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
Children from birth to <7 years
There is no relevant use of agomelatine in children from birth to <7 years for treatment of major depressive episodes. No data are available.
Children and adolescents from 7 to 17 years
The safety and efficacy of agomelatine in children and adolescents aged from 7 to 17 years for treatment of major depressive episodes have not been established. Currently available data are described in sections 4.4, 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

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.

Paediatric population

Valdoxan is not recommended in the treatment of depression in patients under 18 years of age since safety and efficacy of agomelatine have not been established. 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.
For agomelatine reported suicidal events were too few to make any meaningful comparison between agomelatine and placebo. Pooled data from clinical trials with agomelatine 25 mg have shown that suicidal events occurred at a higher frequency in adolescents (3.1%) compared to adults (1.2%), seesection on Suicide/suicidal thoughts below and section 4.8.
In pooled data from clinical trials hepatic adverse events were more frequently reported by adolescents (6.3%) compared to adults (1.7%).
Long-term safety data is limited. This includes long-term experience on growth, pubertal development (see section 5.1) and cognitive function.

Elderly
No effect of agomelatine is documented in patients ≥75 years, therefore agomelatine should not be used by patients in this age group (see also 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.
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)

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 (≥ 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 population 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

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 in 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.

Fertility

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

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 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 adult placebo-controlled and adult active-controlled clinical trials.
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 1.2% of patients on agomelatine 25 mg daily and 2.6 % on agomelatine 50 mg daily vs. 0.5% 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.

Paediatric population

A total of 80 children aged 7 to less than 12 years old and 319 adolescent patients aged between 12 to 17 years with moderate to severe major depressive disorder were treated with agomelatine in a double-blind, active (fluoxetine) and placebo-controlled study.
In general, the safety profile of agomelatine 25 mg in adolescents in the pivotal study (double-blind controlled part) was similar to that seen in adults, except for nausea which occurred at a higher frequency in adolescents (13.3%) than in adults (6.3%).
Pooled data from clinical trials with agomelatine have shown that adverse events and serious adverse events (all-causality) were reported with higher frequency in the adolescents than in the adults (67.2% vs 60.4% of patients who reported at least one adverse event and 10.4% versus 3.5% of the patients who reported at least one serious adverse event).
Hepatic adverse events were reported by 6.3% of adolescents compared to adults (1.7%). Suicidal events (for instance suicidal behavior, suicide thoughts, suicide attempt and self-injury) occurred at a higher frequency in adolescents (3.1%, 10 events reported in 6 patients) compared to adults (1.2%, 66 events reported in 65 patients) (see section 4.4.).
Long-term safety data for agomelatine 25 mg in adolescents is limited. This includes long-term experience on growth, pubertal development (see section 5.1) and cognitive function.

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 listed in Appendix V.

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.

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: N06AX22

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 in adults

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 change 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 where added in order 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 start 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 agomelatine 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.

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 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. In healthy volunteers agomelatine preserved sexual function in comparison with paroxetine.

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

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.
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.
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.

Paediatric population

The efficacy and safety of two doses (10 mg and 25 mg) of agomelatine for the treatment of moderate to severe major depressive episodes, if depression is unresponsive to psychological therapy alone, were assessed in a 12-week, randomized, double-blind, and placebo-controlled, parallel groups, study (see section 4.2). Fluoxetine (10 mg/day with potential adjustment to 20 mg/day) was added to ensure assay sensitivity.

Patients (N=400; whereof 80 children from 7 to less than 12 years and 320 adolescents from 12 to 17 years) with moderate to severe depression according to DSM IV were randomised to receive agomelatine 10 mg (N=102 whereof 81 were adolescents), agomelatine 25 mg (N= 95 whereof 76 were adolescents), placebo (N= 103 whereof 82 were adolescents) and fluoxetine (N= 100 whereof 81 were adolescents).
The patients were to be non-responders to psychosocial therapy before inclusion. During the double-blind period psychosocial counselling was given once a month (Week 4, 8 and 12).

The primary endpoint was the adjusted difference in baseline to Week 12 in the Children's Depression Rating Scale – Revised (CDRS-R) raw total score, using a 3-way ANCOVA. A raw score of ≥ 45 was a prerequisite for enrolment. The CDRS-R was performed at the selection visit, at inclusion (Week 0) and thereafter at each visit (i.e., in the double-blind period: Week 1, Week 2, Week 4, Week 8 and Week 12).
Main secondary efficacy endpoints were Clinical Global Impression – Severity of Illness (CGI-S), Improvement (CGI-I) scales and Adolescent Depression Rating Scale (ADRS) total score.
The majority of the patients in the overall population were female (62.5%) with a median age of 14.0 years (range: 7, 17). Most of the patients had their first episode of depression (71.5%). According to DSM-IV-TR criteria the episode was diagnosed as moderate for 61.8% and severe (without psychotic features) for 38.3%. The mean duration of current episode was 143.4 ± 153.2 days with a median of 96.0 days (range from 29 to 1463 days).
Regarding comorbidities, around 6% patients in the overall population had generalised anxiety disorder, 7% had social anxiety disorder and 2% separation anxiety disorder.

The results for the primary endpoint CDRS-R raw score expressed in terms of change from baseline to last post-baseline value for the overall population showed a difference between agomelatine 25 mg compared to placebo of 4.22; 95%CI [0.63 ; 7.82]. For the adolescent subset the estimated between-group difference was 5.22; 95%CI [1.03; 9.40] for agomelatine 25 mg compared to placebo.
For the secondary endpoints Clinical Global Impression – Severity of Illness (CGI-S) and Improvement (CGI-I) scales no statistically significant differences were observed between any of the groups. The mean difference between the agomelatine 25 mg group and the placebo group in ADRS-score was 4.07, 95% CI [0.68; 7.46].

After the 12-week double-blind period, patients could continue in an optional open-label 21-month extension period at a agomelatine dose of 10 or 25 mg. However, this period was not designed as a relapse-prevention study and all patients received flexible doses of agomelatine. Useful data on efficacy and safety beyond 12 weeks are therefore limited.

Pubertal status was assessed by Tanner stage. Although data are limited, they do not suggest an impact of agomelatine on Tanner stage development (see section 4.8).

For further information on safety, please refer to sections 4.4 and 4.8.

There is only limited data on safety and efficacy in the children subgroup (age range from 7-11 years; in total 80 patients) due to a very limited number of patients (see section 4.2). In the children, the change in the mean CDRS-R raw total score at the end of the short term phase was lower in absolute value in the agomelatine 25 mg group (-17.1 ± 13.3) than in the placebo group (-19.0 ± 18.3).

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 interindividual 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).

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).

Elderly

In a pharmacokinetic study in elderly patients (≥ 65 years), it was showed 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.

Paediatric population

The pharmacokinetics of agomelatine was investigated in 60 children and 166 adolescents receiving daily doses ranging from 1 to 25 mg. Most data derive from saliva concentration measurements, and plasma exposure of agomelatine in the paediatric population is to a large extent uncharacterised. As in adults, the inter-individual variability in agomelatine PK is substantial. The available paediatric data suggest a considerable overlap with the observed exposure range in adults following a 25 mg agomelatine dose.

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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/PVC blister packed in cardboard boxes.
Calendar packs containing 14, 28, 56, 84 and 98 film-coated tablets.
Calendar packs of 100 film-coated tablets for hospital use.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/08/499/002
EU/1/08/499/003
EU/1/08/499/005
EU/1/08/499/006
EU/1/08/499/007
EU/1/08/499/008

9 DATE OF THE FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation : 19 February 2009
Date of latest renewal : 12 December 2018

10 DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Les Laboratoires Servier Industrie, 905, route de Saran - 45520 Gidy, France
Servier (Ireland) Industries Ltd, Gorey Road - Arklow - Co. Wicklow, Ireland
Przedsiebiorstwo Farmaceutyczne ANPHARM S.A., ul. Annopol 6B - 03-236 Warszawa, Poland
Laboratorios Servier, S.L, Avda. de los Madroños, 33 -28043 Madrid, Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder shall agree the format and content of the physician's guide to prescribing with the National Competent Authority prior to launch in the Member State.

The Marketing Authorisation Holder shall ensure that at launch and after launch all physicians who are expected to prescribe or use Valdoxan are provided with the updated educational material containing the following:

- The Summary of Product Characteristics;
- The Physician's guide to prescribing, including a liver monitoring scheme.

The Physician's guide to prescribing should contain the following key messages:

- The need to inform patients about the potential risk of transaminases elevations,the risk of liver injury and interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin);
- The need to perform liver function tests in all patients before starting treatment and periodically thereafter around three, six (end of acute phase), twelve and twenty four weeks (end of maintenance phase), and thereafter when clinically indicated;
- The need to perform liver function tests at the same frequency as at treatment initiation in all patients where the dosage is increased;
- Guidance in case of clinical symptoms of hepatic dysfunction;
- Guidance in case of liver function test abnormality;
- Caution should be exercised when therapy is administered to patients with pretreatment elevated transaminases (> the upper limit of the normal ranges and $\leq$ 3 times the upper limit of the normal range);
- Caution should be exercised when therapy is prescribed for patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, alcohol use disorder and /or substantial alcohol intake or concomitant medicinal products associated with risk of hepatic injury;
- Contra-indication in patients with hepatic impairment (i.e. cirrhosis or active liver disease);
- Contraindication in patients with transaminases exceeding 3 X upper limit of normal;
- Contra-indication in patients receiving concomitantly potent CYP1A2 inhibitors.

The Marketing Authorisation Holder shall agree the format and content of the patient booklet with the National Competent Authority in the Member State.

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Valdoxan, are provided with patient booklets to be distributed to their patients being prescribed this medicine.

The Patient's Booklet should contain the following key messages:

- Information about the risk of hepatic reactions and clinical signs of liver problems
- A guidance on the scheme of hepatic monitoring
- A blood tests appointments reminder.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Valdoxan 25 mg film-coated tablets
agomelatine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg of agomelatine.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
84 film-coated tablets
98 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

[EU/1/08/499/002] 14 film-coated tablets
[EU/1/08/499/003] 28 film-coated tablets
[EU/1/08/499/005] 56 film-coated tablets
[EU/1/08/499/006] 84 film-coated tablets
[EU/1/08/499/007] 98 film-coated tablets
[EU/1/08/499/008] 100 film-coated tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Valdoxan 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Valdoxan 25 mg tablets
agomelatine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Valdoxan 25 mg film-coated tablets
agomelatine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects ,talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Valdoxan is and what it is used for

Valdoxan contains the active ingredient agomelatine. It belongs to a group of medicines called antidepressants. You have been given Valdoxan to treat your depression.
Valdoxan is used in adults.

Depression is a continuing disturbance of mood that interferes with everyday life. The symptoms of depression vary from one person to another, but often include deep sadness, feelings of worthlessness, loss of interest in favourite activities, sleep disturbances, feeling of being slowed down, feelings of anxiety, changes in weight.
The expected benefits of Valdoxan are to reduce and gradually remove the symptoms related to your depression.

2. What you need to know before you take Valdoxan

Do not take Valdoxan
- if you are allergic to agomelatine or any of the other ingredients of this medicine (listed in section 6).
- **if your liver does not work properly (hepatic impairment).**
- if you are taking fluvoxamine (another medicine used in the treatment of depression) or ciprofloxacin (an antibiotic).

Warnings and precautions
There could be some reasons why Valdoxan may not be suitable for you:

- If you are taking medicines known to affect the liver. Ask your doctor for advice on which medicine that is.
- If you are obese or overweight, ask your doctor for advice.
- If you are diabetic, ask your doctor for advice.
- If you have increased levels of liver enzymes before treatment, your doctor will decide if Valdoxan is right for you.
- If you have bipolar disorder, have experienced or if you develop manic symptoms (a period of abnormally high excitability and emotions) talk to your doctor before you start taking this medicine or before you continue with this medicine (see also under "*Possible side effects*" in section 4).
- If you are suffering from dementia, your doctor will make an individual evaluation of whether it is right for you to take Valdoxan.

During your treatment with Valdoxan :

What to do to avoid potential serious liver problems
- Your doctor should have checked that your liver is working properly **before starting the treatment**. Some patients may get increased levels of liver enzymes in their blood during treatment with Valdoxan. Therefore follow-up tests should take place at the following time points:

	before initiation or dose increase	around 3 weeks	around 6 weeks	around 12 weeks	around 24 weeks
Blood tests	✓	✓	✓	✓	✓

Based on the evaluation of these tests your doctor will decide whether you should receive or continue using Valdoxan (see also under "*How to take Valdoxan*" in section 3).

Be vigilant about signs and symptoms that your liver may not be working properly
- **If you observe** any of these signs and symptoms of liver problems: **unusual darkening of the urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, unusual fatigue (especially associated with other symptoms listed above), seek urgent advice from a doctor who may advise you to stop taking Valdoxan.**

Effect of Valdoxan is not documented in patients aged 75 years and older. Valdoxan should therefore not be used in these patients.

Thoughts of suicide and worsening of your depression
If you are depressed you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:
- if you have previously had thoughts about killing or harming yourself.
- if you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in young adults (aged less than 25 years) with psychiatric conditions who were being treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Children and adolescents
Valdoxan is not recommended in children below 7 years due to lack of information. No data is available.
Valdoxan should not be used in children and adolescents aged 7 to 17 years because safety and efficacy have not been established.

Other medicines and Valdoxan
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should not take Valdoxan together with certain medicines (see also under "*Do not take Valdoxan*" in section 2): fluvoxamine (another medicine used in the treatment of depression), ciprofloxacin (an antibiotic) can modify the expected dose of agomelatine in your blood.
Make sure to tell your doctor if you are taking any of the following medicines: propranolol (a beta-blocker used in the treatment of hypertension), enoxacin (antibiotic)

Make sure to tell your doctor if you are smoking more than 15 cigarettes/day.

Valdoxan with alcohol
It is not advisable to drink alcohol while you are being treated with Valdoxan.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breastfeeding should be discontinued if you take Valdoxan.

Driving and using machines
You might experience dizziness or sleepiness which could affect your ability to drive or operate machines. Make sure that your reactions are normal before driving or operating machines.

Valdoxan contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Valdoxan contains sodium
Valdoxan contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Valdoxan

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Valdoxan is one tablet (25 mg) at bedtime. In some cases, your doctor may prescribe a higher dose (50 mg), i.e. two tablets to be taken together at bedtime.

Method of administration
Valdoxan is for oral use. You should swallow your tablet with a drink of water. Valdoxan can be taken with or without food.

Duration of treatment
Valdoxan starts to act on symptoms of depression in most depressed people within two weeks of starting treatment.
Your depression should be treated for a sufficient period of at least 6 months to ensure that you are free of symptoms.
Your doctor may continue to give you Valdoxan when you are feeling better to prevent your depression from returning.

If you have trouble with your kidneys, your doctor will make an individual evaluation of whether it is safe for you to take Valdoxan.

Surveillance of the liver function (see also section 2):
Your doctor will run laboratory tests to check that your liver is working properly before starting treatment and then periodically during treatment, usually after 3 weeks, 6 weeks, 12 weeks and 24 weeks.
If your doctor increase the dose to 50mg, laboratory tests should be performed at this initiation and then periodically during treatment, usually after 3 weeks, 6 weeks, 12 weeks and 24 weeks. Thereafter tests will be taken if the doctor finds it necessary.
You must not use Valdoxan if your liver does not work properly.

How to switch from an antidepressant medicine (SSRI/SNRI) to Valdoxan?
If your doctor changes your previous antidepressant medicine from an SSRI or SNRI to Valdoxan, he/she will advise you on how you should discontinue your previous medicine when starting Valdoxan.
You may experience discontinuation symptoms related to stopping of your previous medicine for a few weeks, even if the dose of your previous antidepressant medicine is decreased gradually.
Discontinuation symptoms include: dizziness, numbness, sleep disturbances, agitation or anxiety, headaches, feeling sick, being sick and shaking. These effects are usually mild to moderate and disappear spontaneously within a few days.
If Valdoxan is initiated while tapering the dosage of the previous medicine, possible discontinuation symptoms should not be confounded with a lack of early effect of Valdoxan.
You should discuss with your doctor on the best way of stopping your previous antidepressant medicine when starting Valdoxan.

If you take more Valdoxan than you should
If you have taken more Valdoxan than you should, or if for example a child has taken medicine by accident, contact your doctor immediately.
The experience of overdoses with Valdoxan is limited but reported symptoms include pain in the upper part of the stomach, somnolence, fatigue, agitation, anxiety, tension, dizziness, cyanosis or malaise.

If you forget to take Valdoxan
Do not take a double dose to make up for a forgotten dose. Just carry on with the next dose at the usual time.
The calendar printed on the blister containing the tablets should help you remembering when you last took a tablet of Valdoxan.

If you stop taking Valdoxan
Do not stop taking your medicine without the advice of your doctor even if you feel better.

If you have any further questions on the use of this product, please ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Most side effects are mild or moderate. They usually occur within the first two weeks of the treatment and are usually temporary.

These side effects include:

- Very common side effects (may affect more than 1 in 10 people) : headache
- Common side effects (may affect up to 1 in 10 people): dizziness, sleepiness (somnolence), difficulty in sleeping (insomnia), feeling sick (nausea), diarrhoea, constipation, abdominal pain, back pain, tiredness, anxiety, abnormal dreams, increased levels of liver enzymes in your blood, vomiting, weight increased.
- Uncommon side effects (may affect up to 1 in 100 people): migraine, pins and needles in the fingers and toes (paraesthesia), blurred vision, restless legs syndrome (a disorder that is characterized by an uncontrollable urge to move the legs), ringing in the ears, excessive sweating (hyperhidrosis), eczema, pruritus, urticaria (hives), agitation, irritability, restlessness, aggressive behaviour, nightmares, mania/hypomania (see also under "Warnings and precautions" in section 2), suicidal thoughts or behaviour,confusion, weight decreased, muscle pain.
- Rare side effects (may affect up to 1 in 1,000 people): serious skin eruption (erythematous rash), face oedema (swelling) and angioedema (swelling of the face, lips, tongue and/or throat that may cause difficulty in breathing or swallowing), hepatitis, yellow coloration of the skin or the whites of the eyes (jaundice), hepatic failure*, hallucinations, inability to remain still (due to physical and mental unrest), inability to completely empty the bladder.

* Few cases resulting in liver transplantation or death have been reported.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Valdoxan

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Valdoxan contains
- The active substance is agomelatine. Each film-coated tablet contains 25 mg of agomelatine.
- The other ingredients are:
    - lactose monohydrate, maize starch, povidone (K30), sodium starch glycolate type A, stearic acid, magnesium stearate, colloidal anhydrous silica,hypromellose, glycerol, macrogol (6000), yellow iron oxide (E172) and titanium dioxide (E171).
    - printing ink : shellac, propylene glycol and indigo carmine aluminium lake (E132)

What Valdoxan looks like and contents of the pack
Valdoxan 25 mg film-coated tablets (tablet) are oblong, orange-yellow with a blue imprint of 'company logo'  on one side.
Valdoxan 25 mg film-coated tablets are available in calendar blisters. Packs contain 14, 28, 56, 84 or 98 tablets. Packs of 100 film-coated tablets are also available for hospital use.
Not all pack sizes may be marketed.

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Les Laboratoires Servier
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/