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: lactose monohydrate 61.84 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet [tablet].
Orange-yellow, oblong, film-coated tablet with blue imprint of company logo on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes in adults
Valdoxan is indicated 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.

Liver function tests should be performed in all patients : at initiation of treatment, and then 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).
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.

Valdoxan tablets may be taken with or without food.

Paediatric population :
The safety and efficacy of Valdoxan in children aged below 18 years have not been established. No data are available. (see section 4.4).

Elderly patients:
Efficacy has not been clearly demonstrated in the elderly (≥ 65 years). Only limited clinical data is available on the use of Valdoxan in elderly patients ≥ 65 years old with major depressive episodes. Therefore, caution should be exercised when prescribing Valdoxan to these patients (see section 4.4).

Patients with 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 Valdoxan in

depressed patients with severe or moderate renal impairment with major depressive episodes is available. Therefore, caution should be exercised when prescribing Valdoxan to these patients.

Patients with hepatic impairment:
Valdoxan is contraindicated in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Treatment discontinuation:
No dosage tapering is needed on treatment discontinuation.

Method of administration:
Valdoxan tablets may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Hepatic impairment (i.e. cirrhosis or active liver disease) (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

Use in paediatric population:
Valdoxan is not recommended in the treatment of depression 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).

Use in elderly patients 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)
Combination with potent CYP1A2 inhibitors is contraindicated. Caution should be exercised when prescribing Valdoxan with moderate CYP1A2 inhibitors (*e.g.* propranolol, grepafloxacine, enoxacine) which may result in increased exposure of agomelatine.

Increased serum transaminases:
In clinical studies, elevations of serum transaminases (>3 times the upper limit of the normal range) have been observed in patients treated with Valdoxan particularly on a 50 mg dose (see section 4.8). When Valdoxan was discontinued in these patients, the serum transaminases usually returned to normal levels. Liver function tests should be performed in all patients: at initiation of treatment and then periodically after around three weeks, six weeks (end of acute phase), after around twelve and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated. Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours. Therapy should be discontinued if the increase in serum transaminases exceeds 3X upper limit of normal and liver function tests should be performed regularly until serum transaminases return to normal.
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).
If any patient develops symptoms suggesting hepatic dysfunction liver function tests should be performed. The decision whether to continue the patient on therapy with Valdoxan should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed therapy should be discontinued.
Caution should be exercised when prescribing Valdoxan for patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, substantial alcohol intake or concomitant medicinal products associated with risk of hepatic injury.

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

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, grepafloxacine, enoxacine) until more experience has been gained (see section 4.4).

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.

Medicinal products highly bound to plasma protein:
Agomelatine does not modify free concentrations of medicinal products highly bound to plasma proteins or *vice versa*.

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 Valdoxan 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 concomitant treatment with Valdoxan 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
Reproduction studies in the rat and the rabbit showed no effect of agomelatine on embryofoetal development and pre- and post natal development. (see section 5.3).
For agomelatine, no clinical data on exposed pregnancies are available. 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). Caution should be exercised when prescribing to pregnant women.

Breast-feeding
It is not known whether agomelatine is excreted into human milk. Agomelatine or its metabolites are excreted in the milk of lactating rats. Potential effects of agomelatine on the breast-feeding infant have not been established. If treatment with Valdoxan is considered necessary, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
However, considering that dizziness and somnolence are common adverse reactions patients should be cautioned about their ability to drive a car or operate machinery.

4.8 Undesirable effects

In clinical trials, over 3,900 depressed patients have received Valdoxan.
Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment.
The most common adverse reactions were nausea and dizziness.
These adverse reactions were usually transient and did not generally lead to cessation of therapy.
Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Valdoxan.
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.

Nervous system disorders:
Common: headache, dizziness, somnolence, insomnia, migraine
Uncommon: paraesthesia

Psychiatric disorders:
Common: anxiety

Uncommon : agitation and related symptoms* (such as irritability and restlessness), aggression*, nightmares*, abnormal dreams*
Rare :
mania/hypomania*. These symptoms may also be due to the underlying disease (see section 4.4). hallucinations*
Frequency not known: suicidal thoughts or behaviour (see section 4.4)

Eye disorders:
Uncommon: blurred vision

Gastrointestinal disorders:
Common: nausea, diarrhoea, constipation, abdominal pain

Skin and subcutaneous tissue disorders
Common: hyperhidrosis
Uncommon: eczema, pruritus*
Rare: erythematous rash

Musculoskeletal and connective tissue disorders
Common: back pain

General disorders and administration site conditions:
Common: fatigue

Hepato-biliary disorders:
Common: increased ALAT and/or ASAT (in clinical studies, increases >3 times the upper limit of the normal range for ALAT and/or ASAT were seen in 1.3% of patients on agomelatine vs. 0.7% on placebo).
Rare: hepatitis, increased gamma-glutamyltransferase* (GGT) (>3 times the upper limit of the normal range), increased alkaline phosphatase*(>3 times the upper limit of the normal range)

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

4.9 Overdose

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 2450 mg agomelatine, recovered spontaneously without cardiovascular and biological abnormalities. No specific antidotes for agomelatine are known. Management of overdose should consist of treatment of clinical symptoms and routine monitoring. Medical follow-up in a specialised environment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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, Valdoxan has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset.

Clinical efficacy and safety

The efficacy and safety of Valdoxan in major depressive episodes have been studied in a clinical programme including 5,800 patients of whom 3,900 were treated with Valdoxan.
Six placebo controlled trials have been performed to investigate the short term efficacy of Valdoxan in major depressive disorder: two flexible dose studies and four fixed dose studies. At the end of treatment (over 6 or 8 weeks), significant efficacy of agomelatine 25-50 mg was demonstrated in 3 of the six short-term double-blind placebo-controlled studies. Agomelatine failed to differentiate from placebo in one study where the active control fluoxetine showed assay sensitivity. In two other studies, it was not possible to draw any conclusions because the active controls, paroxetine and fluoxetine, failed to differentiate from placebo.
Efficacy was also observed in more severely depressed patients (baseline HAM-D $\geq$ 25) in all positive placebo-controlled studies.
Response rates were statistically significantly higher with Valdoxan compared with placebo.
The maintenance of antidepressant efficacy was demonstrated in a relapse prevention study. Patients responding to 8/10-weeks of acute treatment with open-label Valdoxan 25-50 mg once daily were randomised to either Valdoxan 25-50 mg once daily or placebo for further 6-months. Valdoxan 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 Valdoxan and placebo, respectively.

Valdoxan does not alter daytime vigilance and memory in healthy volunteers. In depressed patients, treatment with Valdoxan 25 mg increased slow wave sleep without modification of REM (Rapid Eye Movement) sleep amount or REM latency. Valdoxan 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 study 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 Valdoxan. The pooled analysis of studies using the Arizona Sexual Experience Scale (ASEX) showed that Valdoxan was not associated with sexual dysfunction. In healthy volunteers Valdoxan preserved sexual function in comparison with paroxetine.

Valdoxan had neutral effect on body weight, heart rate and blood pressure in clinical studies.

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Film-coating:
- Hypromellose
- Yellow iron oxide (E172)
- Glycerol
- Macrogol
- Magnesium stearate
- Titanium dioxide (E171)

Printing ink containing shellac, propylene glycol and indigotine (E132) aluminium lake.

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 7, 14, 28, 42, 56, 84 and 98 film-coated tablets.
Packs of 100 film-coated tablets for hospital use.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/08/499/001-008

9 DATE OF THE FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

19/02/2009

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/.