資料 3– 1　アゴメラチン（agomelatine）

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

4.2 Posology and method of administration

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 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.

Children and adolescents:
Valdoxan is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy (see 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.

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 children and adolescents:
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.

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.

Mania / Hypomania:
Valdoxan should be used with caution in patients with a history of mania or hypomania and should be discontinued if a patient develops manic symptoms.

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 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.
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 Valdoxan is administered to patients who consume substantial quantities of alcohol or who are treated with medicinal products associated with risk of hepatic injury.

Lactose intolerance:
Valdoxan 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.

4.6 Pregnancy and lactation

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.

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

Eye disorders:
Uncommon: blurred vision

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

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

Musculoskeletal and connective tissue disorders
Common: back pain

General disorders and administration site conditions:
Common: fatigue

Hepato-biliary disorders:
Common: increases (>3 times the upper limit of the normal range) in ALAT and/or ASAT (i.e. 1.1% on agomelatine 25/50 mg vs. 0.7% on placebo).
Rare: hepatitis

Psychiatric disorders:
Common: anxiety
Frequency not known: Suicidal thoughts or behaviour (see section 4.4)

4.9 Overdose

There is limited experience with agomelatine overdose. During the clinical development, there were a few reports of agomelatine overdose, taken alone (up to 450 mg) or in combination (up to 525 mg) with other psychotropic medicinal products. Signs and symptoms of overdose were limited and included drowsiness and epigastralgia.
No specific antidotes for agomelatine are known. Management of overdose should consist of treatment of clinical symptoms and routine monitoring. Medical follow-up in a specialised environment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants, ATC-code: NO6AX22

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.
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.

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 ≥ 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
22, rue Garnier
F-92200 Neuilly-sur-Seine
France

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF THE FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer 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

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 OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The Marketing Authorisation Holder (MAH) shall ensure that, at launch, all healthcare professionals who are experienced to prescribe/use Valdoxan are provided with educational materials containing the following:

As described in the RMP, additional risk minimisation activity including educational material will be provided to prescribers.

Objectives of agomelatine Educational Plan:

The prescriber educational material about Valdoxan / Thymanax will be focused on:

- The potential risks of agomelatine
  - Transaminases Elevations
  - Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

- Guidance for hepatic function screening (Need to perform liver function tests in all patients: at initiation of treatment, and then periodically after around six weeks (end of acute phase), twelve weeks and twenty four weeks (end of maintenance phase) and thereafter when clinically indicated;

- Guidance in case of clinical symptoms or liver function tests abnormality;

- Caution to be exercised when therapy is administered to patients who consume substantial quantities of alcohol or who are treated with medicinal products associated with risk of hepatic injury;

- Contra-indication in patients with hepatic impairment (i.e. cirrhosis or active liver disease);

- Contra-indication in patients receiving concomitantly potent CYP1A2 inhibitors.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 4.0 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the version 4.0 of the Risk Management Plan (RMP) presented in the module 1.8.2 of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- when new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMEA

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 tablet contains 25 mg of agomelatine.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
42 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight 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
22, rue Garnier
F-92200 Neuilly-sur-Seine
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Valdoxan 25 mg

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 {MM/YYYY}

4. BATCH NUMBER

Lot{number}

5. OTHER

MON
TUE
WED
THU
FRI
SAT
SUN

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Valdoxan 25 mg film-coated tablets
Agomelatine

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Valdoxan is and what it is used for
2. Before you take Valdoxan
3. How to take Valdoxan
4. Possible side effects
5 How to store Valdoxan
6. Further information

1. WHAT VALDOXAN IS AND WHAT IT IS USED FOR

Valdoxan belongs to a group of medicines called antidepressants and you have been given Valdoxan to treat your depression.

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.

2. BEFORE YOU TAKE VALDOXAN

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

Take special care with Valdoxan
There could be some reasons why Valdoxan may not be suitable for you:
- If you have already 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 continue with this medicine.
- If you are taking medicine known to affect the liver. Ask your doctor for advice on which medicine that is.
  Some patients may get increased levels of liver enzymes in their blood during treatment with Valdoxan. Your doctor will therefore run laboratory tests to check that your liver is working

properly at the initiation of the treatment and then periodically during treatment. Based on the evaluation of these tests the doctor will decide whether you should continue using Valdoxan or not (see also under "*How to take Valdoxan*" in section 3).
- If you are suffering from dementia, your doctor will make an individual evaluation of whether it is safe for you to take Valdoxan.

Valdoxan is not intended for use in children and adolescents (under 18 years old).

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.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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).

Taking Valdoxan with food and drink
Valdoxan can be taken with or without food.
It is not advisable to drink alcohol while you are being treated with Valdoxan.

Pregnancy
Talk to your doctor if you become pregnant (or plan to become pregnant) while you are taking Valdoxan. Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding
Talk to your doctor if you are breast-feeding or intending to breast-feed as breastfeeding should be discontinued if you take Valdoxan.
Ask your doctor or pharmacist for advice before taking any medicine.

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

Important information about some of the ingredients of Valdoxan

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

3. HOW TO TAKE VALDOXAN

Always take Valdoxan exactly as your doctor has told you. You should 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.

Valdoxan starts to act on symptoms of depression in most depressed people within two weeks of starting treatment. Your doctor may continue to give you Valdoxan when you are feeling better to prevent your depression from returning.

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

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

Your doctor will run laboratory tests to check that your liver is working properly at the initiation of treatment and then periodically during treatment, usually after 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.

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

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Valdoxan 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.

The frequency of possible side effects listed below is defined using the following system:

- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)
- rare (affects 1 to 10 users in 10,000)
- very rare (affects less than 1 user in 10,000)
- not known (frequency cannot be estimated from the available data)

These side effects include:

- Common side effects: dizziness, sleepiness (somnolence), difficulty in sleeping (insomnia), migraine, headache, feeling sick (nausea), diarrhoea, constipation, upper abdominal pain, excessive sweating (hyperhidrosis), back pain, tiredness, anxiety, increased levels of liver enzymes in your blood.
- Uncommon side effects: pins and needles in the fingers and toes (paraesthesia), blurred vision and eczema.
- Rare side effects: serious skin eruption (erythematous rash), hepatitis.
- Other possible side effects: suicidal thoughts or behaviour (frequency not known).

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE VALDOXAN

Keep out of the reach and sight of children.

Do not use Valdoxan 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Valdoxan contains

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

What Valdoxan looks like and contents of the pack

Valdoxan 25 mg film-coated tablets 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 7, 14, 28, 42, 56, 84 or 98 tablets. Packs of 100 film-coated tablets are also available for hospital use.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder
Les Laboratoires Servier
22, rue Garnier
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Manufacturer
Les Laboratoires Servier Industrie
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Servier (Ireland) Industries Ltd
Gorey road
Arklow – Co. Wicklow – Ireland

and

Anpharm Przedsiebiorstwo Farmaceutyczne S.A.
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in {date}

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