Valdoxan
Agomelatine

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)

PHARMACEUTICAL FORM

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

THERAPEUTIC INDICATIONS

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

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 "Contraindication" and "Special warnings and precautions for use").
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 "Special warnings and precautions for use"). Treatment should be discontinued if transaminases exceed 3 X upper limit of normal (see "Contraindication" and "Special warnings and precautions for use").

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 "Pharmacodynamic Properties").

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

Special populations

Elderly
The efficacy and safety of agomelatine (25 to 50 mg/day) have been established in elderly depressed patients (<75 years). No effect is documented in patients ≥ 75 years. Therefore agomelatine should not be used by patients in this age group (see special warnings and precautions for use and pharmacodynamics properties). No dose adjustment is required in relation to age (see pharmacological properties).

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 Contraindications, special warnings and precautions for use, pharmacological properties)

Paediatric population
The safety and efficacy of agomelatine in children from 2 years onwards for treatment of major depressive episodes have not yet been established. No data are available (see special warnings and precautions for use). There is no relevant use of agomelatine in children from birth to 2 years for treatment of major depressive episodes.

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

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.
Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 X upper limit of normal (see "Posology and method of administration" and "Special warnings and precautions for use").
Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) (see "Interaction with other medicinal products and other forms of interaction").

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 "Undesirable effects"). 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 "Contraindication"). Caution should be exercised when Valdoxan is administered to patients with pretreatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range).

- *Frequency of liver function tests*

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

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

- *During treatment period*

Valdoxan treatment should be discontinued immediately if:

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

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

Use in paediatric population:
Valdoxan is not recommended in 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 "Posology and method of administration").

Elderly
No effect of agomelatine is documented in patients ≥75 years, therefore agomelatine should not be used by patients in this age group (see "Posology and method of administration" and "Pharmacodynamic properties").

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 "Undesirable Effects").

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 "Contraindications" and *"Interaction with other medicinal products and other forms of interaction"*)
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'.

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 "Special warnings and precautions for use").
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 "Pharmacokinetic properties").

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 "Preclinical safety data"). 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.

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 "Preclinical safety data"). 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 preclinical safety data). 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 "Preclinical safety data)

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.

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 placebo-controlled and 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 "Special warnings and precautions for use")
		Agitation and related symptoms* (such as irritability and restlessness)
		Aggression*
		Nightmares*
		Mania/hypomania* These symptoms may also be due to the underlying disease (see "Special warnings and precautions for use").
		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 v	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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 PUSAT FARMAKOVIGILANS-BPOM: Tlp. 021-4245459, 021-4244755 Ext. 111, Fax. 021-4243605, 021-42885404; Email: pv-center@pom.go.id and/or Indonesia-MESO-BadanPOM@hotmail.com.

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 2450 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.

PHARMACOLOGICAL PROPERTIES

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

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 European Medicines Agency has deferred the obligation to submit the results of studies with agomelatine in one or more subsets of the paediatric population in the treatment of major depressive episodes (see section 4.2 for information on paediatric use).

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 "Posology and method of administration").

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 "Posology and method of administration", "Contraindications" and "Special warnings and precautions for use").

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.

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

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.

STORAGE CONDITIONS
Do not store above 30°C.
Shelf-life : 3 years.

PACK SIZES
- Box of 2 blisters of 14 tablets

Reg. No. : DKI1668601517A1

HARUS DENGAN RESEP DOKTER

Manufactured by :
Les Laboratoires Servier Industrie
45520 Gidy – France

Registered by :
PT. Darya-Varia Laboratoria Tbk
Bogor – Indonesia

Imported and Marketed by :
PT. Servier Indonesia
Jakarta - Indonesia

Informasi untuk Pasien

Valdoxan 25 mg tablet salut selaput
Agomelatine

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan ini, karena berisi informasi penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau apoteker Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain, karena dapat membahayakan mereka, meskipun gejala penyakit mereka sama seperti Anda.
- Jika Anda mengalami efek samping obat, konsultasikan dengan dokter atau apoteker Anda. Efek samping ini termasuk yang mungkin tidak tercantum dalam leaflet ini. Lihat Bagian 4.

Apa yang terdapat dalam leaflet ini?

1. Apakah itu Valdoxan, dan apakah kegunaannya

Valdoxan mengandung bahan aktif Agomelatine, yang termasuk dalam golongan obat antidepresan. Anda diberikan Valdoxan untuk mengobati depresi Anda.
Valdoxan hanya digunakan pada orang dewasa.

Depresi merupakan gangguan suasana hati yang terus menerus, yang dapat mengganggu kehidupan sehari-hari. Gejala depresi beragam antara satu orang dengan yang lainnya, tetapi seringkali mencakup rasa sedih, rasa tidak berguna, hilang ketertarikan terhadap aktivitas yang disukai, gangguan tidur, merasa lambat, merasa cemas, perubahan berat badan.

Manfaat yang diharapkan dari penggunaan Valdoxan adalah mengurangi dan sedikit demi sedikit menghilangkan gejala terkait depresi.

2. Apa yang perlu Anda ketahui sebelum Anda meminum Valdoxan

Jangan meminum Valdoxan
- jika Anda memiliki alergi terhadap agomelatine,
- **jika hati Anda tidak bekerja dengan baik (kerusakan hati),**
- jika Anda sedang mengkonsumsi fluvoxamine (obat lain yang juga digunakan untuk mengobati depresi) atau siprofloksasin (antibiotik).

Peringatan dan Perhatian

Ada beberapa alasan mengapa Valdoxan kemungkinan tidak cocok untuk Anda:
- jika Anda sedang meminum obat yang berpengaruh terhadap hati. Mintalah nasehat kepada dokter Anda, obat mana yang mempengaruhi hati.
- jika Anda mengalami obesitas atau berat badan berlebih, mintalah nasehat dokter Anda.
- jika Anda memiliki diabetes, mintalah nasehat dokter Anda.
- jika Anda mengalami peningkatan kadar enzim dalam hati sebelum penggunaan Valdoxan, dokter Anda akan memutuskan, apakah Valdoxan adalah pilihan yang tepat untuk Anda.
- jika Anda memiliki gangguan bipolar, mengalami atau mulai muncul gejala sindrom manik (memiliki perasaan bahagia dan emosi yang berlebihan secara abnormal selama periode

tertentu), konsultasikan pada dokter Anda sebelum Anda memulai minum atau sebelum melanjutkan minum Valdoxan (lihat juga bagian “Efek samping yang mungkin timbul”).
- jika Anda menderita demensia, dokter akan melakukan evaluasi secara individu mengenai apakah Valdoxan merupakan pilihan yang tepat untuk Anda.

Selama pengobatan dengan Valdoxan:

Apa yang harus dilakukan untuk menghindari potensi gangguan hati yang serius:
- Dokter Anda seharusnya memeriksa kondisi hati Anda **sebelum memulai pengobatan dengan Valdoxan**. Beberapa pasien kemungkinan dapat mengalami peningkatan kadar enzim hati dalam darah selama pengobatan dengan Valdoxan. Pemeriksaan lanjutan harus dilakukan pada waktu-waktu berikut:

	Sebelum memulai penggunaan atau sebelum meningkatkan dosis	Sekitar 3 minggu	Sekitar 6 minggu	Sekitar 12 minggu	Sekitar 24 minggu
Tes Darah	✓	✓	✓	✓	✓

Berdasarkan hari evaluasi dari tes tersebut, dokter Anda akan memutuskan apakah Anda dapat menggunakan atau melanjutkan meminum Valdoxan (lihat juga bagian “”Bagaimana aturan minum Valdoxan”)

Waspadalah terhadap tanda-tanda dan gejala yang menunjukkan hati Anda tidak bekerja dengan baik
- **Jika Anda mengalami** tanda dan gejala gangguan hati: warna urin lebih gelap dari biasanya, feses berwarna lebih cerah, kulit atau mata menguning, rasa sakit pada bagian kanan atas perut, rasa lelah yang tidak biasa (terutama terkait dengan gejala yang tertulis di atas), mintalah nasehat pada dokter yang mungkin akan menganjurkan Anda untuk menghentikan pemakaian Valdoxan.

Tidak ada dokumentasi tentang efek penggunaan Valdoxan pada pasien berumur 75 tahun ke atas. Valdoxan sebaiknya tidak untuk digunakan pada pasien ini.

Pemikiran untuk bunuh diri dan depresi yang semakin buruk
Jika Anda mengalami depresi, terkadang Anda dapat memiliki pemikiran untuk menyakiti atau membunuh diri sendiri. Ini dapat meningkat ketika pertama kali mengkonsumsi antidepresan, karena obat ini membutuhkan waku untuk bekerja, biasanya sekitar dua minggu atau lebih.

Mungkin Anda akan memiliki pemikiran seperti ini:
- jika sebelumnya Anda pernah berpikir untuk membunuh atau menyakiti diri sendiri.
- jika Anda seorang dewasa muda. Studi klinik menunjukkan adanya peningkatan risiko bunuh diri pada orang dewasa muda (usia di bawah 25 tahun) dengan kondisi psikiatrik yang sedang dalam pengobatan dengan antidepresan.

Jika Anda memiliki pemikiran untuk menyakiti atau membunuh diri sendiri, hubungi dokter Anda atau segera pergi ke rumah sakit.

Anda mungkin akan terbantu jika Anda bercerita pada keluarga atau teman dekat bahwa Anda depresi dan minta mereka untuk membaca leaflet ini. Anda juga dapat bertanya apakah menurut mereka depresi Anda semakin memburuk, atau jika mereka khawatir dengan perubahan perilaku Anda.

Anak dan remaja
Valdoxan tidak ditujukan untuk pengobatan pada anak dan remaja (di bawah 18 tahun).

Obat lain dan Valdoxan
Beritahukan kepada dokter atau apoteker Anda, jika Anda sedang, atau baru saja menggunakan, atau mungkin akan menggunakan obat lainnya.

Anda disarankan untuk tidak mengkonsumsi Valdoxan bersama dengan obat lainnya (lihat juga bagian "*Jangan meminum Valdoxan*") : fluvoxamine (obat lain yang juga digunakan untuk mengobati depresi), siprofloksasin (antibiotik) dapat mengubah dosis agomelatine yang diperkirakan dalam darah.
Pastikan Anda memberitahukan dokter jika Anda sedang mengkonsumsi obat-obatan berikut : propranolol (beta-bloker yang digunakan pada pengobaan hipertensi), enoxacin (antibiotik), dan jika Anda merokok lebih dari 15 rokok per hari.

Valdoxan dengan alkohol
Tidak disarankan untuk mengkonsumsi alkohol ketika Anda sedang dalam pengobatan dengan Valdoxan.

Kehamilan
Jika Anda sedang hamil atau menyusui, merasa bahwa Anda hamil atau berencana untuk memiliki bayi, tanyakan kepada dokter atau apoteker Anda sebelum meminum obat ini.

Menyusui
Konsultasikan kepada dokter Anda, jika Anda sedang menyusui atau berencana untuk menyusui, karena menyusui harus dihentikan jika Anda meminum Valdoxan.
Tanyakan kepada dokter atau apoteker Anda, sebelum Anda memakai obat-obatan.

Berkendara atau menggunakan mesin
Anda mungkin akan mengalami rasa pusing atau mengantuk yang dapat mempengaruhi kemampuan Anda dalam berkendara atau mengoperasikan mesin. Pastikan reaksi yang muncul kembali normal sebelum berkendara atau mengoperasikan mesin.

Valdoxan mengandung laktosa
Jika Anda pernah diberitahukan bahwa Anda memilki intoleransi terhadap gula, beritahukan dokter Anda sebelum meminum Valdoxan.

Valdoxan mengandung natrium
Valdoxan mengandung kurang dari 1 mmol natrium (23 mg) per tablet, dapat dikatakan pada dasarnya 'bebas natrium'.

3. Bagaimana aturan minum Valdoxan

Selalu minum obat ini sesuai dengan instruksi dokter atau apoteker Anda. Konsultasikan dengan dokter atau apoteker Anda, jika Anda merasa tidak yakin.

Dosis Valdoxan yang direkomendasikan adalah satu tablet (25 mg) sebelum tidur. Pada kasus tertentu, dokter Anda dapat meresepkan dosis yang lebih tinggi (50 mg), contohnya dua tablet dikonsumsi bersama sebelum tidur.

Cara pakai
Valdoxan ditujukan untuk penggunaan oral. Anda harus menelan tablet dengan bantuan air. Valdoxan dapat dikonsumsi dengan atau tanpa makanan.

Lama pengobatan
Valdoxan mulai bekerja mengobati gejala depresi pada sebagian besar pasien dalam waktu dua minggu sejak memulai pengobatan.
Depresi harus diobati dalam periode waktu yang cukup, setidaknya enam bulan untuk memastikan bahwa Anda bebas dari gejala depresi.
Dokter Anda dapat melanjutkan penggunaan Valdoxan jika Anda merasa lebih baik untuk mencegah depresi muncul kembali.

Jangan menghentikan pemakaian obat Anda, tanpa anjuran dari dokter Anda, meskipun Anda sudah merasa lebih baik.

Jika Anda memiliki masalah dengan ginjal, dokter Anda akan melakukan pemeriksaan individual untuk memastikan apakah penggunaan Valdoxan aman atau tidak untuk Anda.

Pengawasan fungsi hati (lihat juga bagian 2):
Dokter Anda akan melakukan pemeriksaan laboratorium untuk memastikan hati Anda bekerja dengan baik sebelum memulai pengobatan dengan Valdoxan, dan secara berkala selama pengobatan, biasanya setelah 3 minggu, 6 minggu, 12 minggu dan 24 minggu.
Jika dokter Anda meningkatkan dosis menjadi 50 mg, pemeriksaan laboratorium sebaiknya dilakukan sebelum dosis ditingkatkan, dan secara berkala selama pengobatan berlangsung, biasanya setelah 3 minggu, 6 minggu, 12 minggu dan 24 minggu. Setelah itu, pemeriksaan akan dilakukan jika dianggap penting oleh dokter Anda.
Anda tidak bolah menggunakan Valdoxan jika hati Anda tidak bekerja dengan baik.

Bagaimana cara untuk mengubah dari obat antidepresan lain (SSRI/SNRI) menjadi Valdoxan?
Jika dokter Anda mengubah obat antidepresan yang sebelumnya dari SSRI atau SNRI menjadi Valdoxan, dokter Anda akan memberikan anjuran mengenai bagaimana cara Anda menghentikan pengobatan dengan obat yang sebelumnya ketika memulai penggunaan Valdoxan.
Anda mungkin akan merasakan gejala putus obat ketika Anda menghentikan pemakaian obat yang sebelumnya selama beberapa minggu, meskipun dosis antidepresan yang sebelumnya dikurangi secara bertahap.
Gejala putus obat dapat berupa: pusing, mati rasa, gangguan tidur, gelisah atau cemas, sakit kepala, merasa mual, merasa sakit dan gemetar. Efek ini biasanya ringan hingga sedang dan akan menghilang secara spontan dalam beberapa hari.
Jika penggunaan Valdoxan dimulai ketika sedang menurunkan dosis obat yang sebelumnya, gejala putus obat yang mungkin muncul sebaiknya tidak boleh dikaitkan dengan kurangnya efek terapi awal dari Valdoxan.
Anda sebaiknya berdiskusi dengan dokter Anda mengenai bagaimana cara terbaik untuk menghentikan obat antidepresan yang sebelumnya, ketika memulai penggunaan Valdoxan.

Jika Anda meminum Valdoxan lebih dari dosis yang seharusnya
Jika Anda meminum Valdoxan berlebih, atau jika seorang anak tanpa sengaja meminum Valdoxan, segera hubungi dokter Anda.
Data terkait overdosis pada penggunaan Valdoxan masih terbatas, namun beberapa gejala yang dilaporkan muncul antara lain sakit pada bagian atas perut, kesadaran menurun, rasa lelah, cemas, tegang, pusing, sianosis, atau rasa tidak enak badan.

Jika Anda lupa meminum Valdoxan
Jangan meminum Valdoxan dengan dosis dua kali lipat untuk menggantikan dosis yang terlewat. Lanjutkan saja pemakaian Valdoxan pada dosis yang berikutnya pada waktu yang biasanya.
Kalender yang tercetak pada kemasan blister dapat membantu Anda untuk mengingat kapan Anda terakhir menggunakan Valdoxan.

Jika Anda berhenti meminum Valdoxan
Anda harus berdiskusi dengan dokter Anda sebelum Anda menghentikan meminum obat ini.
Jika Anda merasa efek terapi Valdoxan terlalu kuat atau terlalu lemah, bicarakan dengan dokter atau apoteker Anda.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan dokter atau apoteker Anda.

4. Efek samping yang mungkin timbul

Seperti obat lainnya, obat ini dapat menimbulan efek samping, meskipun tidak semua orang mengalaminya.

Sebagian besar efek samping yang muncul ringan atau sedang. Biasanya muncul pada dua minggu pertama penggunaan obat dan biasanya bersifat sementara.

Efek samping yang muncul sebagai berikut:
- Sangat umum (mempengaruhi lebih dari 1 dari 10 pasien) : sakit kepala
- Umum (mempengaruhi hingga 1 dari 10 pasien) : pusing, mengantuk (kesadaran menurun), sulit tidur (insomnia), merasa mual (nausea), diare, konstipasi, sakit perut, sakit punggung, rasa lelah, cemas, mimpi tidak normal, peningkatan kadar enzim hati dalam darah, muntah, berat badan meningkat.
- Tidak umum (mempengaruhi hingga 1 dari 100 pasien) : migrain, rasa tertusuk pada jari tangan dan jari kaki (paraesthesia), penglihatan kabur, sindrom kaki gelisah (gangguan yang ditandai dengan keinginan yang tidak terkontrol untuk menggerakkan kaki), telinga berdenging, keringat berlebih (hiperhidrosis), eksema, pruritus, urtikaria (gatal), gelisah, mudah marah, resah, perilaku agresif, mimpi buruk, mania/hipomania (lihat juga bagian "*Peringatan dan perhatian*"), pemikiran atau perilaku ingin bunuh diri, pusing, berat badan menurun, nyeri otot.
- Langka (mempengaruhi hingga 1 dari 1.000 pasien) : iritasi kulit serius, wajah membengkak dan angioedema (pembengkakan wajah, bibir, lidah, dan/atau tenggorokan yang dapat mengakibatkan kesulitan bernapas atau menelan), hepatitis, kulit atau bagian putih mata menguning, gagal hati*, halusinasi, ketidakmampuan untuk tenang (karena kegelisahan secara fisik dan mental), ketidakmampuan untuk mengosongkan kandung kemih secara sempurna.

*Beberapa kasus yang menyebabkan transplantasi hati atau kematian pernah dilaporkan.

Pelaporan efek samping
Apabila Anda mengalami efek samping, beritahu dokter atau apoteker Anda. Termasuk efek samping yang tidak tercantum dalam leaflet ini

5. Bagaimana cara menyimpan Valdoxan

Jangan simpan di atas suhu 30°C.

Simpan dari penglihatan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa, yang tercantum pada dus dan blister setelah tanggal 'EXP'. Tanggal kedaluwarsa mengacu pada tanggal terakhir pada bulan tersebut.

Obat ini tidak membutuhkan kondisi penyimpanan khusus.

Jangan membuang obat-obatan apapun melalui air limbah atau sampah rumah tangga. Tanyakan pada apoteker Anda mengenai bagaimana cara membuang obat-obatan yang sudah tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lain

Apakah yang terkandung dalam Valdoxan?
Setiap tablet salut selaput mengandung 25 mg Agomelatine.

Seperti apa bentuk dan isi kemasan Valdoxan
Valdoxan tablet salut selaput 25 mg berbentuk oval, berwarna jingga-kuning, dengan 'logo perusahaan'  berwarna biru pada satu sisi.

Valdoxan tablet salut selaput 25 mg tersedia dalam blister dengan kalender. Kemasan berisi 28 tablet salut selaput (Dus, 2 blister @ 14 tablet salut selaput).

Reg. No. : DKI1668601517A1

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
Les Laboratoires Servier Industrie
45520 Gidy – France

Didaftarkan oleh:
PT. Darya-Varia Laboratoria Tbk
Bogor - Indonesia

Diimpor dan dipasarkan oleh:
PT. Servier Indonesia
Jakarta - Indonesia

Brosur ini terakhir direvisi pada {MM/YYYY}