AUSTRALIAN PRODUCT INFORMATION
VALOMEL (Agomelatine-citric acid) film-coated tablets

1. NAME OF THE MEDICINE

Agomelatine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablets contain 44.74 mg agomelatine-citric acid (equivalent to 25 mg agomelatine).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

VALOMEL 25 mg is a yellow, oblong biconvex film coated tablet.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Treatment of major depressive disorder (MDD) in adults including prevention of relapse.

4.2. DOSE AND METHOD OF ADMINISTRATION

The recommended daily dose is one tablet taken orally at bedtime.

After two weeks of treatment, if there is no improvement in symptoms, the dose may be increased to 50 mg once daily, taken as a single dose of two tablets at bedtime. The maximum recommended dose should not be exceeded.

Dose escalation has been associated with an increased incidence of serum transaminase elevations. Dose increases to 50 mg should only occur following an assessment of the benefits and risk and assessment of liver function.

Liver function tests should be performed in all patients before initiation of treatment and before a dose increase to 50 mg. Treatment with VALOMEL should not be initiated if serum transaminase levels are > 3 times the upper limit of normal range, see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

During treatment, transaminases should be monitored periodically after around 3, 6 (end of acute phase), 12, and 24 (end of maintenance phase) weeks with regimen to be repeated following dose increase to 50 mg and thereafter when clinically indicated, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Treatment should be discontinued if serum transaminase levels are > 3 times the upper limit of the normal range, see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Treatment duration

MDD is a disease with a chronic course and long-term treatments are therefore warranted to consolidate response and prevent relapse.

Patients with MDD should be treated for a period of at least six months following response to ensure that they are free of symptoms.

VALOMEL (agomelatine) tablets may be taken with or without food.

Switching to agomelatine from other antidepressants (SSRIs or SNRIs)

Patients may experience discontinuation symptoms after cessation from an SSRI/SNRI antidepressant. The product information of the actual SSRI/SNRI should be consulted on how to withdraw the treatment to avoid discontinuation symptoms. VALOMEL (agomelatine) can be started immediately while tapering the dosage of an SSRI/SNRI, see Section 4.3 CONTRAINDICATIONS and Section 5.1 PHARMACODYNAMIC PROPERTIES.

Children and adolescents

Safety and efficacy have not been established in this age group. VALOMEL (agomelatine) is not recommended for use in children and adolescents aged < 18 years (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

Elderly Patients

The efficacy and safety of agomelatine (25 to 50 mg/day) have been established in elderly patients with MDD (aged < 75 years). No adjustment in the usual dose is recommended for elderly patients with MDD (aged < 75 years) solely because of their age. As efficacy has not been established in very elderly patients with MDD aged ≥ 75 years VALOMEL (agomelatine) should not be used in this patient group, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

VALOMEL (agomelatine) should not be used for the treatment of MDD in elderly patients with dementia since the safety and efficacy of VALOMEL (agomelatine) has not been established in these patients.

Patients with renal impairment

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

Patients with hepatic impairment

VALOMEL (agomelatine) is contraindicated in patients with hepatic impairment, see Section 4.3 CONTRAINDICATIONS.

Treatment discontinuation

No dose tapering is needed on treatment discontinuation, as VALOMEL (agomelatine) does not induce discontinuation symptoms after abrupt treatment cessation.

4.3. CONTRAINDICATIONS

Agomelatine is contraindicated in patients:

- with a history of previous hypersensitivity to the active ingredient or any of the excipients
- with hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 times the upper limit of normal, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION.
- taking potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Monitoring of liver function

Caution should be exercised before initiation of treatment and close surveillance should be performed during continuing treatment, especially during combined use with medicines associated with risk of hepatic injury or where risk factors for hepatic injury are present.

In post-marketing experience cases of liver injury, including elevations of liver enzymes (> 10 times upper limit of the normal range), hepatic failure, hepatitis and jaundice have been reported in patients treated with agomelatine, most often during the first months of treatment, see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Isolated cases of transplantation or death in patients with hepatic failure have been reported following the use of agomelatine. Some patients had hepatic risk factors. This highlights the importance of performing liver function tests in all patients.

The pattern of liver damage is predominantly hepatocellular with serum transaminases usually returning to normal levels following discontinuation of agomelatine. In clinical trials, elevations of serum transaminases (> 3 times the upper limit of the normal range) have been observed in patients treated with agomelatine more commonly on a 50 mg dose.

Before initiation of treatment:

Treatment with agomelatine should only be initiated after careful consideration of the benefits and risk in patients with hepatic injury risk factors e.g.:

- overweight, obesity, non-alcoholic fatty liver disease, diabetes or use with medicines associated with risk of hepatic injury

- alcohol use disorder and /or substantial alcohol intake.

Baseline liver function tests should be performed in all patients before initiation of treatment. Treatment with agomelatine should not be initiated if serum transaminase levels are > 3 times the upper limit of the normal range, see Section 4.3 CONTRAINDICATIONS. Caution should be exercised when agomelatine is administered to patients with pre-treatment elevated transaminases (i.e. between the upper limit of the normal ranges and up to ≤ 3 times the upper limit of the normal range).

Frequency of liver function tests:

Before starting treatment and then:

- around 3 weeks
- around 6 weeks (end of acute phase)
- around 12 weeks
- around 24 weeks (end of maintenance phase)
- thereafter when clinically indicated.

When increasing the dosage, liver function tests should again be performed at the same frequency as when starting treatment. Patients who develop any increased serum transaminases should have their liver function tests repeated within 48 hours.

During treatment:

Therapy should be discontinued immediately if any of the following are observed:

- an increase in serum transaminases > 3 times the upper limit of normal, see Section 4.3 CONTRAINDICATIONS.
- signs or symptoms of potential liver injury (such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right abdomen, sustained new-onset and unexplained fatigue).

Liver function tests should continue to be performed regularly following discontinuation of therapy until serum transaminases return to normal.

Suicide Ideation / Suicidality

In clinical trials, agomelatine is not associated with an increased risk of suicide ideation / suicidality.

The risk of suicide attempt is inherent in patients with depression and may persist until significant remission occurs. This risk must be considered in all patients with depression.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Patients with a history of suicide-related events or those exhibiting suicidality prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should be monitored during treatment.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/ behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with MDD (16 trials), obsessive compulsive disorder (four trials) or other psychiatric disorders (four trials) have revealed a greater risk of adverse events representing suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied.

The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medications in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

A further pooled analysis of short-term placebo controlled trials of antidepressant medicines (SSRIs and others) showed the increased risk of suicidality during the initial treatment period (generally the first one to two months) extends to young adults (aged 18-24 years) with MDD and other psychiatric disorders. These trials did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 years and older.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for MDD as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for MDD or for any other condition (psychiatric or non-psychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

When treatment duration was considered the incidence of suicidal events was 0.28 per 100 patient-months for agomelatine compared with 0.50 per 100 patient-months for placebo.

Bipolar disorder / Mania / Hypomania

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone can increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

As with other antidepressants, agomelatine should be used with caution in patients with history of bipolar disorder, mania or hypomania and should be discontinued if a patient develops manic symptoms.

Alcohol

As with all antidepressants, patients should be advised to avoid alcohol consumption.

Combination with CYP1A2 inhibitors (see Section 4.3 CONTRAINDICATIONS, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 5.1 PHARMACODYNAMIC PROPERTIES.

Use caution when combining agomelatine with moderate CYP1A2 inhibitors (e.g. propranolol) as these medicines may result in increased exposure to agomelatine.

Electroconvulsive therapy (ECT)

There is no experience with the combined use of agomelatine and ECT. In animals agomelatine has no proconvulsant properties. Therefore, adverse consequences of combined ECT and agomelatine treatment are considered to be unlikely.

Abuse potential

Agomelatine has no abuse potential. This was assessed in healthy volunteer trials on a specific visual analogue scale or the Addiction Research Centre Inventory 49 (ARCI) check-list.

Use in hepatic impairment

Agomelatine is contraindicated in patients with hepatic impairment (see Section 4.3 - CONTRAINDICATIONS).

Use in renal impairment

As only limited clinical data on the use of agomelatine in patients with moderate or severe renal impairment are available, caution should be exercised when prescribing agomelatine to these patients.

Use in the elderly

No adjustment in the usual dose is recommended for elderly patients solely because of their age.

The efficacy and safety of agomelatine (25 to 50 mg/day) have been established in elderly patients with MDD (aged < 75 years). As efficacy has not been demonstrated in elderly patients aged ≥ 75 years, agomelatine should not be used in this patient group, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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

Paediatric use

As safety and efficacy have not been established in this age group, the use of agomelatine in children and adolescents (aged < 18 years) is not recommended.

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.

Effects on Laboratory Tests

Interactions with laboratory tests have not been established.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential interactions affecting Agomelatine.

Agomelatine is metabolised mainly by cytochromes CYP1A2 (90%) and CYP2C9/19 (10%). Medicines that interact with these isoenzymes may decrease or increase the bioavailability of agomelatine.

Co-administration of agomelatine with potent CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin is contraindicated. Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor, has been shown to markedly inhibit the metabolism of agomelatine resulting in a 60 fold (range 12-412) increase in agomelatine exposure.

Combination of agomelatine with estrogens (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 estrogens, caution should be exercised when prescribing agomelatine with other moderate CYP1A2 inhibitors (e.g. propranolol) until more experience has been gained.

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

Fluconazole, a potent CYP2C9 and CYP2C19 inhibitor, has been shown not to effect the pharmacokinetics of agomelatine.

Table 1 - Summary of CYP1A2 and CYP2C9/C19 interactions from agomelatine clinical trials

Contraindicated:	Caution recommended:	No interaction:
Potent CYP1A2 inhibitors (e.g. fluvoxamine and ciprofloxacin)	**Moderate CYP1A2 inhibitors** (e.g. propranolol) **CYP1A2/CYP2C9/CYP2C19 inducers** (e.g. rifampicin)	**Potent CYP2C9/CYP2C19 inhibitors** (e.g. fluconazole)

As the decrease in agomelatine exposure in cigarette smokers due to induction of CYP1A2 is not clinically relevant, no dose adjustment is necessary because a patient is a cigarette smoker, see Section 5.2 PHARMACOKINETIC PROPERTIES.

Use with other antidepressants

Agomelatine should not be combined with fluvoxamine as fluvoxamine is a potent inhibitor of the metabolism of agomelatine, see Section 4.3 CONTRAINDICATIONS. Caution should be taken when administering agomelatine with other antidepressants as the safety and efficacy of agomelatine in combination with other antidepressants has not been examined.

There is no pharmacokinetic or pharmacodynamic interaction between agomelatine and paroxetine.

Lithium

There is no pharmacokinetic or pharmacodynamic interaction between agomelatine and lithium.

Benzodiazepines (lorazepam)

There is no pharmacokinetic or pharmacodynamic interaction between agomelatine and lorazepam.

Potential for Agomelatine to affect other medicinal products

Agomelatine inhibits neither CYP1A2 *in vivo* nor the other CYP450 *in vitro* and does not induce CYP450 isoenzymes *in vivo*. Therefore, agomelatine will not modify exposure to medicines metabolised by CYP450.

In healthy volunteers agomelatine did not modify the kinetics of theophylline, a CYP1A2 substrate.

Drugs highly bound to plasma protein

Agomelatine does not modify free concentrations of drugs highly bound to plasma proteins (e.g. zolpidem, diazepam, sertraline, warfarin, estrogen and salicylic acid) or *vice versa*.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Oral reproductive toxicity trials with agomelatine in rats showed no effect on fertility at plasma exposures of 60-100 fold human exposure at the maximal recommended clinical dose. No effect of agomelatine on juvenile rat behavioural performances, visual and reproductive function were observed. There were mild, non dose dependent decreases in body weight and food intake, delayed preputial separation and decreased long bone growth related to the pharmacological properties and some minor (reversible) effects (e.g., decreased prostate weight with atrophy /decreased amount of seminal fluid, decreased weight of testis) on male reproductive tract without any impairment on reproductive performances.

Use in pregnancy (Category B1)

Animal trials do not indicate direct or indirect harmful effects with respect to pregnancy, embryofoetal development, parturition or postnatal development at systemic exposures (plasma AUC) of 100-fold or greater the human exposure at the maximal recommended clinical dose. Agomelatine and/or its metabolites passes into the placenta and foetuses of pregnant rats. No clinical data on exposed pregnancies are available. As a precautionary measure, it is recommended to avoid the use of agomelatine during pregnancy.

Use in lactation

It is not known whether agomelatine and/or its metabolites are excreted into human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of agomelatine/metabolites in milk. There were no adverse effects on offspring following oral administration of agomelatine to rats from prior to mating until weaning, with systemic exposures (plasma AUC) of 100-fold human exposure at the maximal recommended clinical dose. The effects of agomelatine on the nursing infant have not been established. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from agomelatine therapy following consideration of the relative benefits of breast feeding for the child and of therapy for the woman.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No trials on the effects on the ability to drive and use machines have been performed. While clinical pharmacodynamic trials have shown that agomelatine treatment does not impair cognitive or psychomotor function in healthy volunteers, dizziness and somnolence were reported during clinical trials. As with all psychoactive medicines, patients should be cautioned about their ability to drive a car or operate machinery.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials, over 9,200 patients have received agomelatine 25 – 50 mg for MDD (N=8,084) or for generalised anxiety disorder (N=1,170). Note that VALOMEL is not indicated for generalised anxiety disorder (GAD).

In clinical trials dose escalation was associated with an increase in liver function abnormalities. The incidence of ALT and/or AST elevations > 3x ULN according to agomelatine dose in clinical trials was: 0.6% on agomelatine 1-10 mg (4/679 patients), 1.3% on agomelatine 25 mg (72/5,581 patients), 2.6% on agomelatine 50 mg (66/2,577 patients) and 3.5% on agomelatine 100 mg (2/57 patients), compared to 0.4% in the placebo group (6/1,629 patients) – see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Whilst 1-10 mg and 100 mg doses were included in dose ranging trials, these are not within the approved therapeutic dose range of 25 mg to 50 mg, see section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Patients with MDD 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 agomelatine.

Adverse events were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse events were headache, nausea, nasopharyngitis and dizziness, which were also commonly reported in the placebo treatment group. These adverse events were usually transient and did not generally lead to cessation of therapy (see Table 2).

Table 2: Treatment Emergent Adverse Events reported by at least 1 % of patients treated with agomelatine 25/50 mg[1]

Preferred term	**Agomelatine 25/50 mg[1] N=9,254 PT=45,612.7**	**Placebo[1] N=1,722 PT=5,450.8**
	%[2]	**%[2]**
ALL	62.62	52.96
Headache	13.92	13.24
Nausea	7.10	5.75
Nasopharyngitis	6.08	3.72
Dizziness	5.45	3.37
Somnolence	4.82	2.67
Dry mouth	4.27	3.19
Diarrhoea	4.26	2.73
Insomnia	3.75	2.96
Upper respiratory tract infection	3.33	1.16
Fatigue	3.30	2.15
Back pain	3.23	2.03
Influenza	3.03	2.85
Anxiety	2.86	1.57
Constipation	2.56	2.09
Dyspepsia	2.07	1.28
Abdominal pain upper	2.02	1.22
Sedation	1.74	1.05

Preferred term	**Agomelatine 25/50 mg[1] N=9,254 PT=45,612.7**	**Placebo[1] N=1,722 PT=5,450.8**
	%[2]	**%[2]**
Bronchitis	1.63	0.87
Sinusitis	1.59	0.58
Vomiting	1.56	1.51
Urinary tract infection	1.37	1.10
Weight increased	1.34	1.16
Arthralgia	1.26	0.58
Gastroenteritis	1.25	1.05
Irritability	1.24	0.52
Depression	1.19	2.61
Abnormal dreams	1.13	0.41
Abdominal pain	1.11	0.75

Notes:

N: Number of patients; PT: Number of patient-Months (PT); (1) Listed adverse events are pooled from trials of patients with MDD and GAD; VALOMEL is not indicated for GAD; (2): (n/N) x 100

Table 3 describes adverse reactions reported with agomelatine in clinical programs. The frequency of side effects is defined by 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), and
- not known (cannot be estimated from the available data),

and have not been corrected for placebo.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse Reactions reported with agomelatine in clinical programs[1]

System organ class	Frequency	Preferred Term
Psychiatric disorders	Common	Anxiety
	Uncommon	Suicidal thoughts or behaviour (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Nervous system disorders	Very common	Headache
	Common	Dizziness
		Somnolence
		Insomnia
	Uncommon	Migraine
		Paraesthesia
Eye disorders	Uncommon	Blurred vision
Gastrointestinal disorders	Common	Nausea
		Diarrhoea
		Constipation
		Abdominal pain
Hepato-biliary disorders	Common	Increased ALT and/or AST (in clinical trials, increases >3 times the upper limit of the normal range for ALT and/or AST were seen in 1.3% of patients on agomelatine 25 mg daily and 2.6 % on agomelatine 50 mg daily vs. 0.4% on placebo).
	Rare	Hepatitis
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis
		Eczema
	Rare	Erythematous rash
Musculoskeletal and connective tissue disorders	Common	Back pain
General disorders and administration site conditions	Common	Fatigue

Notes: (1) Listed adverse events are pooled from trials of patients with MDD and GAD; VALOMEL is not indicated for GAD

Table 4 describes adverse reactions reported with agomelatine during post-marketing experience.

Table 4: Adverse Reactions reported during post-marketing experience

System organ class	Frequency*	Preferred Term
Psychiatric disorders	Common	Abnormal dreams
	Uncommon	Agitation and related symptoms (such as irritability and restlessness)
		Aggression
		Nightmares
		Mania/hypomania. These symptoms may also be due to the underlying disease (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
		Confusional state
	Rare	Hallucinations
Nervous system disorders	Uncommon	Restless leg syndrome
	Rare	Akathisia
Ear and labyrinth disorders	Uncommon	Tinnitus
Gastrointestinal disorders	Common	Vomiting
Hepato-biliary disorders	Uncommon	Increased gamma-glutamyltransferase (GGT) (>3 times the upper limit of the normal range)
	Rare	Increased alkaline phosphatase (>3 times the upper limit of the normal range)
		Hepatic failure (1) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
		Jaundice
Skin and subcutaneous tissue disorders	Uncommon	Pruritus
		Urticaria
	Rare	Face oedema and angioedema
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
Renal and urinary disorders	Rare	Urinary retention
Investigations	Common	Weight increased
	Uncommon	Weight decreased

Notes: * Frequency estimated from clinical trials for adverse reactions detected from spontaneous reports; (1) Few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

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 2,450 mg of 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: Other antidepressants (ATC-code: NO6AX22)

Agomelatine is a melatonin receptor (MT_1 and MT_2) agonist and 5-HT_{2C} receptor antagonist. Agomelatine has shown an antidepressant-like effect in animal models of depression (learned helplessness test, despair test, chronic mild stress), in models with circadian rhythm desynchronisation and in models related to stress and anxiety.

In vitro studies indicate that agomelatine has no effect on monoamine uptake and no affinity for α or β adrenergic, histaminergic, cholinergic, dopaminergic, or benzodiazepine receptors. Agomelatine has no influence on the extracellular levels of serotonin and increases dopamine and noradrenaline release specifically in the prefrontal cortex. These properties may explain why, compared with other antidepressants, it has less gastrointestinal (e.g. vomiting, constipation) and sexual function (e.g. libido decrease) side effects, and no cardiovascular side effects in clinical trials.

In humans, agomelatine has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset.

Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption.

In patients with MDD, 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.

At therapeutic doses, in healthy volunteers, agomelatine preserves daytime alertness and memory, with no sedation in the morning following drug intake.

Cardiovascular

In clinical trials, agomelatine had no effect on QT interval and no clinically-significant effect on heart rate, blood pressure and ECG tracings

Withdrawal / Discontinuation

The abrupt discontinuation of agomelatine was evaluated in a specific active control trial (CL3-030) using the Discontinuation Emergent Signs and Symptoms (DESS) check-list. Patients with major depression were treated under double-blind conditions with agomelatine 25 mg or paroxetine 20 mg over a 12 week period. Only those who remitted at week eight and sustained that remission until week 12 were randomised to placebo or the initial active treatment for a two-week double-blind period. Patients discontinued from agomelatine to placebo were compared to those who continued treatment on agomelatine and, likewise for the active control paroxetine.

The abrupt discontinuation of agomelatine was not associated with discontinuation symptoms [$p=0.250$ for difference between the agomelatine and placebo groups]. The sensitivity of the trial was demonstrated by the presence of significant emergent discontinuation symptoms following the abrupt discontinuation of treatment with the active control paroxetine [$p<0.001$ for difference between the paroxetine and placebo groups].

Sexual function

No deleterious effect on sexual function (SEX-FX total score and SEX-FX sub-scores and items) was observed during agomelatine 50 mg treatment over 12 or 24-week treatment periods in a specific sexual dysfunction comparative trial in remitted depressed patients. There was a numerical trend towards less sexual emergent dysfunction on agomelatine 50 mg than venlafaxine 150 mg for SEX-FX drive arousal or orgasm scores but statistical separation was not achieved.

A separate pooled analysis of trials using the Arizona Sexual Experience Scale (ASEX) showed that agomelatine was not associated with sexual dysfunction. In healthy volunteers agomelatine did not affect sexual function, in contrast to paroxetine.

Clinical trials

Acute treatment of Major Depressive Disorder (MDD)

The efficacy and safety of agomelatine in the treatment of major depression have been studied in a clinical development programme including 8,084 patients treated with therapeutic doses of 25 mg or 50 mg. Among over 7,130 patients treated with agomelatine for between six weeks and one year, 2,356 patients were treated with agomelatine for six months and 1,094 patients were treated with agomelatine for one year.

Ten placebo-controlled trials have been performed to investigate the short-term efficacy of agomelatine in MDD in adults, with fixed dose and/or dose up-titration. At the end of treatment (over six or eight weeks), five one step up-titration trials and one of the fixed dose trials showed statistically the superiority of agomelatine over placebo on the primary outcome criterion HAM-D total score and consistent results across secondary criteria (trials CL2-014, CL3-042, CL3-043, CL3-069, CAGO178A2301 for 50 mg dose (but not 25 mg dose), CAGO178A2302 for 25 mg dose (but not 50 mg dose)). Response rates were statistically significantly higher with agomelatine compared with placebo. The response to treatment of MDD was defined as a decrease in HAM-D total score of at least 50 % from baseline.). The superiority of agomelatine over placebo was shown after two weeks of treatment.

Agomelatine did not differentiate from placebo in two trials (CL3-022, CAGO178A2303) where the active control fluoxetine or paroxetine showed assay sensitivity. In these trials agomelatine was not compared directly with paroxetine or fluoxetine as these comparators were included only to validate the assay sensitivity of the trials. In two other trials (CL3-023, 024), it was not possible to draw any conclusions because the active controls, paroxetine and fluoxetine, failed to differentiate from placebo.

Table 5 - Efficacy results in the pivotal short-term placebo-controlled trials agomelatine 25-50 mg

Trial (duration) Treatment group	**HAM-D total score**			**HAM-D Responder#**	**CGI## Severity**		
	n	**Baseline** mean	**Final** Mean	**Final** Mean	**n**	**Baseline** mean	**Final** Mean
CL2-014 (8 weeks)							
agomelatine 25 mg	135	27.4	12.8^	61.5%^	135	4.7	2.8^
placebo	136	27.4	15.3	46.3%	136	5.0	3.3
paroxetine 20mg	144	27.3	13.1^	56.3%	-	-	-
CL3-042 (6 weeks)							
agomelatine 25-50 mg	116	27.4	13.9^	54.3%^	116	4.9	3.1^
placebo	119	27.2	17.0	35.3%	119	4.9	3.6
CL3-043 (6 weeks)							
agomelatine 25-50 mg	106	26.5	14.1^	49.1%^	106	4.8	3.2^
placebo	105	26.7	16.5	34.3%	105	4.8	3.6
CL3-069 (6 weeks)							
agomelatine 25 mg	138	26.7	14.0^	50.7%^	138	4.7	3.1^
agomelatine 25-50 mg	136	26.7	13.9^	52.2%^	136	4.6	3.1^
placebo	141	26.6	18.7	24.8%	141	4.6	3.7

Notes: #Percentage of patients with a decrease in baseline HAM-D total score ≥ 50%
CGI: Clinical Global Impression; ^statistically significant difference from placebo.

The short term efficacy of 25-50 mg/day of agomelatine was also demonstrated in trial CL3-046 which assessed the antidepressant efficacy of agomelatine as a secondary objective compared to sertraline (50-100 mg/day) over a double-blind treatment period of six weeks where male or female patients, aged 18-60 years fulfilling DSM-IV criteria for MDD, received agomelatine 25-50 mg/day or sertraline 50-100 mg/day (see Table 6).

Table 6 - Efficacy results in short-term trial CL3-046 versus sertraline

Trial (duration) Treatment group	**HAM-D total score**			**HAM-D Responder#**	**CGI## Severity**		
	n	**Baseline** mean	**Final** Mean	**Final** Mean	**n**	**Baseline** mean	**Final** Mean
CL3-046 (6 weeks)							
agomelatine 25-50 mg	150	26.1	10.3^	70.0%	150	4.7	2.5^
sertraline 50-100 mg	156	26.5	12.1	61.5%	157	4.7	2.8

Notes: # Percentage of patients with a decrease in baseline HAM-D total score ≥ 50%
CGI: Clinical Global Impression; ^Statistically significant difference in favour of agomelatine

The short term efficacy of agomelatine was also shown in trial CL3-045 which demonstrated the antidepressant efficacy of agomelatine vs fluoxetine after a double-blind treatment period of eight weeks where male or female patients, aged 18-65 years fulfilling DSM-IV criteria for MDD, received agomelatine 25-50 mg/day or fluoxetine 20-40 mg/day (see Table 7).

Table 7 – Primary efficacy criterion results in short-term trial CL3-045 versus fluoxetine

Trial (duration) Treatment group	**HAM-D total score**				**Superiority test^^**
	n	**Baseline** W0 mean	**Final** W8 Mean	**Difference W8-W0** E [95% CI]	p-value
agomelatine 25-50 mg fluoxetine 20-40 mg	247 257	28.5 28.7	11.1 12.7	1.49^ [0.20; 2.77]	0.024

Notes:
^Statistically significant difference in favour of agomelatine
^^a priori superiority test: two sided p-value to be compared to 0.05 following a non-inferiority test centred on a non-inferiority margin of –1.5: one-sided p-value of <0.001 compared to 0.025

Superiority (CL3-045 and CL3-046) or non-inferiority (CL3-052, CL3-035, CL3-056 and CL3-063) with agomelatine has been shown in six short-term efficacy trials in heterogeneous populations of adult patients with depression compared to SSRI/SNRI (sertraline, escitalopram, fluoxetine or venlafaxine). The antidepressant effect was assessed with the HAMD-17 score either as the primary (two studies) or secondary endpoint (four studies).

Acute treatment of MDD in the elderly

A double-blind, placebo-controlled eight week trial of agomelatine 25-50 mg/day in male and female patients with MDD aged ≥ 65 years (N=222, of which 151 were treated with 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 were treated with agomelatine), and agomelatine should not be used in that group.

Prevention of Relapse of Depression

The primary objective of trial CL3-041 was to assess the efficacy of agomelatine at flexible dose in the prevention of depressive relapse compared to placebo. In this trial, 492 patients received open label treatment with agomelatine 25 mg/day for eight to ten weeks, with an increase to 50 mg/day in patients who were not sufficiently improved after two weeks. Thereafter, the patients who responded to therapy (HAM-D total score ≤ 10) were randomised to receive treatment with agomelatine or placebo until relapse occurred for up to 44 weeks. 338 patients participated in the double blind, long-term portion of the trial: 165 were treated with agomelatine and 174 were treated with placebo. The primary efficacy criterion was the relapse, defined as HAM-D 17-item total score ≥ 16, or any withdrawal for lack of efficacy during the 44-week double-blind period.

The risk over time of relapse was significantly reduced by 54.2 % in the agomelatine group compared to the placebo group in trial CL3-041 (see Figure 1). As is indicated in Table 8, the percentage of patients with a relapse during the 24-week double-blind period was more than two times lower in the agomelatine group than in the placebo group.

Figure 1 – Time to relapse over the 24 week double blind trial period

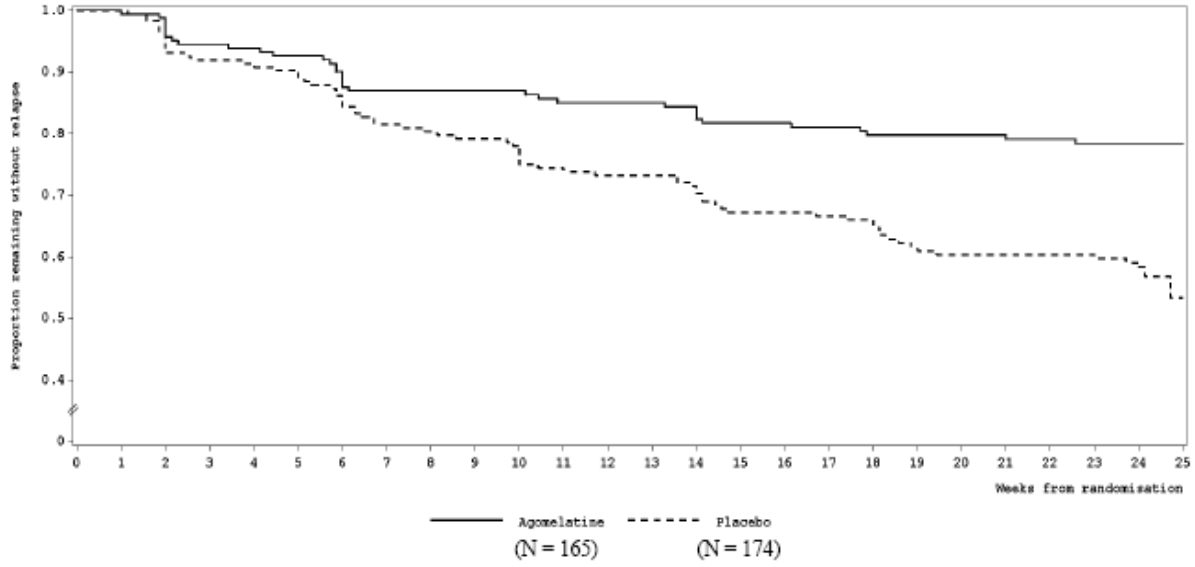


Table 8 – Time to relapse analysis over 24 weeks

Group	No. of patients	Relapses		Cumulative incidence of relapse at 175 days E[95%CI]	Cox model HR E[95%CI]	Logrank p-value
		N	%			
Agomelatine 25-50 mg	165	34	20.6	21.7 [15.19;28.10]	0.458	<0.0001
Placebo	174	72	41.4	46.6 [36.84; 56.41]	[0.305;0.690]	

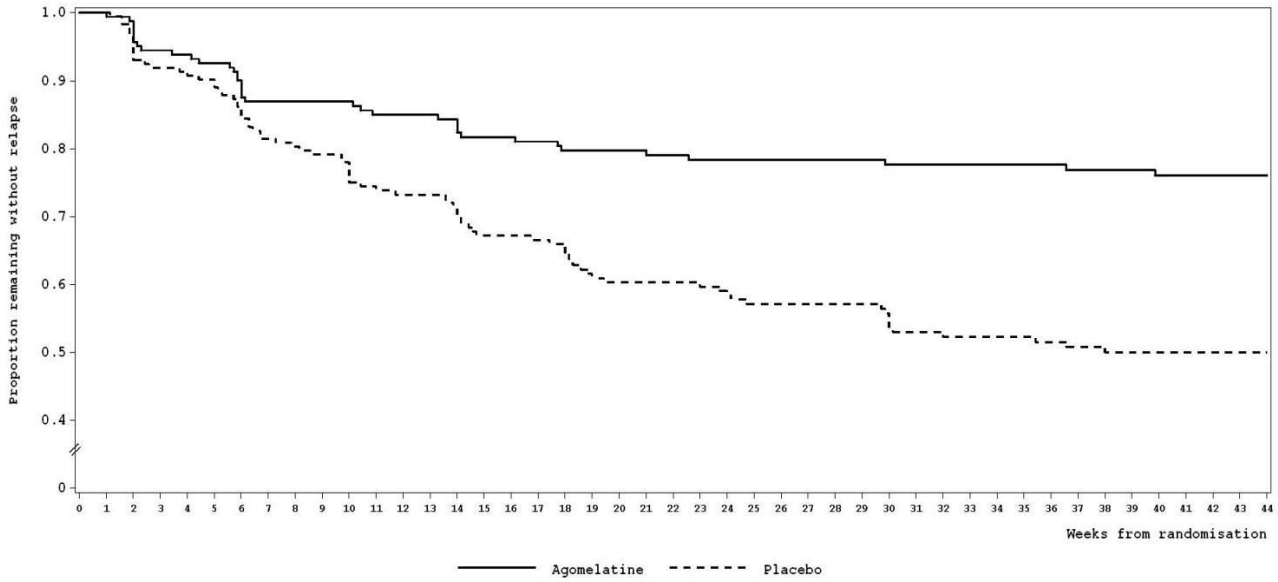
Results over the 44-week double-blind treatment period confirm the efficacy of agomelatine 25-50 mg to prevent depressive relapse in patients with MDD and showed the maintenance of long-term efficacy. The percentage of patients with a relapse over the whole 44-week double-blind period remained more than two times lower in the agomelatine group than in the placebo group (see Table 9).

Table 9 – Time to relapse analysis over 44 weeks

Group	No. of patients	Relapses		Cumulative incidence of relapse at 308 days E[95%CI]	Cox model HR E[95%CI]	Logrank p-value
		N	%			
Agomelatine 25-50 mg	165	39	23.6	23.9 [17.16;30.70]	0.437	<0.0001
Placebo	174	83	47.7	50.0 [42.20; 57.75]	[0.298;0.640]	

As shown in Figure 2, the risk over time of relapse was significantly reduced by more than half, 56.3 % in the agomelatine group compared to the placebo group.

Figure 2 - Time to relapse over the 44 week double blind trial period



In another relapse-prevention trial (CL3-021), agomelatine did not separate from placebo as a result of an unexplained low relapse rate in the placebo group (23.5%) compared to the agomelatine group (25.9%) which was unexpected and markedly lower than the mean placebo relapse rate reported in the literature.

Switching to agomelatine from other antidepressants (SSRIs or SNRIs)

A specific controlled, three week trial (CL3-073) was conducted in 316 patients with MDD who had experienced insufficient improvement with paroxetine (an SSRI) or venlafaxine (an 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 was stopped was lower in the long tapering group (gradual cessation of the previous SSRI/SNRI within two weeks) than in the short tapering group (gradual cessation of the previous SSRI/SNRI within one week) and in the abrupt substitution group (abrupt cessation): 56.1%, 62.6% and 79.8% respectively.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Agomelatine is rapidly and well absorbed (≥ 80%) after oral administration. The peak plasma concentration is reached within one to two hours after administration of agomelatine. Absolute bioavailability is low (approximately 1% at the therapeutic oral dose), and is highly variable due to the first pass effect and the inter-individual differences of CYP1A2 activity. The bioavailability is increased in women compared to men.

Although not clinically relevant, the bioavailability is increased by intake of oral contraceptives and reduced by smoking. In the therapeutic dose-range, agomelatine exposure appears to increase proportionally with dose with saturation of the first pass effect occurring at supra-therapeutic doses (from 200 to 1200 mg).

Food intake (standard meal or high fat meal) reduced the peak concentration (C_{max}) by approximately 20 – 30% but did not modify overall absorption or bioavailability. The variability is increased with high fat food.

Distribution

Steady state volume of distribution is about 35 L. Plasma protein binding is 95% irrespective of concentration and is not modified with age and in patients with renal impairment but the free fraction is doubled in patients with hepatic impairment.

Metabolism

Following oral administration, agomelatine is rapidly oxidized mainly by the hepatic cytochromes CYP1A2 (90%) and CYP2C9/CYP2C19 (10%). The major metabolites, hydroxylated and demethylated agomelatine, are not pharmacologically active and are rapidly conjugated and eliminated in the urine.

Excretion

Elimination is rapid. The mean plasma half-life is between one and two hours. Clearance is high (about 1100 mL/min) and essentially metabolic. Excretion is mainly urinary (80%) and corresponds to metabolites. Urinary excretion of the unchanged compound is negligible. Pharmacokinetics remained unchanged following repeated administration.

Special Populations

Severe renal impairment:
In subjects with severe renal impairment the pharmacokinetic parameters C_{max} and AUC were slightly higher than in healthy subjects. However, due to the high inter-individual variability of agomelatine pharmacokinetics, this result was not clinically relevant. Renal impairment did not affect the protein binding of agomelatine.

Hepatic Impairment:
Following a single oral dose of 25 mg agomelatine in patients with hepatic impairment, C_{max} increased by a factor of ~60 and ~110, while AUC increased by ~70-times and ~140-times, in mild (Child-Pugh score of 5 or 6) and moderate (Child-Pugh score of 7 to 9) hepatic impairment, respectively compared to healthy subjects. Both mild and moderate liver impairment increased the half-life of agomelatine by a factor of ~3. The unbound fraction of agomelatine was also increased in subjects with hepatic insufficiency. The inter-individual variability decreased with mild hepatic impairment, with a further decrease in moderate hepatic impairment, suggesting a progressive saturation of the hepatic first-pass effect. Agomelatine is therefore contraindicated in patients with hepatic impairment, see Section 4.3 CONTRAINDICATIONS.

Gender, smoking and age:
No significant difference in exposure was shown between the young and the elderly as well as between males and females. Although not clinically relevant:

- a 3.7-fold decrease in mean exposure was observed in volunteers without depression who were heavy smokers (≥ 15 cigarettes per day);
- a decrease of 33 % of agomelatine exposure has been shown in the smoker population (healthy volunteers and patients with depression smoking > 5 cigarettes per day) compared to non-smoker population, suggesting that cigarette smoking could induce CYP1A2 which is involved in the metabolism of agomelatine.
- in a pharmacokinetic study in elderly patients (aged ≥ 65 years), mean AUC and mean C_{max} were about 4-fold and 13-fold respectively higher for very elderly patients aged ≥ 75 years compared to elderly patients aged < 75 years, after an agomelatine dose of 25 mg. The results of that study were derived from a population pharmacokinetic analysis using data from saliva samples. No plasma samples were used in the study to determine or confirm correlation with the saliva samples. The total number of patients receiving agomelatine 50 mg was too low to draw any conclusions. No dose adaptation is recommended in elderly patients solely because of their age (up to the age of 75 years). Agomelatine should not be used in patients aged 75 years and older.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

Based on results from a standard battery of *in vitro* and *in vivo* assays, agomelatine is not considered to have genotoxic potential in humans receiving the maximum proposed clinical dose.

Carcinogenicity

Oral lifetime carcinogenicity trials with agomelatine were conducted in mice and rats. Male and female mice showed increased incidences of hepatocellular adenomas and hepatocellular carcinomas at systemic exposures (plasma AUC) about 15-fold human exposure at the maximal recommended clinical dose; the no-effect exposure was about 4-fold clinical exposure. Male rats showed an increased incidence of hepatocellular carcinomas at systemic exposures (plasma AUC) about 45-fold human exposure at the maximal recommended clinical dose; the no-effect exposure was about 8-fold clinical exposure. These effects were associated with liver enzyme induction in these species and are unlikely to be relevant to humans. In male and female rats, the frequency of benign mammary fibro adenomas was increased at high systemic exposures (30-fold or greater the exposure at the maximal recommended clinical dose) but remained within the historical control range. Malignant mammary tumours were not observed.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

VALOMEL 25 mg film coated tablet contain the following inactive ingredients: silicified microcrystalline cellulose, mannitol, povidone, colloidal anhydrous silica, crospovidone, sodium stearyl fumarate, magnesium stearate, stearic acid, hypromellose, macrogol 6000, titanium dioxide, purified talc and iron oxide yellow.

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

VALOMEL film coated tablets should be stored below 25°C in their original packaging.

6.5. NATURE AND CONTENTS OF CONTAINER

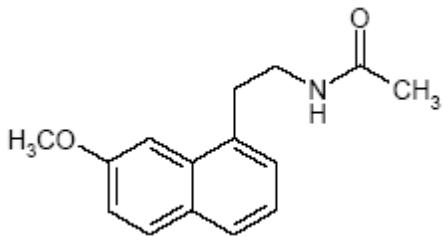
VALOMEL film coated tablet are packed in OPA/Al/PVC/Al blister packs of 28 tablets.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS Number: 138112-76-2

Chemical Name: *N*-[2-(7-methoxynaphthalen-1-yl)ethyl]acetamide

Molecular Formula: $C_{15}H_{17}NO_2$

Molecular Weight: 243.3

Agomelatine is practically insoluble in purified water (< 0.1 mg/mL) but freely soluble (> 100 mg/mL) in various organic solvents (96% ethanol, methanol, methylene chloride). Agomelatine has no asymmetric carbon atom.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Helix Pharmaceuticals

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Melbourne VIC 3044

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9. DATE OF FIRST APPROVAL

05 January 2024

10. DATE OF REVISION

19 February 2026

Summary table of changes

Section Changed	Summary of new Information
4.4 & 4.8	Minor Editorial Changes