AGOTINE
(AGOMELATINE)

Innovator's Specs.

COMPOSITION
Each film-coated tablet contains ..... Agomelatine 25 mg

DESCRIPTION
Agomelatine is melatonergic antidepressant, used for the treatment of major depressive disorder. It is chemically designated as N-[2-(7-methoxynaphthalen-1-yl) ethyl] acetamide and its molecular formula is $C_{15}H_{17}NO_2$

CLINICAL PHARMACOLOGY

Mechanism of Action
Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C 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 resynchronizes 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.

Pharmacokinetics

Absorption
Agomelatine is rapidly and well (≥80%) absorbed after oral administration. Absolute bioavailability is low (<5% at the therapeutic oral dose) and the inter-individual 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.

Metabolism
Following oral administration, agomelatine is rapidly metabolized 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 one and two hours. Clearance is high (about 1100 mL/min) and essentially metabolic. Excretion is mainly urinary (80%) and in the form of metabolites. Urinary excretion of the unchanged compound is negligible. Pharmacokinetics remained unchanged following repeated administration.

INDICATIONS
Treatment of major depressive disorder in adults including prevention of relapse

DOSAGE AND ADMINISTRATION
The recommended dose is 25 mg once daily taken orally at bedtime. After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets, taken together at bedtime.

Increase of dose 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 LFT monitoring. Liver function tests should be performed in all patients before starting treatment. Treatment should not be initiated if transaminases exceed 3 times the upper limit of normal.
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. Treatment should be discontinued if transaminases exceed 3 times the upper limit of normal. 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. Agomelatine can be started immediately while tapering the dosage of an SSRI/SNRI

Treatment discontinuation
No dosage tapering is needed on treatment discontinuation. Agomelatine is not associated with withdrawal symptoms after abrupt treatment discontinuation.

Dosing Considerations in Special populations

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.

Administration Requirements
Agomelatine film-coated tablets may be taken with or without food.

CONTRAINDICATIONS
• Hypersensitivity to Agomelatine
• Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 times the upper limit of normal.
• Concomitant use of potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)

WARNINGS AND PRECAUTIONS

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. Most of them occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with 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 use of drugs associated with risk of hepatic injury are present.

Before starting treatment
Treatment with Agomelatine 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, substantial alcohol intake and in patients receiving concomitant drugs 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 times the upper limit of normal. Caution should be exercised when Agomelatine 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
Agomelatine treatment should be discontinued immediately if:
• Patient develops symptoms or signs of potential liver injury (such as dark urine, light colored stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue).
• The increase in serum transaminases exceeds 3 times the upper limit of normal.
Following discontinuation of Agomelatine therapy liver function tests should be repeated until serum transaminases return to normal.

Older people
No effect of Agomelatine is documented in patients ≥75 years; therefore agomelatine should not be used by patients in this age group.

Use in older people with dementia
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.

Bipolar disorder/ mania / hypomania
Agomelatine 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.

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. 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 behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms occur
Combination with CYP1A2 inhibitors
Caution should be exercised when prescribing Agomelatine with moderate CYP1A2 inhibitors (e.g. propranolol, enoxacin) which may result in increased exposure of agomelatine.

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

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

ADVERSE REACTIONS

Psychiatric disorders
Common: Anxiety
Uncommon: Agitation and related symptoms (such as irritability and restlessness), Aggression Nightmares, Abnormal dreams, confusional state
Rare: Mania/hypomania, Hallucinations
Frequency not known: Suicidal thoughts or behavior
Nervous system disorders
Common: Headache, Dizziness, Somnolence, Insomnia, Migraine
Uncommon: Paraesthesia, Restless leg syndrome
Rare: Akathisia
Eyes disorders
Uncommon: Blurred vision
Ear and vestibular system disorders
Uncommon: Tinnitus
Gastrointestinal Disorders
Common: Nausea, Diarrhoea, Constipation, Abdominal pain, vomiting
Hepato- biliary disorders
Common: Increased ALAT and/or ASAT
Rare: Hepatitis, Increased gamma-glutamyltransferase (GGT) (>3 times the upper limit of the normal range), Increased alkaline phosphatase (>3 times the upper limit of the normal range), Hepatic failure Jaundice
Skin and subcutaneous tissue disorders
Common: Hyperhidrosis
Uncommon: Eczema, Pruritus, Urticaria
Rare: Erythematous rash, Face edema and angioedema
Musculoskeletal and connective tissue disorders
Common: Back pain
General disorders and administration site conditions
Common: Fatigue
Renal and Urinary disorders
Rare: Urinary retention
Investigations
Rare: Weight increased, weight decreased

DRUG INTERACTIONS

Potential interactions affecting Agomelatine exposure
Agomelatine is metabolized mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Drugs 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 Agomelatine 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.
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)

USE IN SPECIAL POPULATIONS

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. As a precautionary measure, it is preferable to avoid the use of Agomelatine during pregnancy.

Nursing mothers
It is not known whether agomelatine/metabolites are excreted in human milk. Available pharmacodynamics/toxicological data in animals have shown excretion of agomelatine/metabolites in milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Agomelatine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Elderly
The efficacy and safety of Agomelatine (25 to 50mg/day) have been established in elderly depressed patients (<75years). No effect is documented in patients ≥75 years. Therefore, Agomelatine should not be used by patients in this age group. No dose adjustment is required in relation to age. In addition, agomelatine is not recommended in elderly patients with dementia because safety and efficacy has not been demonstrated.

Pediatric population
The safety and efficacy of Agomelatine in children and adolescents (aged < 18 years) for treatment of major depressive episodes have not yet been established.

Renal impairment
No relevant modification of pharmacokinetic parameters in patients with severe renal impairment has been observed but caution should be exercised in patients with severe or moderate renal impairment as only limited clinical data are available in these patients. Renal impairment does not affect the protein binding of agomelatine.

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. Agomelatine is contraindicated in patients with hepatic impairment.

OVER DOSAGE

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 has been reported.

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.

PRESENTATION

Agomelatine 25 mg: Pack of 10, 14 and 28 Tablets.

INSTRUCTIONS

Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from heat, light and moisture.
Store below 30°C.

ہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، **30°C** سے کم درجہ حرارت پر رکھیں۔

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