Agotin

Agomelatine

COMPOSITION

Agotin Tablet: Each tablet contains Agomelatine INN 25 mg.

DESCRIPTION

The active component of Agotin is agomelatine which has the chemical name: N-[2-(7-methoxy-1-naphthyl)ethyl] acetamide. 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.

PHARMACLOGICAL INFORMATION

Pharmacological action

Agomelatine is a melatonin analogue which represents a novel class of antidepressants. Agomelatine is currently being investigated for other indications such as seasonal affective disorder, generalized anxiety disorder and bipolar depression.

Mechanism of action

This compound binds to the melatoninergic receptors and the serotoninergic 5-HT2c receptor giving rise to the Melatonin Agonist and Selective Serotonin Antagonist (MASSA) concept. The melatoninergic receptors MT1 and MT2, are G protein coupled receptors and they act through decreasing cAMP and cGMP. Agomelatine strongly binds to and stimulates the activity of MT1 and MT2 receptors normalizing the disturbed circadian rhythms and disrupted sleep-wake cycles. Unlike the existing antidepressants, agomelatine does not inhibit the uptake of serotonin, norepinephrine or dopamine. It inhibits 5HT-2C receptor (G protein coupled receptor which increases IP3/DAG secondary messenger system) found abundantly in the SCN, frontal cortex, hippocampus and basal ganglia involved in the mood, motor and cognitive deficits associated with depressive states. 5HT-2C receptor antagonism increases norepinephrine and dopamine levels in the frontal cortex of the brain. This action of agomelatine produces antidepressant, antianxiety and also increases slow-wave sleep which is decreased in depression. It has been observed that it can increase neurogenesis in the hippocampus and may also have neuroprotective effects (by influencing glutamate release, glucocorticoid receptor gene expression and various neurotropic factors) which might also contribute to its antidepressant effects. A study has shown that agomelatine alleviates sleep disturbances after one week of therapy and by two weeks antidepressant effects manifest. The combined actions of agomelatine at MT1, MT2, and 5HT-2C receptors can improve the disturbed circadian rhythm and abnormal sleep pattern thus produce the antidepressant effect. These unique effects suggest that it might be effective for the treatment of seasonal affective disorder like anxiety and bipolar depression.

PHARMACOKINETIC PROPERTIES

Absorption: In humans, agomelatine is well absorbed following oral administration, but absolute bioavailability is relatively low (about 5-10%) due to its high first-pass metabolism, which may be considered in special populations such as the elderly or hepatic disordered patients. When given as a single 25/50mg amount, blood concentrations increased more than proportionately to the dose, possibly due to saturation of first-pass metabolism.

Distribution: Agomelatine has also moderate distribution in humans, with a volume of distribution of approximately 35 L., and is 85-95% bound to plasma proteins (again, this could taken in account prior prescription in special populations).

Metabolism: Agomelatine appears to be extensively metabolized by the cytochrome P450 isoforms 1A1, 1A2 and 2C9 (majority of psychiatric medications undergo 2D6 or 3A4 or 1A2) to hydroxyl, desmethyl and epoxide metabolites with less activity than the parent drug. A major oxidative metabolite in humans, 3-hydroxy-7-desmethyl-agomelatine, has low affinity for MT1, MT2 and 5-HT2C receptors.

Elimination: The drug is eliminated mostly by urinary excretion of the metabolites (61-81% of dose in humans), with a small amount of the diol metabolite undergoing fecal excretion; the mean terminal elimination half-life is 2.3 hours.

CLINICAL INFORMATION

Indication & uses

Agomelatine is indicated for:

- Major depressive disorder especially in non-responders and intolerant to SSRIs
- Generalized anxiety disorder
- Bipolar depression
- Sleep disturbances
- Seasonal affective disorder
- Migraine and cluster headaches

Dosage and Administration

Dose: The effective dose of agomelatine is 25 mg per day given once at bed time for two weeks and can be increased to 50 mg per day in patients with inadequate response. Night time dosing is recommended because agomelatine improves the quality of sleep without day time sedation.

Administration: For oral administration with or without food. Most adult patients should take a dosage of 25mg (one tablet) daily. It is usually taking prior to bed time. If no improvement is noticed after two weeks, the dosage can be increased to 50mg (two tablets) daily.

Children under 18 years: Should be given only on medical advice.

Use in pregnancy: For agomelatine, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see Toxicology: Preclinical Safety Data under Actions). Caution should be exercised when prescribing to pregnant women.

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

Use in children and adolescents: Agomelatine is not recommended in the treatment of depression in patients <18 years since safety and efficacy of agomelatine have not been established in this age group. In clinical trials among children and adolescents treated with other antidepressants, suicide-related behavior (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behavior and anger) were more frequently observed compared to those treated with placebo.

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

Adverse Effects

The commonly reported adverse effects in the clinical trials of agomelatine are headache, nausea and diarrhea. It is found to increase the level of liver enzymes and so monitoring of enzyme level is warranted before starting therapy and therefore every 6 weeks. It is also contraindicated in patients with hepatic impairment. A meta-analysis of the treatment emergent sexual dysfunction with antidepressants has revealed that it has no significant difference with placebo.

Drug interaction

Potential interactions affecting agomelatine:

Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9 (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 agomelatine with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.

Over dose

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

Precaution

- Agomelatine is not recommended in the treatment of depression in patients under 18 years of age.
- The specific data on safety for its use in pregnancy and lactating mothers is not available but animal studies have not shown any risk.
- Agomelatine should be used with caution in the elderly (≥ 66 years of age) due to lack of clinical data.

Contraindication

Hypersensitivity to the active substances or any of the excipients. Hepatic impairment (i.e cirrhosis or active liver disease) Concommitant use of potent CYP IA inhibitors (eg. Fluvoxamine, ciprofloxacin)

PHARMACEUTICAL INFORMATION

Storage Conditions

Store in a cool and dry place away from light. Keep out of the reach of children.

Presentation & Packaging

Agotin Tablet: Each commercial box contains 10 tablets in blister pack.

Manufactured By
BEACON®
Pharmaceuticals PLC
Bhaluka, Mymensingh, Bangladesh

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