Meladep® (Agomelatine) 25mg Tablets

میلاڈیپ (ایگومیلاٹین) ٹیبلٹس ۲۵ ملی گرام

QUALITATIVE AND QUANTITATIVE COMPOSITION

Meladep Tablets 25mg
Each film-coated tablet contains:
Agomelatine 25mg
Innovator's Specification

DESCRIPTION

The Agomelatine is the component of Meladep Tablet.

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 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.
Pharmacodynamics: Psychoanaleptics, other antidepressants, ATC-code: N06AX22.
Pharmacokinetics: Absorption: 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 firstpass 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, sin-gle 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. 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. Elderly: In a pharma-

cokinetic 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.

INDICATION

Treatment of major depressive episodes in adults.

CONTRAINDICATIONS

Dementia in patients over 75 years of age. Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 X upper limit of normal Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

INTERACTIONS

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 bio-availability 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 Meladep 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). 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 CYP450.

Other medicinal products: No evidence of pharmacokinetic or pharmacodynamic interaction with medicinal products which could be prescribed concomitantly with Meladep 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. 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.

USE IN SPECIFIC POPULATION

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 Meladep during pregnancy. Breastfeeding, 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. A risk to the newborns/inants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Meladep therapy taking into account the benefit of breastfeeding 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.

WARNINGS AND PRECAUTIONS

Alcoholism, bipolar disorder, diabetes, excessive alcohol consumption, hypomania, mania, nonalcoholic fatty liver disease, obesity.

ADVERSE REACTIONS

Adverse reactions were usually mild or moderate and occurred within first two weeks. Common: nausea, dizziness, headache, somnolence, insomnia, migraine, diarrhoea, constipation, abdominal pain, vomiting, hyperhidrosis, back pain, fatigue, anxiety, increases in AST and ALT. Uncommon: aggression, restless leg syndrome, tinnitus. Rare: mania/hypomania, hepatitis, increases in GGT and ALP, hepatic failure (exceptionally with fatal outcome or liver transplantation in patients with hepatic risk factors.), jaundice, facial oedema and angioedema. Frequency unknown: Suicidal thoughts or behaviour.

DOSAGE AND ADMINISTRATION

The recommended dose is 25mg once daily taken orally at bedtime. After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50mg once daily, i.e. two 25mg tablets, taken together at bedtime. Decision of dose increase has to be balanced with a higher risk of transaminases elevation. Any dose increase to 50mg 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. 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 discon-tinued if transaminases exceed 3 X 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. 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 an SSRI/SNRI. Treatment discontinuation: No dosage tapering is needed on treatment discontinuation.

SPECIAL POPULATIONS

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. 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.

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. 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: Meladep film coated tablets may be taken with or without food.

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 2,450mg 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.

INSTRUCTIONS

Dosage as directed by the physician. Store below 30°C. Protect from heat, light & moisture. For Oral use Only.
Keep all medicines out of the reach of children.

PRESENTATION

Meladep (Agomelatine) 25mg tablets are available in Alu-Alu blister pack of 14's with leaflet.

خوراک : خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

علامات : بالغ افراد میں شدید ذہنی دباؤ کے شکار افراد کے لئے تجویز کردہ ہے۔

مضر اثرات : اُلٹی، چکر آنا، سر درد، کمر درد، جگر کی خرابی، یرقان۔

احتیاطی تدابیر: ذیابیطس، بائے پولر ڈس آرڈر، موٹاپا۔

ہدایات : ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ روشنی، گرمی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔ صرف کھانے کیلئے

For detailed information:

Genix Pharma (Pvt.) Ltd.
44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com
www.genixpharma.com

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