For the Use of Registered Medical Practitioner (Psychiatrists Only)

1. GENERIC NAME & BRAND NAME

Amisulpride Controlled Release Tablets 400 mg

Amisant ® 400 OD

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated bilayered controlled release tablet contains:

Amisulpride I.P. 400mg

Colour: Ponceau 4R

3. DOSAGE FORM & STRENGTH

Refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

Amisulpride tablets are indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms and or negative symptoms are prominent, including patients characterized by predominant negative symptoms.

4.2 POSOLOGYAND METHOD OF ADMINISTRATION

Posology: For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended. In individual cases, the daily dose may be increased up to 1200 mg/day. Doses above 1200 mg/day have not been extensively evaluated for safety and therefore should not be used. No specific titration is required when initiating the treatment with Amisulpride. Doses should be adjusted according to individual response.

For patients with mixed positive and negative symptoms, doses should be adjusted to obtain optimal control of positive symptoms. Maintenance treatment should be established individually with the minimally effective dose.

For patients characterized by predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually. Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid. The minimum effective dose should be used.

Special Populations: Elderly patients: The safety of amisulpride has been examined in a limited number of elderly patients. Amisulpride should be used with particular caution because of a possible risk of hypotension or sedation. Reduction in dosage may also be required because of renal insufficiency.

Paediatric population: The efficacy and safety of amisulpride from puberty to the age of 18 years have not been established. There are limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, the use of amisulpride from puberty to the age of 18 years is not recommended; in children up to puberty amisulpride is contraindicated, as its safety has not yet been established.

Renal insufficiency: Amisulpride is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance (CRCL) between 30-60 ml/min and to a third in patients with CRCL between 10-30 ml/min.

As there is no experience in patients with severe renal impairment (CRCL <10 ml/min) particular care is recommended in these patients.

Hepatic insufficiency: since the drug is weakly metabolised a dosage reduction should not be necessary. Method of administration:

For oral use only. Patient should be advised to swallow the tablet whole, not to be chewed or crushed. Do not exceed the stated dose or take it as directed by the Physician.

4.3 CONTRAINDICATIONS

Amisulpride tablet is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients.

- Concomitant prolactin-dependent tumors, e.g. pituitary gland prolactinomas and breast cancer.
- Pheochromocytoma.
- Children before the onset of puberty, and lactation.
- Combination with levodopa.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with other neuroleptics, Neuroleptic Malignant Syndrome, a potentially fatal complication, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic drugs, including Amisulpride should be discontinued.

Hyperglycaemia has been reported in patients treated with some atypical antipsychotic agents, including amisulpride, therefore patients with an established diagnosis of diabetes

mellitus or with risk factors for diabetes who are started on amisulpride, should get appropriate glycaemic monitoring.

Amisulpride is eliminated by the renal route. In cases of severe renal insufficiency, the dose should be decreased and intermittent treatment should be prescribed. Amisulpride may lower the seizure threshold. Therefore, patients with a history of epilepsy should be closely monitored during Amisulpride therapy.

In elderly patients, Amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation. Reduction in dosage may also be required because of renal insufficiency.

As with other antidopaminergic agents, caution should be also exercised when prescribing Amisulpride to patients with Parkinson's disease since it may cause worsening of the disease. Amisulpride should be used only if neuroleptic treatment cannot be avoided.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Prolongation of the QT interval: Caution should be exercised when amisulpride is prescribed in patients with known cardiovascular disease or family history of QT prolongation. Concomitant antipsychotics should be avoided.

Stroke:

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs, or other populations of patients cannot be excluded. Amisulpride should be used with caution in patients with stroke risk factors.

Elderly patients with dementia:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., hearth failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Amisulpride is not licensed for the treatment of dementia-related behavioural disturbances.

Venous thromboembolism: Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Amisulpride and preventive measures undertaken.

Breast cancer: Amisulpride may increase prolactin levels. Therefore, caution should be exercised and patients with a history or a family history of breast cancer should be closely monitored during Amisulpride therapy. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including Amisulpride. Unexplained infections or fever may be evidence of blood dyscrasia and requires immediate haematological investigation.

4.5 DRUG REACTIONS

Combinations which are contraindicated: Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics. Amisulpride may oppose the effect of dopamine agonists e.g. bromocriptine, ropinirole. Combinations which are recommended:

Amisulpride may enhance the central effects of alcohol.

Combinations to be taken into account: CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives. Antihypertensive drugs and other hypotensive medications

Caution is advised when prescribing amisulpride with medicines known to prolong the QT interval, e.g., class IA antiarrythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistamines, some other antipsychotics and antimalarials (e.g., mefloquine).

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy In animals, amisulpride did not show direct reproductive toxicity. A decrease in fertility linked to the pharmacological effects of the drug (prolactin mediated effect) was observed. No teratogenic effects of amisulpride were noted.

Very limited clinical data on exposed pregnancies are available. Therefore, the safety of amisulpride during human pregnancy has not been established. Use of the drug is not recommended during pregnancy unless the benefits justify the potential risks.

For women of childbearing potential, effective contraception should be fully discussed with the physician prior to treatment. Neonates exposed to antipsychotics (including Amisulpride) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast feeding

It is not known whether Amisulpride is excreted in breast milk, breast-feeding is therefore contra-indicated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Even used as recommended, Amisulpride may cause somnolence so that the ability to drive vehicles or operate machinery can be impaired.

4.8 UNDESIRABLE EFFECTS

Adverse effects have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000 ;< 1/100); rare (≥1/10,000 ;<1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Clinical trials data: The following adverse effects have been observed in controlled clinical trials. It should be noted that in some instances it can be difficult to differentiate adverse events from symptoms of the underlying disease.

Nervous system disorders: Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, and dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day. Common: Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence. Uncommon: Tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms. Seizures.

Psychiatric disorders: Common: Insomnia, anxiety, agitation, orgasmic dysfunction. Gastrointestinal disorders: Common: Constipation, nausea, vomiting, and dry mouth.

Endocrine disorders: Common: Amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.

Metabolism and nutrition disorders: Uncommon: Hyperglycaemia. Cardiovascular disorders: Common: Hypotension. Uncommon: Bradycardia. Investigations: Common: Weight gain. Uncommon: Elevations of hepatic enzymes, mainly transaminases. Immune system disorders: Uncommon: Allergic reaction.

Post-marketing data: In addition, cases of the following adverse reactions have been reported through spontaneous reporting only: Blood and Lymphatic system disorders: Frequency not known: Leukopenia, neutropenia and agranulocytosis. Metabolism and nutrition disorders: Frequency not known: hypertriglyceridemia and hypercholesterolemia. Psychiatric disorders: Frequency not known: confusion.

Nervous system disorders: Frequency not known: Neuroleptic Malignant Syndrome, which is a potentially fatal complication. Cardiac disorders: Frequency not known: QT interval prolongation and ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death.

Vascular disorders: Frequency not known: Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs.

Skin and subcutaneous tissue disorders: Frequency not known: Angioedema, urticaria. Pregnancy, puerperium and perinatal conditions: Frequency not known: Drug withdrawal syndrome neonatal.

4.9 OVERDOSE

Experience with amisulpride in overdosage is limited. Exaggerations of the known pharmacological effects of the drug have been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms. Fatal outcomes have been reported mainly in combination with other psychotropic agents.

In cases of acute overdosage, the possibility of multiple drug intakes should be considered. Since Amisulpride is weakly dialysed, hemodialysis should not be used to eliminate the drug. There is no specific antidote to Amisulpride. Appropriate supportive measures should therefore be instituted with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the QT interval until the patient recovers. If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 MECHANISM OF ACTION

Kindly refer to Section 5.2

5.2 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics.

Amisulpride binds selectively with a high affinity to human dopaminergic D2/D3 receptor subtypes whereas it is devoid of affinity for D1, D4 and D5 receptor subtypes. Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, -adrenergic, histamine H1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites. In animal studies, at high doses, amisulpride blocks dopamine receptors located in the limbic structures in preference to those in the striatum. At low doses it preferentially blocks pre-synaptic D2/D3 receptors; producing dopamine release responsible for its disinhibitory effects. This pharmacological profile explains the clinical efficacy of amisulpride against both negative and positive symptoms of schizophrenia.

5.3 PHARMACOKINETIC PROPERTIES

Absorption : In man, amisulpride shows two absorption peaks: one which is attained rapidly, one hour post-dose and a second between 3 and 4 hours after administration. Corresponding plasma concentrations are 39 ± 3 and 54 ± 4 ng/ml after a 50 mg dose.

Distribution : The volume of distribution is 5.8 l/kg, plasma protein binding is low (16%) and no drug interactions are suspected. Absolute bioavailability is 48%.

Biotransformation : Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remains unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Elimination : Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.

A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUCs, Tmax and Cmax of amisulpride but no changes were seen after a high fat meal. However, the significance of these findings in routine clinical use is not known.

Special Populations: Hepatic insufficiency: Since the drug is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

Renal insufficiency: The elimination half-life is unchanged in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two-fold and almost tenfold in moderate renal failure. Experience is however limited and there is no data with doses greater than 50 mg. Amisulpride is very weakly dialysed.

Elderly: Limited pharmacokinetic data in elderly subjects (> 65 years) show that a 10-30% rise occurs in Cmax, T1/2 and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

6.0 NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Preclinical safety data : An overall review of the completed safety studies indicates that Amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/d) and dog (120 mg/kg/d), respectively in terms of AUC No carcinogenic risk, relevant to man was identified in the rat at up to 1.5 to 4.5 times the expected human AUC. Amouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

In animal trials, amisulpride has an effect on fetal growth and development at doses that correspond to Human Equivalent Dose of 2000 mg/day and upwards for a 50 kg patient. No evidence for a

teratogenic potential of amisulpride has been observed. Studies on the impact of amisulpride on the behaviour of the offspring have not been conducted.

7. DESCRIPTION

AMISANT OD is supplied for oral administration, as an uncoated bilayered controlled release tablet of Amisulpride. Each uncoated bilayered controlled release tablet contains Amisulpride 400mg.

8. PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES

Not Applicable

8.2 SHELF LIFE

Refer Pack

8.3 PACKAGING INFORMATION

Refer Pack

8.4 STORAGE CONDITION AND HANDLING INSTRUCTIONS

Refer Pack

9. PATIENT COUNSELLING INFORMATION

Do not take Amisulpride if you:

- Are allergic to amisulpride or any of the other ingredients of this medicine
- Signs of an allergic reaction may include a rash, difficulty swallowing or breathing, swelling of the lips, face, throat or tongue
- Have breast cancer or something called a 'prolactin dependent tumour'.
- Have a tumour on the adrenal gland called phaechromocytoma.
- Are breast-feeding.
- Are taking levodopa (used to treat Parkinson's disease) or medicines to treat heart rhythm disorders, or medicines that may cause an abnormal heart rhythm when used at the same time as amisulpride [For more details Refer – Section 4.4]

10. MANUFACTURED BY:

Refer Pack for manufacturer details.

Marketed by:

Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4, Gala No. 1 to 6 &

11 to 16 Ground Floor, 101 to 106 &

111 to 116 First Floor, 201 to 206 & 211 to 216

2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

11. DETAILS OF PERMISSION OR LICENSE NUMBER

Refer Pack for Permission/License details

12. DATE OF REVISION

Version 2.0, dated 27th September 2023