AMISULPRIDE

AMIABEL®

200 mg and 400 mg FILM-COATED TABLET

ANTIPSYCHOTIC

FORMULATION
Each film-coated tablet contains:
Amisulpride ……..200 mg or 400 mg

PRODUCT DESCRIPTIONS
Amisulpride (Amiabel) 200 mg is a white, biconvex, film-coated, elliptical tablet, bisected on one side
Amisulpride (Amiabel) 400 mg is a white, biconvex, film-coated, elliptical tablet

PHARMACOLOGY
Amisulpride is a substituted benzamide atypical antipsychotic. It binds selectively with high affinity to human dopaminergic D_2 and D_3 receptor subtypes while having no affinity for D_1, D_4 and D_5 receptor subtypes. Unlike conventional and other atypical antipsychotics, amisulpride has no affinity for serotonin, α-adrenergic, histamine H_1, and cholinergic receptors. It does not bind to sigma sites.

In animal studies, at high doses, amisulpride antagonizes postsynaptic dopamine D_2 and D_3 receptors, preferentially in the limbic system rather than those in the striatum, thereby reducing dopaminergic transmission. In addition, amisulpride does not induce catalepsy and does not produce D_2 hypersensitivity after repeated treatment. At low doses, it enhances dopaminergic neurotransmission by preferentially blocking presynaptic D_2/D_3 dopamine 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.
Amisulpride's reduced tendency to produce extrapyramidal side effects may be related to its preferential limbic activity**.**

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

A high-carbohydrate low-fat meal significantly decreases the area under the drug curve (AUC), time to reach maximum concentration (T_{max}), and maximum concentration (C_{max}) of amisulpride, but no changes were seen after a high fat meal. The significance of these findings in routine clinical use is not known.

Amisulpride's volume of distribution is 5.8 L/kg. Plasma protein binding is low (16%) and drug interactions due to displacement are unlikely**.** The absolute bioavailability of amisulpride is 48%.

Amisulpride is weakly metabolized: 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 administration of repeated doses. Amisulpride is eliminated unchanged in the urine. Amisulpride's elimination half-life ($t_{1/2}$) is approximately 12 hours after an oral dose.
Amisulpride is very weakly dialyzed.

Special Population:
Renal Insufficiency: The elimination $t_{1/2}$ is unchanged in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride increased two-fold in mild renal failure and almost tenfold in moderate renal failure. There are no data with doses greater than 50 mg.

Geriatric: Limited pharmacokinetic data in elderly patients (>65 years) showed that a 10% to 30% increase occurs in C_{max}, $t_{1/2}$, and AUC after a single oral 50 mg dose. No data are available after repeated dosing.

INDICATIONS
- For the treatment of psychoses, such as acute and chronic schizophrenic disorders, in which positive symptoms (e.g., delusions, hallucinations, thought disorders) and/or negative symptoms (e.g., blunted affect, emotional and social withdrawal) are prominent, including patients characterized by predominant negative symptoms.

DOSAGE AND ADMINISTRATION
- Doses should preferably be given before meals.
- Amisulpride should be administered twice a day for doses above 400 mg.
- Doses should be adjusted based on individual patient response.
- There is no specific titration required when initiating treatment with amisulpride.
- Maintenance treatment should be established individually with the minimally effective dose.

Recommended Adult Oral Amisulpride Dose:
For acute psychotic episodes:
Oral doses between 400 mg and 800 mg per day;
In individual cases, the daily dose may be increased up to 1,200 mg per day**.**
Doses above 1,200 mg per day have not been evaluated for safety and should not be used.
For patients with mixed positive and negative symptoms:
Initially, 400 mg to 800 mg per day;
Doses should then be adjusted to obtain optimal control of positive symptoms.
For patients with predominant negative symptoms:
Oral doses between 50 mg and 300 mg per day
Special Population:
Renal Insufficiency: Dose should be reduced to half in patients with creatinine clearance (CL_{cr}) between 30 to 60 mL/min and to a third in patients with CL_{cr} between 10 to 30 mL/min.
As there is no experience in patient with severe renal impairment (CL_{cr} < 10 mL/min), particular care is recommended in these patients.
Hepatic Impairment: Dose reduction is not necessary since amisulpride is weakly metabolized.

Or, as prescribed by a physician.

CONTRAINDICATIONS
- Hypersensitivity to amisulpride or to any ingredient in the product;
- Concomitant prolactin-dependent tumors such as pituitary gland prolactinomas and breast cancer;
- Pheochromocytoma;
- Children below 15 years old;
- Pregnancy and lactation
- Women of childbearing potential unless using adequate contraception;
- In combination with the following drugs which could induce *torsades de pointes*:
  - Class Ia antiarrhythmic agents (e.g., quinidine, procainamide and disopyramide)
  - Class III antiarrhythmic agents (e.g., amiodarone, sotalol)
  - Certain antipsychotic drug (e.g., sertindole)
  - Other drugs such as bepridil, cisapride, sultopride, thioridazine, IV erythromycin, IV vincamine, halofantrine, pentamidine, and sparfloxacin

  Note: This list is not exhaustive.
- In combination with Levodopa (see DRUG INTERACTIONS)

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Analyses of 17 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 were varied, most of the deaths appeared to be either cardiovascular (e.g., heart 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 behavioral disturbances.

Stroke
A three-fold increased risk of cerebrovascular events has been observed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs. The mechanism of the increased risk 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.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially fatal syndrome that has been associated with antipsychotic drugs, including amisulpride. NMS is characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated creatinine phosphokinase (CPK). In case of hyperthermia, particularly with high daily doses, all antipsychotic drugs, including amisulpride should be discontinued.

Seizure
Amisulpride can lower the seizure threshold. Patients with a history of epilepsy should be closely monitored during amisulpride therapy**.**

Dystonia
Acute dystonia characterized by spasm torticollis, oculogyric crisis and trismus may appear**.** This is reversible without amisulpride discontinuation upon treatment with an antiparkinsonian agent.

Extrapyramidal Symptoms
Extrapyramidal symptoms such as tremor, rigidity, hypokinesia, hypersalivation, and akathisia may occur**.** These symptoms are generally mild at optimal doses and partially reversible without amisulpride discontinuation upon administration of an antiparkinsonian agent. With doses of 50 mg to 300 mg per day, the incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms.

Tardive Dyskinesia
There have been reports of tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face, usually after long-term administration. Antiparkinsonian drug is ineffective or may aggravate these symptoms.

Hyperglycemia
There have been reports of hyperglycemia in patients treated with some atypical antipsychotic drugs, including amisulpride. Therefore, patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are on amisulpride therapy should get appropriate glycemic monitoring.

Increased Plasma Prolactin
Amisulpride increases plasma prolactin levels which are reversible after discontinuation of the drug. This may result in galactorrhea, amenorrhea, gynecomastia, breast pain, orgasmic dysfunction, and impotence.

Prolongation of the QT Interval
Amisulpride induces a dose-dependent prolongation of the QT interval. This effect, known to potentiate the risk of serious ventricular arrhythmias such as *torsades de pointes*, is enhanced by the pre-existence of bradycardia, hypokalemia, congenital or acquired long QT interval.
Hypokalemia should be corrected.
Before amisulpride administration, and if possible according to the patient's clinical status, it is recommended to monitor factors which could favor the occurrence of this rhythm disorder:
- Bradycardia less than 55 bpm
- Cardiac disease or family history of sudden death or QT prolongation
- Electrolyte imbalance, in particular hypokalemia
- Congenital prolongation of the QT interval
- On-going treatment with drugs likely to produce pronounced bradycardia (<55 bpm), hypokalemia, decreased intracardiac conduction, or prolongation of the QT interval.

Baseline ECG is recommended before treatment in all patients particularly in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g., at dose escalation) should be assessed on an individual patient basis.
Amisulpride dose should be reduced if QT is prolonged and discontinued if QTc is > 500 ms.
Periodic electrolyte monitoring is recommended particularly if the patient is taking diuretics or during intercurrent illness.
Concomitant antipsychotic drugs should be avoided.

Venous Thromboembolism
Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Amisulpride should be used with caution in patients with risk factors for thromboembolism.

Use in Patients with Concomitant Illness
Like other antidopaminergic agents, caution should be exercised when prescribing amisulpride to patients with Parkinson's disease because it may cause worsening of the disease. Amisulpride should be used only if antipsychotic treatment cannot be avoided.
Amisulpride is eliminated by the renal route. In cases of severe renal insufficiency, the dose should be decreased or intermittent treatment should be considered.
There are limited data on the potential for renally-cleared drugs to interfere with amisulpride clearance. Therefore, amisulpride should be used with caution with other renally-excreted drugs, including lithium.
The impact of hepatic impairment on amisulpride's hepatic metabolism and hepato-biliary excretion has not been studied. Amisulpride should be used with caution in patients with moderate or severe hepatic impairment.

Withdrawal Symptoms
Acute withdrawal symptoms (e.g., nausea, vomiting and insomnia) have been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur. The emergence of involuntary movement disorders (e.g., akathisia, dystonia and dyskinesia) has been reported with amisulpride. Therefore, gradual withdrawal of the drug is advisable.

Effect on Ability to Drive and Use Machines
Amisulpride may affect reaction time; therefore, the ability to drive vehicles or operate machinery can be impaired even when used as recommended.

DRUG INTERACTIONS (see also Contraindications)
- **Dopamine Agonists** (e.g., levodopa)**:** Reciprocal antagonism of effects between levodopa and antipsychotics. Concomitant use is contraindicated.
- **Alcohol:** Amisulpride may enhance the effects of alcohol. Concomitant use is not recommended.
- **Bradycardia-inducing drugs such as beta-blockers** (e.g., bisoprolol, carvedilol, metoprolol), bradycardia-inducing calcium-channel blockers (e.g., diltiazem, verapamil), **guanfacine, clonidine; digitalis:** These drugs induce bradycardia. Concomitant use enhances the risk of *torsades de pointes***.** Caution is required when used concomitantly**.**
- **Hypokalemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, and tetracosactides:** These drugs cause hypokalemia or electrolyte imbalance. Concomitant use enhances the risk of *torsades de pointes*. Caution is required when used concomitantly**.**
- **Antipsychotics** (e.g., thioridazine, chlorpromazine, trifluperazine, pimozide, haloperidol, imipramine antidepressants, lithium)**:** Concomitant use enhances the risk of *torsades de pointes***.** Caution is required when used concomitantly**.**
- **Other antipsychotics:** Concomitant use may increase the risk of developing NMS.
- **CNS depressants** (e.g., narcotics, anesthetics, analgesics, sedative H1-antihistamines, barbiturates, benzodiazepines and other anxiolytic drugs, clonidine and derivatives)**:** Amisulpride may enhance the effects of CNS depressants.
- **Antihypertensives and other hypotensive drugs:** Amisulpride may enhance the effects of these drugs.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
- **PREGNANCY AND LACTATION**

  Pregnancy

  Pregnancy Category B3: The safety of amisulpride during human pregnancy has not been established. Therefore, use of this drug is not recommended during pregnancy unless the benefits justify the potential risk to the fetus.

  Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms after delivery**.** There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

  Lactation

  It is not known whether amisulpride or its metabolites are excreted in animal or human breast milk. Therefore, breastfeeding during amisulpride treatment is not recommended.
- **GERIATRIC**

  Caution should be exercised when giving amisulpride to elderly patients because of possible risk of hypotension or sedation.
- **PEDIATRIC**

  Amisulpride is not recommended in children less than 15 years old because its efficacy and safety have not yet been established in this age group.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS
Cardiovascular: Hypotension; bradycardia, QT interval prolongation, and ventricular arrhythmias such as *torsades de pointes*; ventricular tachycardia which may result in ventricular fibrillation or cardiac arrest; sudden death; venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis
Dermatologic and Sensitivity Reactions: Allergic reaction, angioedema, urticaria
Endocrine/Metabolic: Weight gain; increased plasma prolactin levels which may result in galactorrhea, amenorrhea, gynecomastia, breast pain, orgasmic dysfunction and impotence; hyperglycemia
Gastrointestinal: Constipation, nausea, vomiting, dry mouth
Hepatic: Elevations of hepatic enzymes, mainly transaminases
Nervous System: Insomnia, anxiety, agitation, somnolence, extrapyramidal symptoms (e.g., tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia), acute dystonia (e.g., spasm torticollis, oculogyric crisis, trismus), tardive dyskinesia (characterized by rhythmic, involuntary movements primarily of the tongue and/or face), NMS, seizures

OVERDOSAGE AND MANAGEMENT
Experience with amisulpride in overdosage is limited. There have been reports of exaggeration of the known pharmacological and adverse effects of amisulpride. Symptoms include drowsiness, 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 intake should be considered.
There is no specific antidote to amisulpride. Appropriate supportive measure should be instituted with close observation of vital functions including continuous cardiac monitoring because of the risk of prolongation of QT interval. If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.
Hemodialyis is not recommended as a method of elimination since amisulpride is weakly dialyzed.

STORAGE CONDITION
Store at temperatures not exceeding 30°C. Keep the product out of reach and sight of children.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Amisulpride (Amiabel) 200 mg Film-Coated Tablet **-** Alu / Clear PVC Blister Pack x 10's (Box of 30's) **-** DR-XY41219
Amisulpride (Amiabel) 400 mg Film-Coated Tablet **-** Alu / Clear PVC Blister Pack x 10's (Box of 30's) **-** DR-XY41217

Trusted Quality Healthcare

CAUTION
Foods, Drugs, Devices, and Cosmetics Act
Prohibits dispensing without prescription.

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