APO-AMISULPRIDE

Amisulpride 50mg, 100mg & 200mg tablets and 400mg film-coated tablets

Presentation
APO-AMISULPRIDE 50mg are white to off-white, 6.0mm, round, biconvex tablets, with break line on one side.

APO-AMISULPRIDE 100mg are white to off-white, 8.0mm, round, flat tablets, with break line on one side.

APO-AMISULPRIDE 200mg are white to off-white, 11.0mm, round, flat tablets, with break line on one side.

APO-AMISULPRIDE 400mg are white to off-white, 18.0mm long and 8.0mm wide, capsule shaped tablets, with break line on one side.

Indications
Apo-Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterized by predominant negative symptoms.

Dosage and Administration
For acute psychotic episodes, oral doses between 400mg/day and 800mg/day are recommended. In individual cases, the daily dose may be increased up to 1200mg/day. Doses above 1200mg/day have not been extensively evaluated for safety and therefore should not be used. Doses above 800mg/day have not been shown to be superior to lower doses and may increase the incidence of adverse events. No specific titration is required when initiating the treatment with amisulpride. Doses should be adjusted according to individual response.

Doses should preferably be administered before meals.

Amisulpride should be administered b.i.d for doses above 400mg.

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 characterised by predominant negative symptoms, oral doses between 50mg/day and 300mg/day are recommended. Doses should be adjusted individually.

Elderly:
Amisulpride should be used with particular caution because of a possible risk of hypotension or sedation.

Children:
Amisulpride is contra-indicated in children up to puberty 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 (CR\textsubscript{CL}) between 30-60mL/min and to a third in patients with CR\textsubscript{CL} between 10-30mL/min. As there is no experience in patients with severe renal impairment (CR\textsubscript{CL} <10mL/min) particular care is recommended in these patients (see WARNINGS AND PRECAUTIONS).

Hepatic insufficiency:
Since amisulpride is weakly metabolised, a dosage reduction should not be necessary (see WARNING AND PRECAUTIONS).

Maximum Tolerated Daily Dose
1200mg/day

Contraindications
Hypersensitivity to the active ingredient or to other ingredients of the product.

Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer.

Phaeochromocytoma.

Children up to puberty.

Lactation.

In combination with the following medication which could induce torsades de pointes:
- Class Ia antiarrhythmic agents such as quinidine and disopyramide
- Class III antiarrhythmic agents such as amiodarone and sotalol
- Other medications such as bepridil, cisapride, sulitopride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin.

Levodopa; reciprocal antagonism between levodopa and neuroleptics (See INTERACTIONS WITH OTHER MEDICINES).

In hepatic impairment, amisulpride may be contraindicated to avoid the possible risk of adverse events due to an influence of the disease on amisulpride metabolism.

Warnings and Precautions
Neuroleptic Malignant Syndrome (NMS) is a potentially fatal syndrome that has been reported in association with anti-psychotic medicines, including amisulpride. Neuroleptic malignant syndrome is characterised by hyperthermia, muscle rigidity, autonomic instability, and elevated CPK, may occur. In the event of any symptoms which could suggest NMS, in particular hyperthermia, particularly with high daily doses, all antipsychotic medicines including amisulpride should be discontinued.

Hyperglycemia 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 renal insufficiency, the dose should be decreased and intermittent treatment should be considered (see DOSAGE AND ADMINISTRATION).

There is limited data on the potential for renally-cleared medicines to interfere with the clearance of amisulpride. Therefore, amisulpride should be used with caution with other renally excreted medicines, including lithium (see INTERACTIONS WITH OTHER MEDICINES).

The impact of hepatic impairment on hepatic metabolism and hepato-biliary excretion of amisulpride has not been studied. Amisulpride should be used with caution in patients with moderate or severe hepatic impairment.

Amisulpride can lower the seizure threshold. Therefore patients with a history of seizures should be closely monitored during amisulpride therapy.

In elderly patients, amisulpride therapy, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension or sedation.

Withdrawal symptoms have been described after abrupt cessation of high therapeutic doses of antipsychotic drugs. The emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported with amisulpride. Therefore, gradual withdrawal of amisulpride is advisable.

Leucopenia, 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.

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.

Amisulpride causes an increase in plasma prolactin levels which is reversible after discontinuation of the medicine. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, orgasmic dysfunction and impotence.

Acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent.

Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia. 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 50-300mg/day.

Tardive dyskinesia characterised 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.
Prolongation of QT Interval
Amisulpride produces a dose-dependent prolongation of the QT interval (see ADVERSE EFFECTS). This effect is known to potentiate the risk of occurrence of serious ventricular arrhythmias such as torsades de pointes. Before any administration, and if possible according to the patient’s clinical status, it is recommended to monitor factors which could favour the onset of this rhythm disorder, for example:
  - Bradycardia less than 55bpm
  - Electrolyte imbalance, in particular hypokalaemia
  - Congenital prolongation of the QT interval
  - On-going treatment with a medication likely to produce pronounced bradycardia (<55 bpm), hypokalaemia, slowing of the intracardiac conduction, or prolongation of the QTc interval (see INTERACTIONS WITH OTHER MEDICINES).

Stroke
In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic medicines, 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 medicines, 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. Although the causes of death in clinical trials with atypical antipsychotics 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.

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

Suicide
The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder and close supervision of high-risk patients should be accompany therapy.

Use in Pregnancy
Category B3
There was no evidence of teratogenicity in embryo foetal development studies in mice and rabbits following oral doses of up to 2 (mice) and 4 (rabbits) times the maximum recommended human dose based on body surface area, administered daily during the period of organogenesis. Oral treatment of female rats from prior to mating to late gestation or weaning, achieving systemic drug exposure (plasma AUC) similar to that in humans at the maximum dose, was associated with increased preimplantation loss, slight impairment of ossification and reduced pup weight gain to weaning. Teratogenicity was not observed. The safety of
amisulpride during human pregnancy has not been established, and therefore use of this medicine is not recommended during pregnancy unless the benefits justify the potential risks.

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.

**Use in Lactation**
It is not known whether amisulpride or its metabolites are excreted in animal or human breast milk. Breast-feeding is therefore contraindicated during amisulpride treatment.

**Effects on ability to drive and use machines**
Likely to produce minor or moderate adverse effects on the ability to drive or use machinery. Even used as recommended, amisulpride may affect reaction time and/or cause somnolence so that the ability to drive vehicles or operate machinery can be impaired.

**Paediatric use**
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, the use of amisulpride is contraindicated (see **CONTRAINDICATIONS**).

**Other**

**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 (200mg/kg/day) and dog (120mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the mouse (up to 120mg/kg/day) and in the rat (up to 240mg/kg/day), corresponding for the rat to 1.5 to 4.5 times the expected human AUC.

Reproductive studies performed in the rat, rabbit and mouse did not show any teratogenic potential.

**Carcinogenicity, Mutagenicity and Impairment of Fertility**
In carcinogenicity studies, amisulpride was administered in the diet of mice and rats for up to two years. Treatment of mice was associated with increases in malignant mammary gland tumours and pituitary adenomas in females at all dose levels, but there was no tumourigenic response in males (doses were equivalent to 0.1, 0.2 and 0.5 times the maximum human dose of 1200mg/day on a body surface area basis). Treatment of rats resulted in increased incidences of malignant mammary gland tumours in both sexes, malignant pituitary tumours and adrenal medullary phaeochromocytomas in males, and malignant pancreatic islet cell tumours in both sexes, at doses achieving lower systemic drug exposure (plasma AUC) than in humans at the maximal recommended dose. Increases in mammary gland, pituitary, adrenal and pancreatic
endocrine tumours in rodents have been reported for other antipsychotic medicines, and are considered to result from increased prolactin secretion.

The relevance of prolactin-mediated endocrine tumours in rodents for human risk is unknown. In clinical trials, amisulpride substantially elevated plasma prolactin concentrations, although to date neither clinical nor epidemiological studies have shown an association between chronic administration of neuroleptic medicines and mammary tumourigenesis. However, since tissue culture experiments indicate that about one-third of human breast cancers are prolactin dependent in vitro, amisulpride should be used cautiously in patients with previously-detected breast cancer or in patients with pituitary tumours (see CONTRAINDICATIONS).

Amisulpride showed no genotoxicity in in vitro tests for bacterial gene mutation, or in in vitro and in vivo tests for clastogenic activity.

Male rat fertility was unaffected by an amisulpride oral dose resulting in systemic drug exposure (plasma AUC) similar to that in humans, when treatment was carried out prior to mating. Female rat mating was reduced by concurrent amisulpride treatment, but it was normalised within days of cessation of dosing with overall fertility being unaffected, although some adverse effects were observed (see Use in Pregnancy).

### Adverse 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 Trial 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.

<table>
<thead>
<tr>
<th>Nervous System Disorders:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common:</strong></td>
<td>Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, 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 50-300mg/day.</td>
</tr>
<tr>
<td><strong>Common:</strong></td>
<td>Acute dystonia (spasm torticolis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an anti-parkinsonian agent.</td>
</tr>
<tr>
<td><strong>Uncommon:</strong></td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td>Tardive dyskinesia characterised by rhythmic, involuntary movements primarily of the tongue and/or face has been reported, usually after long-term administration. Anti-parkinsonian medication is</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Psychiatric Disorders:</th>
<th>ineffective or may induce aggravation of the symptoms. Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Insomnia, anxiety, agitation, orgasmic dysfunction</td>
</tr>
<tr>
<td>Gastrointestinal Disorders:</td>
<td>Constipation, nausea, vomiting, dry mouth</td>
</tr>
<tr>
<td>Endocrine Disorders:</td>
<td>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.</td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutritional Disorders:</td>
<td>Hyperglycaemia (see Precautions)</td>
</tr>
<tr>
<td>Uncommon:</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Disorders:</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Investigations:</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Common:</td>
<td>Elevations of hepatic enzymes, mainly transaminases</td>
</tr>
<tr>
<td>Uncommon:</td>
<td></td>
</tr>
<tr>
<td>Immune System Disorders:</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Uncommon:</td>
<td></td>
</tr>
</tbody>
</table>

Post-marketing Experience
In addition, cases of the following adverse reactions have been reported through spontaneous reporting only:

**Blood and Lymphatic system disorders:**
Leucopenia, neutropenia and agranulocytosis have been reported.

**Nervous System Disorders:**
Very rare cases of Neuroleptic Malignant Syndrome have been reported (see PRECAUTIONS), which is a potentially fatal complication.

**Cardiac Disorders:**
Cases of QT interval prolongation and ventricular arrhythmias such as torsades de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death, have been reported (see WARNINGS AND PRECAUTIONS).

**Vascular Disorders:**
Cases of venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis have been reported (see WARNING AND PRECAUTIONS).

**Skin and Subcutaneous Tissue Disorders:**
Angioedema and urticaria have been reported.

**Pregnancy, puerperium and perinatal conditions:**
Neonatal drug withdrawal syndrome has been reported.

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
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Interactions

Pharmacokinetics Interactions

Interactions with other medicines

A number of medicines can increase the risk of ventricular arrhythmias including *torsades de pointes*.

The use of the following medicines is contraindicated:

- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.
- Other medications such as bepridil, cisapride, sulproide, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin.
- Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics

Caution is required with the use of the following medicines:

- Medicines which induce bradycardia, such as bradycardia-inducing calcium channel blockers (diltiazem, verapamil), beta-blockers, clonidine, guanfacine, digitalis.
- Medicines which can cause hypokalaemia, such as diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides.
- Neuroleptics such as thioridazine, chlorpromazine, trifluperazine, pimozide, haloperidol, imipramine antidepressants, lithium.

Concomitant use of amisulpride with other anti-psychotics may increase the risk of developing neuroleptic malignant syndrome.

Amisulpride may enhance the effects of alcohol.

Amisulpride may enhance the effects of the following medicines:

- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1-antihistamines, barbiturates, benzodiazepines and other anxiolytic medicines, clonidine and derivatives.
- Antihypertensive medicines and other hypotensive medications.

A placebo-controlled study of concomitant use of lithium carbonate 500mg twice daily and a low dose of amisulpride (100mg) twice daily in healthy young male volunteers showed no effect of amisulpride on the pharmacokinetics of lithium. A small trend towards prolongation of the QTc interval was observed when lithium and amisulpride were co-administered but is not regarded as clinically important.

A study of the effect of concomitant use of cimetidine on amisulpride excretion has not been conducted.

*In vitro* studies using human liver microsomes and cryopreserved human hepatocytes did not show evidence of significant amisulpride metabolism. Based on these results, it is unlikely that drug interactions involving amisulpride would occur due to inhibition or induction of cytochrome P450–mediated metabolism.

Pharmacodynamic Interactions

Doses should preferably be administered before meals.
Overdosage

Symptoms
Experience with amisulpride in overdosage is limited. Exaggerations of the known pharmacological and adverse effects of amisulpride have been reported. These may include drowsiness, sedation, hypotension, extrapyramidal symptoms and coma.

Fatal outcomes have been reported mainly in combination with other psychotropic agents.

Treatment
In cases of acute overdose, the possibility of multiple drug intakes should be considered.

There is no specific antidote to amisulpride. Appropriate supportive measure should therefore be instituted: close supervision of vital functions and, because of the risk of prolongation of QT interval, continuous cardiac monitoring until the patient recovers.

If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.

Since amisulpride is weakly dialysed, haemodialysis is not recommended as a method of elimination.

Contact the Poisons Information Centre for advice on management of overdosage.

Further Information

Actions

Class
Neuroleptic of the benzamide class

Pharmacodynamics

Amisulpride binds selectively to the human dopaminergic D₂ (Ki 2.8nM) and D₃ (Ki 3.2nM) receptor subtypes without any affinity for D₁, D₄ and D₅ receptor subtypes (Ki > 1µM). Unlike classical and atypical neuroleptics, amisulpride displays low affinity for serotonin, α-adrenergic, histamine receptor subtypes, muscarinic receptors and sigma sites.

In the rodent, it preferentially blocks post-synaptic D₂ receptors located in the limbic structures as compared to those in the striatum as indicated by its reversal of d-amphetamine-induced hyperactivity without affecting stereotypes. In addition, it does not induce catalepsy and it does not produce D₂ hypersensitivity after repeated treatment.

Moreover, it preferentially blocks pre-synaptic D₂/D₃ dopamine receptors, producing dopamine release responsible for its disinhibitory effects.

This atypical pharmacological profile may explain amisulpride's antipsychotic effect at higher doses through post-synaptic dopamine receptor blockade located in the limbic areas and its efficacy against negative symptoms, at lower doses, through presynaptic dopamine receptor blockade. In addition, the reduced tendency of amisulpride to produce extrapyramidal side effects may be related to its preferential limbic activity.
Pharmacokinetics
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±4ng/mL after a 50mg dose.

The volume of distribution is 5.8L/kg. As plasma protein binding is low (16%), drug interactions due to displacement are unlikely.

The absolute bioavailability of amisulpride tablets is 48%.

Bioequivalence between the solution and the 200mg tablet has been demonstrated ($C_{\text{max}}$ mean ratio 0.95, 90% confidence interval 0.81-1.12; $AUC_{0-\infty}$ mean ratio 0.89, 90% confidence interval 0.81-0.97). However, bioequivalence has not been demonstrated between the solution and the 400mg tablet ($C_{\text{max}}$ mean ratio 0.88, 90% confidence interval 0.75-1.04; $AUC_{0-\infty}$ mean ratio 0.86, 90% confidence interval 0.78-0.94).

Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Fifty percent of an intravenous dose is excreted via the urine, the majority as unchanged drug. Ninety percent of the intravenous dose is eliminated in the first 24 hours. Renal clearance is in the order of 20L/h or 330mL/min.

Following a single intravenous dose, about 20% of the dose was recovered from the faeces, about 70% of which was as unchanged amisulpride. Hepatic metabolism has a limited role in healthy patients.

A high-carbohydrate low-fat meal (14g protein, 8g fat, 108g CHO) significantly decreases the AUC, $T_{\text{max}}$ and $C_{\text{max}}$ 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.

Hepatic insufficiency: See WARNINGS AND PRECAUTIONS.

Renal insufficiency: In patients with renal insufficiency 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 50mg.

Amisulpride is very weakly dialysed.

Limited pharmacokinetic data in elderly subjects (>65 years) show that a 10-30% rise occurs in $C_{\text{max}}$, $T_{1/2}$ and AUC after a single oral dose of 50mg. No data are available after repeat dosing.

Other
Clinical Trials
The efficacy of amisulpride in the treatment of schizophrenia has been established on the basis of eleven phase II and III studies conducted in 20 countries and involving 1933 patients (1247 treated with amisulpride) belonging to two distinct populations:
patients with acute exacerbations of schizophrenia
patients with predominant negative schizophrenia

These studies form the basis of the registration documentation for amisulpride. Seven of them are considered pivotal for efficacy and their results are summarized below.

**Acute exacerbations of schizophrenia**
In four well-controlled double-blind studies versus reference medicines in patients with acute schizophrenia according to DSM III-R and DSM-IV criteria, amisulpride was at least as effective as haloperidol, flupenthixol and risperidone. In addition to its global antipsychotic activity, amisulpride significantly alleviated secondary negative symptoms as well as affective symptoms such as depressed mood and retardation.

1. A 4-week double-blind active-controlled trial (n=319) compared four fixed doses of amisulpride (100mg/day, 400mg/day, 800mg/day and 1200mg/day) and a fixed dose of haloperidol (16mg/day). A dose response relationship was clearly established in comparison to 100mg/day, chosen as a potentially subtherapeutic dose in acute schizophrenia. Amisulpride at doses of 400 and 800mg/day statistically significantly improved positive symptoms (BPRS total score, PANSS positive symptoms subscale) compared with amisulpride 100mg/day. 800mg/day of amisulpride was also statistically significantly superior to 100mg/day for response rates based on the CGI.

2. Efficacy results were similar in the three other short-term controlled studies where 800mg/day of amisulpride was compared with 20mg/day of haloperidol (n=191), 1000mg/day of amisulpride with 25mg/day of flupenthixol (n=132) and 800mg/day of amisulpride with 8mg of risperidone (n=228). On BPRS total score and PANSS positive subscale, amisulpride was not found to be different from haloperidol and flupenthixol and showed equivalent efficacy to risperidone. Additionally, amisulpride significantly improved the response rate with CGI versus haloperidol.

**Predominant negative schizophrenia**
Three pivotal trials were conducted versus placebo in schizophrenic patients with predominant negative symptoms according to DSM III and DSM III-R, showing that low doses of amisulpride are active against negative symptoms.

1. In a six-week dose finding study (n=104), amisulpride 100mg/day and 300mg/day were significantly better than placebo on the basis of the SANS total score.

2. In an additional 3-month dose finding study (n=242) testing two fixed dose of amisulpride (50mg/day and 100mg/day) versus placebo, both doses of amisulpride were significantly more active in improving the negative symptoms than placebo on the SANS total score. Additionally, there was a significant improvement of the MADRS scores in the two amisulpride groups.

3. A medium-/long-term placebo controlled study with amisulpride 100mg/day over 6 months with the possibility of extension up to 12 months was conducted to demonstrate the maintenance of efficacy over time. Amisulpride improved negative symptoms (SANS total score) significantly compared with placebo, and the response rate with CGI was significantly higher in the amisulpride group versus placebo. The results were confirmed...
by the significant improvement of global functioning measured with the GAF. SANS total score remained stable over time up to 12 months, indicating that 100mg/day not only maintains the improvement of negative symptoms but has also an effect on preventing the recurrence of positive symptoms.

Amisulpride is a white to off-white powder, which is practically insoluble in water, sparingly soluble in ethanol, soluble in methanol and freely soluble in dichloromethane.

Non-proprietary Name: Amisulpride
Chemical Name: (R,S)-4-Amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-ethylsulfonyl-2-methoxybenzamide
Molecular Weight: 369.48
Molecular Formula: C_{17}H_{27}N_{3}O_{4}S
CAS Number 71675-85-9

APO-AMISULPRIDE Tablets contain amisulpride (50mg, 100mg, 200mg and 400mg) and the following excipients:

List of excipients
50mg, 100mg and 200mg tablets contain: Lactose monohydrate, Methylcellulose, Sodium starch glycolate (Type A), Microcrystalline Cellulose and Magnesium stearate

400mg tablets contain: Lactose monohydrate, Methylcellulose, Sodium starch glycolate (Type A), Microcrystalline Cellulose Magnesium stearate, Eudragit E100, Titanium dioxide, Talc and Macrogol 6000

Each Tablet:
Contains lactose. Gluten free

Pharmaceutical Precautions
Instructions for Handling
Nil

Incompatibilities
Interactions with other medicines
The use of the following medicines is contraindicated:
- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.
- Other medications such as bepridil, cisapride, sulfoxpride, thioridazine, methadone,
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- intravenous, erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin.
- Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics

Caution is required with the use of the following medicines:
- Medicines which induce bradycardia, such as bradycardia-inducing calcium channel blockers (diltiazem, verapamil), beta-blockers, clonidine, guanfacine, digitalis.
- Medicines which can cause hypokalaemia, such as diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides.
- Neuroleptics such as thioridazine, chlorpromazine, trifluperazine, pimozide, haloperidol, imipramine antidepressants, lithium.

Concomitant use of amisulpride with other anti-psychotics may increase the risk of developing neuroleptic malignant syndrome.

Amisulpride may enhance the effects of alcohol.

Amisulpride may enhance the effects of the following medicines:
- CNS depressants including narcotics, anaesthetics, analgesics, sedative H1-antihistamines, barbiturates, benzodiazepines and other anxiolytic medicines, clonidine and derivatives.
- Antihypertensive medicines and other hypotensive medications.

Shelf-Life
Shelf life: 3 years from the date of manufacture.

Special Precautions for Storage
Store at or below 25°C
Protect from heat light and moisture.

Package Quantities
<table>
<thead>
<tr>
<th>APO-AMISULPRIDE</th>
<th>50mg</th>
<th>Blisters containing 60, 90 or 100 tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100mg</td>
<td>Blisters containing 30, 50, 60, 90 or 100 tablets</td>
</tr>
<tr>
<td></td>
<td>200mg</td>
<td>Blisters containing 50, 60, 90 or 100 tablets</td>
</tr>
<tr>
<td></td>
<td>400mg</td>
<td>Blisters containing 10, 50, 60, 90 or 100 tablets</td>
</tr>
</tbody>
</table>

Medicine Schedule
Prescription Medicine

Sponsor Details
Apotex NZ Ltd
32 Hillside Road
Glenfield
Private Bag 102-995
North Shore Mail Centre

Please refer to Medsafe website (www.medsafe.govt.nz) for the most recent datasheet
APO-AMISULPRIDE
Amisulpride 50mg, 100mg & 200mg tablets
and 400mg film-coated tablets

Auckland
Telephone: (09) 444 2073
Fax: (09) 444 2951

Date of Preparation
15 October 2013