NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Amisulpride (Max Health) 50mg tablets
Amisulpride (Max Health) 100mg tablets
Amisulpride (Max Health) 200mg tablets
Amisulpride (Max Health) 400mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amisulpride 50mg tablet: Each tablet contains 50mg of amisulpride
Amisulpride 100mg tablet: Each tablet contains 100g of amisulpride
Amisulpride 200mg tablet: Each tablet contains 200mg of amisulpride
Amisulpride 400mg tablet: Each tablet contains 400mg of amisulpride

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet (50mg, 100mg, 200mg)
Film coated tablet (400mg)

Amisulpride 50 mg tablets are white to off-white 6.0mm, round bi-convex tablets with break line on one side and embossed with A50 on the other side. The tablets can be divided into equal halves.

Amisulpride 100 mg tablets are white to off-white 8.0mm, round flat tablets with break line on one side and embossed with A100 on the other side. The tablets can be divided into equal halves.

Amisulpride 200 mg tablets are white to off-white 11.00mm, round flat tablets with break line on one side and embossed with A200 on the other side. The tablets can be divided into equal halves.

Amisulpride 400 mg white to off white, 18 x 8mm capsule shaped, film-coated tablets with break line on one side. The tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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 characterised by predominant negative symptoms.

4.2 DOSE AND METHOD OF ADMINISTRATION

For acute psychotic episodes, oral doses between 400 mg/d and 800 mg/d are recommended. In

individual cases, the daily dose may be increased up to 1200 mg/d. Doses above 1200 mg/d have not been extensively evaluated for safety and therefore should not be used. Doses above 800 mg/d 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 twice daily for doses above 400 mg.

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 50 mg/d and 300 mg/d 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 tohalf in patients with creatinine clearance (CRCL) between 30-60 mL/min and to a third in patientswith 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 (see Section 4.4).

Hepatic Insufficiency:

Since amisulpride is weakly metabolised, a dosage reduction should not be necessary (see Section 4.4).

4.3 CONTRAINDICATION

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, sultopride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin.

Levodopa; reciprocal antagonism between levodopa and neuroleptics (see Section 4.5).

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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 Section 4.2).

There are 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 Section 4.5).

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.

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.

Caution should be also exercised when prescribing amisulpride to patients with Parkinson'sdisease 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 reversiblewithout 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 section 4.8). 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 55 bpm
- 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 Section 4.8).

Sleep Apnoea

No cases of sleep apnoea clearly attributed to amisulpride have been reported and no epidemiology studies can substantiate this. However, sleep apnoea and related disorders have been reported in patients treated with other antipsychotic medicines, with or without prior historyof sleep apnoea, in patients with or without concomitant weight-gain. Patients who have a historyof or are at risk for sleep apnoea, or who are concomitantly using central nervous system depressants, should be medically monitored.

Suicide

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

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.

Benign Pituitary Tumour

Amisulpride may increase prolactin levels. Cases of benign pituitary tumours, such as prolactinoma, have been observed during amisulpride therapy. In case of very high levels of prolactin or clinical signs of pituitary tumour (such as visual field defect and headache), pituitary imaging should be performed. If the diagnosis of pituitary tumour is confirmed, the treatment with amisulpride must be stopped (see Section 4.3).

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 Section4.3).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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

The use of the following medicines is contraindicated:

Medications 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, sultopride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin.

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

The use of the following medicines is not recommended:

- Amisulpride may enhance the effects of alcohol.
- Medications which enhance the risk of torsades de pointes or could prolong the QTinterval:
- 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. Hypokalaemia should be corrected.
- Neuroleptics such as thioridazine, chlorpromazine, trifluperazine, pimozide, haloperidol, imipramine antidepressants, lithium.

The use of the following medicines should be taken into account:

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

Co-administration of amisulpride and clozapine may lead to an increase in plasma levels of amisulpride.

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 500 mg twice daily and a low dose of amisulpride (100 mg) 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 cytochromeP450 –mediated metabolism.

4.6 PREGNANCY AND LACTATION

Pregnancy (Category B3)

There was no evidence of teratogenicity in embryofoetal development studies in mice and rabbits following oral doses vehicle 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 symptomsthat 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.

Lactation

It is not known whether amisulpride or its metabolites are excreted in animal or human breastmilk. Breast-feeding is therefore contraindicated during amisulpride treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Even used as recommended, amisulpride may affect reaction time and/or cause somnolence and blurred vision 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).

The following adverse reactions have been observed in controlled clinical trials and through spontaneous reporting:

Blood and Lymphatic System Disorders:

Uncommon:	Leukopenia, neutropenia
Rare:	Agranulocytosis (see Section 4.4)

Immune System Disorders:

Uncommon: Allergic reactions

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

Rare: Benign pituitary tumour such as prolactinoma (see Section 4.3 and Section 4.4)

Metabolism and Nutritional Disorders:

Uncommon: Hyperglycaemia (see Section 4.4), hypertriglyceridaemia and hypercholesterolaemia

Rare: Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Psychiatric Disorders:

Common: Insomnia, anxiety, agitation, orgasmic dysfunction

Uncommon: Confusion

Nervous System Disorders:

Very common: Extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mildat 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

Common: Acute dystonia (spasm torticolis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an anti parkinsonian agent. Somnolence.

Uncommon: 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 ineffective or may induce aggravation of the symptoms. Seizures.

Rare: Neuroleptic Malignant Syndrome (see Section 4.4), which is a potentially fatal complication.
Somnambulism (sleepwalking) and related behaviours including sleep-related eating disorder have been reported with the use of atypical antipsychotic medicines, including amisulpride.

Eye Disorders:

Common: Blurred vision (see Section 4.7)

Cardiac Disorders:

Common: QT interval prolongation

Uncommon:	Bradycardia
Rare:	Ventricular arrhythmias such as torsades de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest,sudden death, have been reported (see Section 4.4).

Vascular Disorders:

Common:	Hypotension
Uncommon:	Increase in blood pressure
Rare:	Venous thromboembolism, including pulmonary embolism, sometimesfatal, and deep vein thrombosis (see Section 4.4).

Respiratory, Thoracic and Mediastinal Disorders:

Uncommon:	Nasal congestion, pneumonia aspiration (mainly in association with other antipsychotics).

Gastrointestinal Disorders:

Common:	Constipation, nausea, vomiting, dry mouth

Skin and Subcutaneous Tissue Disorders:

Rare:	Angioedema and urticaria

Musculoskeletal and Connective Tissue Disorders:

Uncommon:	Osteopenia and osteoporosis

Renal and Urinary Disorders:

Uncommon:	Urinary retention

Injury, poisoning and procedural complications:
Fall as a consequence of adverse reactions compromising body balance has been reported.

Pregnancy, Puerperium and Perinatal Conditions:
Neonatal drug withdrawal syndrome has been reported.

Investigations:

Common:	Weight gain
Uncommon:	Elevations of hepatic enzymes, mainly transaminases

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Symptoms

Experience with amisulpride in overdosage is limited. Exaggeration of the known pharmacological and adverse effects of amisulpride have been reported. These may includedrowsiness, 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 intake 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.

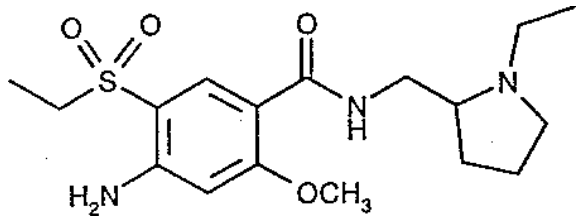
If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

CHEMICAL STRUCTURE



Chemical Name: (R, S)-4-Amino-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-ethylsulfonyl-2-methoxybenzamide

Molecular Weight: 369.48

Molecular Formula: $C_{17}H_{27}N_3O_4S$

CAS Number: 71675-85-9

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.

5.1 PHARMACODYNAMIC PROPERTIES

Neuroleptic of the benzamide class.

Amisulpride binds selectively to the human dopaminergic D2 (Ki 2.8 nM) and D3 (Ki 3.2 nM) receptor subtypes without any affinity for D1, D4 and D5 receptor subtypes (Ki > 1 μM). 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 stereotypies. 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 effectsmay be related to its preferential limbic activity.

5.2 PHARMACOKINETIC PROPERTIES

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.

The volume of distribution is 5.8 L/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 200 mg tablet has been demonstrated (Cmax mean ratio 0.95, 90% confidence interval 0.81-1.12; AUC0-∞ mean ratio 0.89, 90% confidence interval 0.81-0.97). However, bioequivalence has not been demonstrated between the solution and the 400 mg tablet (Cmax mean ratio 0.88, 90% confidence interval 0.75-1.04; AUC0-∞ 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 inthe order of 20 L/h or 330 mL/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 (14 g protein, 8 g fat, 108 g CHO) significantly decreases the AUC, 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.

Hepatic insufficiency: see Section 4.4.

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 greaterthan 50 mg.

Amisulpride is very weakly dialysed.

Limited pharmacokinetic data in elderly subjects (>65 years) show that a 10-30% rise occurs in Cmax, T½ and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

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 (100 mg/d, 400 mg/d, 800 mg/d and 1200 mg/d) and a fixed dose of haloperidol (16 mg/d). A dose response relationship was clearly established in comparison to 100 mg/d, chosen as a potentially subtherapeutic dose in acute schizophrenia. Amisulpride at doses of 400 and 800mg/d statistically significantly improved positive symptoms (BPRS total score, PANSS positive symptoms subscale) compared with amisulpride 100 mg/d. 800 mg/d of amisulpride was also statistically significantly superior to 100 mg/d for response rates based on the CGI.

2. Efficacy results were similar in the three other short-term controlled studies where 800 mg/d of amisulpride was compared with 20 mg/d of haloperidol (n=191), 1000 mg/d of amisulpride with 25 mg/d of flupenthixol (n=132) and 800 mg/d of amisulpride with 8 mg 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 versushaloperidol.

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 100 mg/d and 300 mg/d 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(50 mg/d and 100 mg/d) 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 100 mg/d 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 100 mg/d not only maintains the improvement of negative symptoms but has also an effect on preventing the recurrence of positive symptoms.

5.3 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 mouse (up to 120 mg/kg/d) and in the rat (up to 240 mg/kg/d), 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 teratogenicpotential.

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 1200 mg/dayon 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 Section 4.3).

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 Section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Amisulpride tablets contain the following excipients:

50, 100 and 200 mg tablets:
Lactose monohydrate
Methylcellulose
Sodium starch glycolate (Type A)
Microcrystalline cellulose
Magnesium stearate

400 mg tablets:
Core:
Lactose monohydrate
Methylcellulose
Sodium starch glycolate (Type A)
Microcrystalline cellulose
Magnesium stearate

Coating:
Eudragit (E100)
Titanium dioxide
Talc
Magnesium stearate
Macrogol 6000

6.2 INCOMPATIBILITIES

None known.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C

Protect from heat light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

50mg: Blister pack containing 30, 60, 90, 100 tablets
100mg: Blister pack containing 30 50, 60, 90, 100 tablets
200mg: Blister pack containing 50, 60, 90, 100 tablets
400mg: Blister pack containing 10, 50, 60, 90, 100 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Max Health Ltd
PO Box 44452
Pt Chevalier, Auckland 1246

Telephone: (09) 815 2664.

9 DATE OF FIRST APPROVAL

21 September 2023

10 DATE OF REVISION OF THE TEXT

21 September 2023

SUMMARY OF CHANGES

Section changed	Summary of new information
All	New data sheet