Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dolmatil 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg sulpiride.

Excipient: Lactose 23mg/tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Product imported from the UK:
Plain white round tablets with 'D200' on one side and a breakline on the other. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acute and chronic schizophrenia.

4.2 Posology and method of administration

Adults
A starting dose of 400 mg to 800 mg daily, given as one or two tablets daily (morning and early evening) is recommended.

Predominantly positive symptoms (formal thought disorder, hallucinations, delusions, incongruity of affect) respond to higher doses, and a starting dose of at least 400 mg twice daily is recommended, increasing if necessary up to a suggested maximum of 1200 mg twice daily. Increasing the dose beyond this level has not been shown to produce further improvement.

Predominantly negative symptoms (flattening of affect, poverty of speech, anergia, apathy), as well as depression, respond to doses below 800 mg daily; therefore, a starting dose of 400 mg twice daily is recommended. Reducing this dose towards 200 mg twice daily will normally increase the alerting effect of Dolmatil.

Patients with mixed positive and negative symptoms, with neither predominating, will normally respond to dosage of 400-600 mg twice daily.

Children
Clinical experience in children under 14 years of age is insufficient to permit specific recommendations.

Elderly
The same dose ranges may be required in the elderly, but should be reduced if there is evidence of renal impairment.

4.3 Contraindications

Phaeochromocytoma and acute porphyria. Hypersensitivity to the active ingredient or to other ingredients of the medicinal product.
Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer *(see section 4.8 Undersirable effects.)*
Association with levodopa *(see section 4.5 Interaction with other medicinal products and other forms of interaction).*

4.4 Special warnings and precautions for use

Increased motor agitation has been reported at high dosage in a small number of patients: in aggressive, agitated or excited phases of the disease process, low doses of Dolmatil may aggravate symptoms. Care should be exercised where hypomania is present.

Extrapyramidal reactions, principally akathisia and tremor have been reported in a small number of cases. If warranted, reduction in dosage or anti-parkinsonian medication may be necessary.

As with other neuroleptics, Neuroleptic Malignant Syndrome a potentially fatal complication, characterised by hyperthermia, muscle rigidity and autonomic dysfunction may occur. In case of hyperthermia of undiagnosed origin, sulpiride should be discontinued.

Dolmatil induces slight EEG modifications. Neuroleptics may lower the epileptogenic threshold and some cases of convulsions have been reported with sulpiride *(see section 4.8 Undesirable Effects)*. Therefore patients with a history of epilepsy should be closely monitored during sulpiride therapy.

In elderly patients, as with other neuroleptics, sulpiride should be used with particular caution *(See section 4.2 Posology and method of administration).*

In children, efficacy and safety of sulpiride have not been thoroughly investigated. Therefore, caution should be exercised when prescribing to children *(see section 4.2 Posology and method of administration).*

In patients with aggressive behaviour or agitation with impulsiveness, sulpiride could be given with a sedative.

When neuroleptic treatment is absolutely necessary in a patient with Parkinson’s disease, sulpiride can be used, although caution is in order.

In patients requiring Dolmatil who are receiving anti-convulsant therapy, the dose of the anti-convulsant should not be changed.

Cases of convulsions, sometimes in patients with no previous history, have been reported.

Dolmatil has no significant anticholinergic effect or cardiovascular activity. As with all drugs for which the kidney is the major elimination pathway, the dose should be reduced and titrated in small steps in cases of renal insufficiency.

Initiation of treatment in schizophrenia should only be undertaken by a specialist under whose regular supervision the patients should remain.

Prolongation of the QT interval:
Sulpiride may induce a prolongation of the QT interval *(see section 4.8 undesirable Effects)*. This effect is known to potentiate the risk of serious ventricular arrhythmias such as torsade 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 occurrence of this rhythm disorder, such as 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, decreased intracardiac conduction, or prolongation of the QTc interval *(see section 4.5 Interaction with other medicinal products and other forms of interactions.)*

Sulpiride should be prescribed with caution in patients presenting with these factors and patients with cardiovascular disorders which may predispose to prolongation of the QT interval.

Stroke:
In randomised 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 population of patients cannot be excluded. Sulpiride should be used with caution in patients with stroke risk factors.

Increased Mortality in Elderly people with Dementia:
Data from two large observational studies showed that elderly patients with dementia who are treated with antipsychotics are at small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. Dolmatil is not licensed for the treatment of dementia-related behaviour 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 Dolmatil and preventative measures undertaken.

As hyperglycaemia has been reported in patients treated with atypical antipsychotic agents, patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on sulpiride, should get appropriate glycaemic monitoring.

Avoid concomitant prescription of other antipsychotics.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Associations contra-indicated:
Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

Associations not recommended:
Alcohol: alcohol enhances the sedative effect of neuroleptics. Avoid the consumption of alcoholic beverages and drugs containing alcohol.

Combination with the following medications which could induce torsades de pointes or prolong the QT interval *(see section 4.4 Special Warnings and Precautions for Use)*:

- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine, guanfacine, digitalis.
- Medications which induce electrolyte imbalance, in particular those causing hypokalaemia (such as hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides). Hypokalaemia should be corrected.

Electrolyte imbalance should be corrected:

- Class Ia antiarrhythmic agents such as quinidine, disopyramide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Other medications such as pimozide, sultopride, haloperiol; imipramine antidepressants; lithium, bepridil, cisapride, thioridazine, methadone, IV erythromycin, IV vincamine, halofantrine, pentamidine, sparfloxacin.

Associations to be taken into account:
Antihypertensive agents: antihypertensive effect and possibility of enhanced postural hypotension (additive effect).

CNS depressants including: narcotics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.

Antacids or sucralfate: The absorption of sulpiride is decreased after co-administration. Therefore, sulpiride should be administered two hours before these drugs.

Lithium.

Dolmatil may modify response to metoclopramide therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy:
A decrease in fertility linked to the pharmacological effects of the drug (prolactin mediated effect) was observed in treated animals. Animals studies do not indicate direct of indirect harmful effects with respect to pregnancy, embryonal/foetal development, or and/or postnatal development. In human, very limited clinical data on exposed pregnancies are available. In most cases of foetal or neonatal disorders reported in the context of sulpiride use during pregnancy, alternative explanations can be suggested and seem more likely. Therefore, the use of sulpiride is not recommended during pregnancy because of the limited experience. If sulpiride is used during pregnancy, appropriate monitoring of the neonate should be considered in view of sulpiride safety profile.

Lactation:
Sulpiride has been found in breast milk in treated women. Therefore breast-feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

Even used as recommended, sulpiride may cause sedation so that the ability to drive vehicles or operate machinery can be impaired *(see section 4.8 Undesirable effects).*

4.8 Undesirable effects

Cardiovascular disorders:
- Postural hypotension.
- QT interval prolongation and ventricular arrhythmias sush as torsade de pointes, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest, sudden death *(see section 4.4 Special Warnings and Precautions for Use).*

Endocrine disorders:
- Hyperprolactinaemia.

General disorders and administration site conditions:
- As with all neuroleptics, malignant syndrome *(see Section 4.4 Special Warnings and Special Precautions for Use)* which is a potentially fatal complication.
- Weight gain.

Hepatobiliary disorders:
- Increase in hepatic enzymes.

Nervous system disorders:
- Sedation or drowsiness. Insomnia has been reported.
- Extrapyramidal symptoms and related disorders.
- Parkinsonism and related symptoms: tremor, hypertonia, hypokinesia, hypersalivation.
- Acute dyskinesia and dystonia (spasm torticollis, oculogyric crisis, trismus).
- Akathisia.

These symptoms are generally reversible upon administration of antiparkinsonian medication:
- Tardive dyskinesia (characterised by rhythmic, involuntary movements primarily of the tongue and/or the face) have been reported, as with all neuroleptics, after a neurolpetic administration of more than 3 months.
- Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.
- Convulsions have been reported. *(See Section 4.4 Special Warnings and Special Precautions for Use).*

Reproductive system and breast disorders: Disorders related to hyperprolactinaemia:
- Galactorrhoea.
- Amenorrhoea.
- Gynaecomastia.
- Breast enlargement and breast pain.
- Orgasmic dysfunction and erectile dysfunction.

Skin and subcutaneous tissue disorders:
- Maculo-papular rash.

Vascular Disorders:

- Venous thromboembolism, including pulmonary embolism, sometimes fatal and deep vein thrombosis - Frequency Unknown (See Section 4.4 Special Warnings and Special Precautions for Use)

4.9 Overdose

Experience with sulpiride in overdosage is limited.

In the event of an overdose, dyskinetic manifestations with spasmodic torticollis. protrusion of the tongue, and trismus may occur. Some patients may develop life-threatening parkinsonian manifestations and coma.

Sulpirde is partly removed by hemodialysis.

There is no specific antidote to sulpiride. Treatment is only symptomatic. Appropriate supportive measures should therefore be instituted, close supervision of vital functions and cardiac monitoring (risk of QT interval prolongation and subsequient ventricular arrhymias) is recommended until the patient recovers.

If severe extrapyramidal symptoms occur, anticholinergics should be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dolmatil is a member of the group of substituted benzamides, which are structurally distinct from the phenothiazines, butyrophenones and thioxanthenes. Current evidence suggests that the actions of Dolmatil hint at an important distinction between different types of dopamine receptors or receptor mechanisms in the brain.

Behaviourally and biochemically, Dolmatil shares with these classical neuroleptics a number of properties indicative of cerebral dopamine receptor antagonism. Essential and intriguing differences include lack of catalepsy at doses active in other behavioural tests, lack of effect in the dopamine sensitive adenylate cyclase systems, lack of effect upon noradrenaline or 5HT turnover, negligible anticholinesterase activity, no effect on muscarinic or GABA receptor binding, and a radical difference in the binding of tritiated sulpiride to striatal preparations in-vitro, compared to ^{3}H-spiperone or ^{3}H-haloperidol. These findings indicate a major differentiation between Dolmatil and classical neuroleptics which lack such specificity.
One of the characteristics of Dolmatil is its bimodal activity, as it has both antidepressant and neuroleptic properties. Schizophrenia characterised by a lack of social contact can benefit strikingly. Mood elevation is observed after a few days treatment, followed by disappearance of the florid schizophrenic symptoms. The sedation and lack of affect characteristically associated with classical neuroleptics of the phenothiazine or butyrophenone type are not features of Dolmatil therapy.

5.2 Pharmacokinetic properties

Peak sulpiride serum levels are reached 3-6 hours after an oral dose. The plasma half-life in man is approximately 8 hours. Approximately 40% sulpiride is bound to plasma proteins. 95% of the compound is excreted in the urine and faeces as unchanged sulpiride.

5.3 Preclinical safety data

In long-term animal studies with neuroleptic drugs, including sulpiride, an increased incidence of various endocrine tumours (some of which have occasionally been malignant) has been seen in some but not all strains of rats and mice studied. The significance of these findings to man is not known: there is no current evidence of any association between neuroleptic use and tumour risk in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch
Lactose
Methylcellulose
Magnesium stearate
Talc
Silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Blister strips of 10 tablets in an over-labelled outer carton.
Pack size: 100 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/167/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT