Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dolmatil 400mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400mg sulpiride.
Also contains 133.75mg lactose monohydrate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.
A white, stick shaped film-coated tablet with break-bar and engraved 'SLP 400' on one side.
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 substance or any of the excipients listed in section 6.1
Concomitant prolactin-dependent tumours e.g. pituitary gland prolactinomas and breast cancer (see section 4.8 Undesirable effects).

Association with levodopa or antiparkinsonian drugs (including ropinirole) (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.

A Neuroleptic Malignant Syndrome (NMS), a potentially fatal complication, reported to occur with antipsychotics is characterised by hyperthermia, muscle rigidity, rhabdomyolisis, elevated serum creatine phosphokinase levels and autonomic dysfunction. Cases with atypical features, such as hyperthermia without muscle rigidity or hypertonia, have been observed. In case of hyperthermia of undiagnosed origin, which may be considered either as an early sign/symptom of NMS or as an atypical NMS, sulpiride and all other antipsychotics should be discontinued promptly under medical supervision.

Dolmatil only 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.

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.

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including Dolmatil. Unexplained sore throat, lymphadenopathy, infections or fever may be evidence of blood dyscrasia (See section 4.8) and requires immediate haematological investigation.

Sulpiride has an anticholinergic effect and, therefore, should be used with caution in patients with a history of glaucoma, ileus, congenital digestive stenosis, urine retention or hyperplasia of the prostate.

Sulpiride should be used with caution in hypertensive patients, especially in the elderly population, due to the risk of hypertensive crisis. Patients should be adequately monitored.

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 is enhanced by the pre-existence of bradycardia, hypokalaemia, congenital or acquired long QT interval.

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 patients with Dementia:
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. 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. 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.
Dolmatil is not licensed for the treatment of dementia-related behaviour disturbances.

Venous thromboembolism:
Cases of venous thromboembolism, (VTE), sometimes fatal, 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.

Breast cancer
Sulpiride 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 sulpiride therapy (See Section 4.3).

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.

Sodium needs to be taken into consideration by patients on a controlled sodium diet.

Dolmatil should be used with caution in patients with a history of glaucoma, ileus, congenital digestive stenosis, urine retention or hyperplasia of the prostate.

4.5 Interaction with other medicinal products and other forms of interactions

Associations contra-indicated

Levodopa, antiparkinsonian drugs (including ropinirole): reciprocal antagonism of effects between levodopa or antiparkinsonian drugs (including ropinirole) 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.
- Class Ia antiarrhythmic agents such as quinidine, disopyramide.
- Class III antiarrhythmic agents such as amiodarone, sotalol.
- Other medications such as pimozide, sultopride, haloperidol; 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: lithium increases the risk of extrapyramidal adverse reactions. Discontinuation of both drugs is recommended at first signs of neurotoxicity.

Dolmatil may modify response to metoclopramide therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are only very limited data available from the use of sulpiride in pregnant women. The safety of sulpiride during human pregnancy has not been established.

Sulpiride crosses the placenta. Studies in animals are insufficient with respect to reproductive toxicity (see section 5.3).

The use of sulpiride is not recommended during pregnancy and in women of child bearing potential not using effective contraception, unless the benefits justify the potential risks.

Neonates exposed to antipsychotics, including Dolmatil, 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 (see Section 4.8). There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breastfeeding
Sulpiride is excreted into breastmilk in rather large amounts, far above the accepted value of 10% of the maternal weight-adjusted dosage in some cases, but blood concentrations in breastfed infants have not been evaluated. There is insufficient information on the effects of sulpiride in newborns/ infants.

A decision must be made whether to discontinue breast-feeding or to abstain from sulpiride therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

A decrease in fertility linked to the pharmacological effects of the drug (prolactin mediated effect) was observed in treated animals.

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

The following CIOMS frequency rating is used, when applicable:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders (see Section 4.4 Special warnings and precautions for use)
Uncommon: leukopenia
Not known: neutropenia, agranulocytosis

Immune system disorders
Not known: anaphylactic reactions: urticaria, dyspnea, hypotension, and anaphylactic shock

Endocrine disorders
Common: hyperprolactinaemia

Psychiatric disorders
Common: insomnia
Not known: confusion

Nervous system disorders
Common: sedation or drowsiness, extrapyramidal disorder, Parkinsonism, Tremor, Akathisia
Uncommon: hypertonia, dyskinesia, dystonia
Rare: oculogyric crisis
Not known: malignant neuroleptic syndrome, hypokinesia, tardive dyskinesia (have been reported, as with all neuroleptics, after a neuroleptic administration of more than 3 months. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms), convulsion

Cardiac disorders
Rare: ventricular arrhythmias, ventricular fibrillation, ventricular tachycardia
Not known: electrocardiogram QT prolonged, cardiac arrest, torsade de pointes, sudden death (see section 4.4)

Vascular disorders
Uncommon: orthostatic hypotension
Not known: venous embolism, pulmonary embolism, deep vein thrombosis (see section 4.4), increase in blood pressure (see section 4.4)

Respiratory, thoracic and mediastinal disorders:
Not known: pneumonia aspiration (mainly in association with other CNS depressants)

Metabolism and nutrition disorders:
Not known: hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Gastrointestinal disorders
Common: constipation
Uncommon: salivary hypersecretion

Hepatobiliary disorders
Common: hepatic enzyme increased
Not known: hepatocellular, cholestatic or mixed liver injury

Skin and subcutaneous tissue disorders
Common: maculo-papular rash

Musculoskeletal and connective tissue disorders
Not known: torticollis, trismus, rhabdomyolysis

Pregnancy, puerperium and perinatal conditions
Not known: extrapyramidal symptoms, drug withdrawal syndrome neonatal (see section 4.6)

Reproductive system and breast disorders
Common: breast pain, galactorrhoea
Uncommon: breast enlargement, amenorrhoea, orgasm abnormal, erectile dysfunction
Not known: gynaecomastia

General disorders and administration site conditions
Common: weight gain
Not known: hyperthermia (see section 4.4)

Investigations:
Not known: blood creatine phosphokinase increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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.
Fatal outcomes have been reported mainly in combination with other psychotropic agents.
Sulpride 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 subsequent ventricular arrhythmias) is recommended until the patient recovers.
If severe extrapyramidal symptoms occur, anticholinergics should be administrated.

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

Lactose Monohydrate
Sodium Starch Glycollate
Microcrystalline Cellulose
Hypromellose
Magnesium Stearate
Titanium Dioxide
Polyoxyl 40 Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Strip-wrapped in a moulded bubble blister pack in 200 μg PVC, heat sealed with 0.02 mm printed laminated aluminium foil.

Pack size: 100 tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/147/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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