**Doctor leaflet**

## 1. Name of the medicinal product
**Modal Capsules**
**Modal Forte Tablets**

## 2. Qualitative and quantitative composition
Active ingredient:
Each capsule of Modal contains sulpiride 50 mg.
Each tablet of Modal Forte contains sulpiride 200mg.

Modal Forte contains approximately 27 mg of lactose.
For full list of excipients, see section 6.1.

## 3. Pharmaceutical form
Modal: Capsules
Modal Forte: Tablets

## 4. Clinical particulars

### 4.1 Therapeutic indications
Modal Capsules:
Anti - dopaminergic agent for use in vertigo and prepsychotic states.
Modal Forte Tablets:
Anti-dopaminergic agent.
1) For use in vertigo and prepsychotic states.
2) At high doses - in psychiatric patients for treatment of depression and apathy.

### 4.2 Posology and method of administration

## Vertigo
Average dosage:
The treatment is initiated with low dosages in adults, with 50-100mg per day, in divided doses.
As a rule, the maintenance dose for adults is 150-300 mg per day, in divided doses.
Severe cases:
The dosage may be increased. The duration of treatment should not be less than 15 days and should be continued for several weeks if necessary.

## Psychiatry
Initial dose of 200-400 mg twice daily, increasing if necessary to a maximum of 1200 mg twice daily. Maintenance dose 600-800 mg per day in divided doses.
Psychiatry - Elderly:
The same dose ranges may be required in the elderly, but, as a general rule with the use of psychotropics in elderly patients, starting doses should be lower and increased gradually, particularly in those with renal impairment.
Psychiatry - Children aged above 6 years old:
3-5 mg/kg body weight/day in devided doses

Renal Failure*:*
Sulpiride is primarily excreted renally, and dose adjustments have been suggested in renal insufficiency.
- creatinine clearance 30 to 60 mL/minute – 50% of normal dose
- creatinine clearance 10 to 30 mL/minute – 30% of normal dose
- creatinine clearance <10 mL/minute – 20% of normal dose.

**4.3 Contraindications**
Phaeochromocytoma and acute porphyria.
Hypersensitivity to sulpiride or to any of the excipients.
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 Interactions with other medicinal products and other forms of interaction).

**4.4 Special warnings and precautions for use**
**Warnings:**
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 sulpiride may aggravate symptoms. Care should be exercised where hypomania is present.

Extrapyramidal reactions, principally akathisia 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, which is characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK levels, has been reported. In such an event, or in the event of hyperthermia of undiagnosed origin, all antipsychotic drugs, including sulpiride, should be discontinued.

Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects.

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

Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) have been reported. Therefore, gradual withdrawal is advisable.

Increased Mortality in Elderly people with dementia:
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a 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.

Sulpiride is not licenced for the treatment of dementia-related behavioural 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 sulpiride and preventative measures undertaken.

**Precautions:**
In elderly patients, as with other neuroleptics, sulpiride should be used with particular caution (see section 4.2).

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

Neuroleptics may lower the epileptogenic threshold. Cases of convulsions, sometimes in patients with no previous history, have been reported with sulpiride. Caution is advised in prescribing it for patients with unstable epilepsy, and patients with a history of epilepsy should be closely monitored during therapy with sulpiride.

In patients requiring sulpiride 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.

Sulpiride has no significant anticholinergic effect.

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.

Prolongation of the QT interval:
Sulpiride induces a prolongation of the QT interval (see section 4.8). 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, 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)
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.

Avoid concomitant treatment with other neuroleptics (see section 4.5).

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 populations of patients cannot be excluded. Sulpiride should be used with caution in patients with stroke risk factors.

Modal Forte tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

**Associations contra-indicated:**
Levodopa, antiparkinsonian drugs (including ropinirole): reciprocal antagonism of effects between levopoda or antiparkinsonian drugs (including ropinirole) and neuroleptics.

**Associations not recommended:**
Alcohol: alcohol enhances the sedative effects 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):
- Bradycardia-inducing medications such as beta-blockers, bradycardia-inducing calcium channel blockers such as diltiazem and verapamil, clonidine; digitalis.
- Medications which induce electrolyte imbalance, in particular those causing hypokalaemia: hypokalaemic diuretics, stimulant laxatives, IV amphotericin B, glucocorticoids, tetracosactides.
  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, haloperidol; methadone, imipramine antidepressants; lithium, cisapride, thioridazine, IV erythromycin, halofantrine, pentamidine.

**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, Modal caplets or Modal Forte Tablets should be administered two hours before these drugs.

Lithium: lithium increases the risk of extrapyramidal side effects. Discontinuation of both drugs is recommended at first signs of neurotoxicity.

**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.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development and/or postnatal development. In humans, very limited clinical data on exposed pregnancies are available. In almost all 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.

Neonates exposed to antipsychotics (including sulpiride) 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.

**Lactation:**
Sulpiride has been found in the breast milk of 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)

**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)
Uncommon: leukopenia
Not known: neutropenia, agranulocytosis

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

Endocrine disorders
Common: hyperprolactinaemia

Psychiatric disorders
Common: insomnia
Not known: confusion

Nervous system disorders
Common: sedation or drowsiness, extrapyramidal disorder (these symptoms are generally reversible upon administration of antiparkinsonian medication), Parkinsonism, tremor, akathisia
Uncommon: hypertonia, dyskinesia, dystonia
Rare: oculogyric crisis
Not known: neuroleptic malignant 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 arrhythmia, 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)

Gastrointestinal disorders
Uncommon: salivary hypersecretion

Hepatobiliary disorders
Common: hepatic enzyme increased

Skin and subcutaneous tissue disorders
Common: maculo-papular rash

Musculoskeletal and connective tissue disorders
Not known: torticollis, trismus

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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il )

**4.9 Overdose**
Experience with sulpiride in overdosage is limited.

The range of single toxic doses is 1 to 16g but no death has occurred even at the 16g dose.

The clinical manifestations of poisoning vary depending upon the size of the dose taken. After single doses of 1 to 3g restlessness and clouding of consciousness have been reported and (rarely) extrapyramidal symptoms. Doses of 3 to 7g may produce a degree of agitation, confusion and extrapyramidal symptoms (see section 4.8 Undesirable Effects); more than 7g can cause, in addition, coma and low blood pressure.

The duration of intoxication is generally short, the symptoms disappearing within a few hours. Comas which have occurred after large doses have lasted up to four days.

No haematological or hepatic toxicity has been reported.

Sulpiride is partly removed by haemodialysis.

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 arrythmias) is recommended until the patient recovers.

If severe extrapyramidal symptoms occur anticholinergics should be administrated. Overdose may be treated with alkaline osmotic diuresis and, if necessary, anti-parkinsonian drugs. Coma needs appropriate nursing, and cardiac monitoring is recommended until the patient recovers. Emetic drugs are unlikely to be effective in sulpiride overdosage.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; Benzamides,
ATC code: N05AL01

Sulpiride 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 sulpiride hint at an important distinction between different types of dopamine receptors or receptor mechanisms in the brain.

Behaviourally and biochemically, sulpiride 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 sulpiride and classical neuroleptics which lack such specificity.

One of the characteristics of sulpiride 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 sulpiride 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 an association between neuroleptic use and tumour risk in man.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Each capsule of Modal contains:

Cellulose microcrystalline, magnesium stearate, FD&C Blue 2 (E132), titanium dioxide (E171), gelatin.
Each tablet of Modal Forte contains:
Cellulose microcrystalline, magnesium stearate, lactose, potato starch, methylcellulose, talc, silicon dioxide colloidal.
Each tablet of Modal Forte contains approximately 27 mg of lactose.

**6.2 Incompatibilities**
Not applicable

**6.3 Special precautions for storage**
Store below 25°C.

**6.4 Contents of container**
Modal Capsules: box of 30
Modal Forte Tablets: box of 40

**6.5 Special precautions for disposal and other handling**
No special requirements.

## 7. Registration holder:
Rafa Laboratories Ltd, P.O. Box 405, Jerusalem, 9100301
Registration numbers:
Modal capsules: 0292721906
Modal Forte tablets: 0292921895

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