**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.

Excipient with known effect:
Modal Forte contains approximately 27 mg of lactose.
For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form
Modal: white powder in light-blue (sea blue) capsules.
Modal Forte: white tablets with scoreline, imprinted with Modal F.

## 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**

- Hypersensitivity to the active substance (sulpiride) or to any of the excipients listed in section 6.1.
- Concomitant prolactin-dependent tumours, for example pituitary gland prolactinomas and breast cancer (see section 4.8).
- Phaeochromocytoma.
- Association with levodopa or antiparkinson drugs (including ropinirole) (see section 4.5).
- Acute porphyria.

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

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.

Modal Capsules and Modal Forte Tablets induce slight electroencephalogram (EEG) modifications. Neuroleptics may lower the epileptogenic threshold and some cases of convulsions, sometimes in patients with no previous history, have been reported with sulpiride (see section 4.8). Therefore, caution is advised in prescribing it for patients with unstable epilepsy, and patients with a history of epilepsy should be closely monitored during sulpiride therapy.

In patients requiring Modal Capsules or Modal Forte Tablets who are receiving anti-convulsant therapy, the dose of the anti-convulsant should not be changed.

In elderly patients, as with other neuroleptics, sulpiride should be used with particular caution (see section 4.2). Elderly patients are more susceptible to postural hypotension, sedation and extrapyramidal effects.

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).

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.

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.

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including sulpiride. 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.

As hyperglycaemia has been reported in patients treated with atypical antipsychotic agents, patients with diagnosed diabetes mellitus or with risk factors for diabetes who have started treatment with sulpiride, should get appropriate glycaemic monitoring.

Avoid concomitant prescription of other antipsychotics.

QT prolongation:
Sulpiride can induce QT prolongation (see section 4.8). It is known that this effect may potentiate the risk of serious ventricular arrhythmias such as torsade de pointes. Before any administration, and if possible taking into account the clinical condition of the patient, it is advisable to monitor factors which could favour the occurrence of this rhythm disorder, such as:
- bradycardia less than 55 bpm,
- electrolyte imbalance, particularly hypokalaemia,
- congenital QT prolongation,
- ongoing treatment with medicines that may produce pronounced bradycardia (< 55 bpm),
- hypokalaemia,
- decreased intracardiac conduction,
- or QT prolongation (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.

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 for this increased risk is not known. An increase in the risk with other antipsychotic drugs or in other patient populations cannot be excluded. Sulpiride should be used with caution in patients with risk factors for stroke.

Increased mortality in elderly patients with dementia:

Elderly patients with dementia-related psychosis, who are treated with antipsychotic drugs, are at 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. Sulpiride is not licenced for the treatment of dementia-related behavioural disturbances.

Venous thromboembolism:
There have been reports of venous thromboembolism (VTE), sometimes fatal, 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 Modal Capsules or Modal Forte Tablets 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).

Neuroleptic Malignant Syndrome:
A Neuroleptic Malignant Syndrome (NMS), a potentially fatal complication, reported to occur with antipsychotics is characterised by hyperthermia, muscle rigidity, rhabdomyolysis, 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.

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

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

**Contraindications of concomitant use**

- Levodopa, antiparkinson medicines (including ropinirole): reciprocal antagonism of effects between levopoda or antiparkinsonian medicines (including ropinirole) and neuroleptics (see section 4.3).

**Concomitant use not recommended:**

- Alcohol: alcohol may potentiate the sedative effects of neuroleptics. Consumption of alcoholic drinks and medicines containing alcohol must be avoided.

- Combination with drugs that may prolong the QT interval or induce torsade de pointes (see section 4.4):
    - Bradycardia-inducing medicines such as beta-blockers, calcium channel blockers and bradycardia-inducing medicines such as diltiazem and verapamil, clonidine, guanfacine; digitalis.
    - Drugs that induce electrolyte imbalance, in particular those causing hypokalaemia: hypokalaemic diuretics, stimulant laxatives, amphotericin B IV, glucocorticoids, tetracosactides. Hypokalaemia must be corrected.
    - Class Ia antiarrhythmics such as quinidine and disopyramide.
    - Class III antiarrhythmics such as amiodarone and sotalol.
    - Other drugs such as pimozide, sultopride, haloperidol, thioridazine; methadone, imipramine antidepressants; lithium, bepridil, cisapride, erythromycin IV, vincamine IV, halofantrine, pentamidine and sparfloxacin.

**Interactions to be considered:**

- Antihypertensive agents: antihypertensive effect and the possibility of increasing the occurrence of 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 coadministration. Therefore, Modal Capsules or Modal Forte Tablets must be administered at least two hours before antacids.

- Lithium: lithium increases the risk of extrapyramidal adverse effects. Discontinuation of both medicines at the first sign of neurotoxicity is recommended.

- Modal Capsules and Modal Forte Tablets 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 Modal and Modal Forte, 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**

The medicine may cause drowsiness, dizziness, visual disturbances and impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a vehicle. Caution should be used while driving or operating machinery, especially because the particular sensitivity of each patient to the medicine has not been established.

**4.8 Undesirable effects**

Adverse reactions are presented according to the MedDRA system organ classes and MedDRA frequency convention: 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
Uncommon: leukopenia (see section 4.4)
Not known: neutropenia, agranulocytosis (see section 4.4)

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

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

Endocrine disorders
Common: hyperprolactinaemia

Psychiatric disorders
Common: insomnia
Not known: confusion

Nervous system disorders
Common: sedation or somnolence, extrapyramidal symptoms, parkinsonism, tremor, akathisia
Uncommon: hypertonia, dyskinesia, dystonia
Rare: oculogyric crisis
Not known: neuroleptic malignant syndrome, hypokinesia, tardive dyskinesia (characterized by rhythmic and involuntary movements mainly of the tongue and/or face, has 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). As with all neuroleptics, the neuroleptic malignant syndrome (see section 4.4) is a life-threatening complication), convulsion.

Cardiac disorders (see section 4.4)
Rare: ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia
Not known: QT prolongation on electrocardiogram, cardiac arrest, torsade de pointes, and sudden death.

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

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

Gastrointestinal disorders
Common: constipation
Uncommon: salivary hypersecretion

Hepatobiliary disorders
Common: Increase in liver enzymes
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 (see section 4.6)
Not known: extrapyramidal symptoms, withdrawal syndrome in neonates (see section 4.6)

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

General disorders and alterations at the site of administration
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

**4.9 Overdose**
Signs and symptoms
Experience with sulpiride overdose is limited.

In case of overdose, signs of dyskinetic type may occur with spasmodic torticollis, protrusion of the tongue and trismus may occur. Some patients may develop lifethreatening parkinsonian manifestations and coma. Cases of fatal outcomes have been reported mainly in combination with other psychotropic agents.

Sulpiride is partially removed by haemodialysis.

Treatment

There is no specific antidote for sulpiride. The treatment is strictly symptomatic. Nevertheless, appropriate supportive measures must be instituted, with close monitoring of vital functions; monitoring of cardiac function is recommended until the patient recovers (risk of QT prolongation and subsequent ventricular arrhythmias). In case of severe extrapyramidal symptoms, anticholinergic agents should be administered

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

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

**6.2 Incompatibilities**
Not applicable

**6.3 Shelf life**
The expiry date of the product is indicated on the packaging materials.

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

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

**6.6 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

Revised in Jun 2023 according to MOHs guidelines.