SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Product name] 50 mg tablets
[Product name] 100 mg tablets

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of [Product name] 50 mg tablets contains 50 mg levosulpiride.
Each tablet of [Product name] 100 mg tablets contains 100 mg levosulpiride.

Excipients with known effect: lactose monohydrate
Each tablet of [Product name] 50 mg tablets contains 85 mg of lactose monohydrate.
Each tablet of [Product name] 100 mg tablets contains 170 mg of lactose monohydrate.
For the full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM

Tablet
[Product name] 50 mg tablets: White, round, convex tablet, with 8 mm diameter imprinted with "50" on one side.
[Product name] 100 mg tablets: White, round, convex tablet, with 10.3 mm diameter.

4.CLINICAL PARTICULARS

4.1 Therapeutic indications

- Somatic symptom disorders.
- Treatment of chronic schizophrenia with negative symptoms.

4.2 Posology and method of administration

Posology
Adults (according to medical prescription)

- 2-3 tablets of 100 mg per day.

Maintenance therapy: 3 tablets of 50 mg per day.
This dose may be gradually reduced.

Pediatric population
No data are available.

Elderly
In the treatment of elderly patients, the dosage should be decided by the physician which must carefully evaluate a possible reduction of the dosages above mentioned.

Method of administration
Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Levosulpiride 50 mg and 100 mg should be used with caution in epilepsy, manic states, in the manic phase of manic-depressive disorder
- Levosulpiride 50 mg and 100 mg is contraindicated in patients with pheochromocytoma because it can cause a hypertensive crisis probably due to the release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine.
- Regarding the supposed correlation between the hyperprollactinemic effect of most psychotropic medicines and mammary dysplasia, levosulpiride should not be used in subjects who are already carriers of a malignant mastopathy.

4.4 Special warnings and precautions for use

- In randomized clinical trials versus placebo performed in a population of patients with dementia treated with some atypical antipsychotics, an increase of about three times of the cerebrovascular events risk was observed. The mechanism for this increased risk is not known. An increased risk for other antipsychotics and other patient populations can not be ruled out. Levosulpiride should be used with caution in patients with risk factors for stroke.
- A complex symptoms disorder, potentially fatal, called Neuroleptic Malignant Syndrome has been reported with use of neuroleptics (in general in the course of treatment with antipsychotic drugs).Clinical manifestations of this syndrome are hyperpyrexia, muscle rigidity, akinesia, vegetative disorders (irregular pulse or blood pressure, sweating, tachycardia, arrhythmias), altered state of consciousness that may progress to stupor and coma.The treatment of Neuroleptic Malignant Syndrome consists of immediate discontinuation of the antipsychotic medicines and

other not essential medicinesand settingof an intensive symptomatic treatment (care must be taken in reducing hyperthermia and in correcting dehydration). In case the resumption of the treatment with antipsychotics is held to be essential, the patient should be carefully monitored. Concomitant therapy with other neuroleptics must be avoided.

- Levosulpiride should not be used when the stimulation of gastrointestinal motility can be detrimental, for example in the presence of gastrointestinal bleeding, mechanical obstructions or perforations.
- Levosulpiride should be used with caution in patients with cardiovascular disease or with a family history of QT prolongation.
- There have been reports of venous thromboembolism (VTE) with antipsychotic medicines use. Since patients treated with antipsychotics often present with acquired risk factors for VTE, these factors need to be identified before and during treatment with levosulpiride, in order to take appropriate preventive measures.
- Simultaneous intake of alcohol must be avoided.

[Product name] contains lactose monohydrate. Patients with rarehereditary 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

The association with other medicines requires special caution and vigilance from the physician, in order to avoid unexpected effects from unwanted interaction.

- Concomitant administration of neuroleptics with medicines that prolong the QT interval, increases the risk of cardiac arrhythmias.
- Levosulpiride should not be administered concomitantly with medicines that cause electrolyte disturbances.

4.6 Fertility, pregnancy and lactation

Patients should be advised of the need to inform their doctor in case of current or planned pregnancy during treatment with levosulpiride. There are no adequate and well-controlled studies on pregnant women. Therefore, [Product name] should not be used in pregnancy, possible pregnancy and during the breastfeeding period unless the potential benefit justifies a potential risk to the fetus or newborn. Neonates exposed to conventional or atypical antipsychotics included levosulpiride during the third trimester of pregnancy are at risk for side effects including extrapyramidal symptoms or withdrawal symptoms that may vary by severity and duration following delivery. There have been reports of

agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder. Therefore, newborns should be carefully monitored.

4.7 Effects on ability to drive and use machines

Patients under treatment may experience drowsiness, numbness, dizziness and dyskinesia, therefore they should be advised to avoid driving or operating machine and to be engaged in activities where a full alertness is required for their possible hazard.

4.8 Undesirable effects

Tabulated list of adverse reactions

According to MedDRA system, organ classification, frequency categories are defined as follows: 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).

System Organ Class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very Rare*	*Frequency not known*
Metabolism and nutrition disorders					Weight gain	
Nervous system disorders	Somnolence, Torpor	Dizziness, Vertigo			Parkinsonism, Dyskinesia, Tremor, Dystonia, Psychomotor agitation, Disorders of the autonomic nervous system	Neuroleptic Malignant Syndrome (see section 4.4)
Reproductive system and breast						Amenorrhea, Gynaecoma

System Organ Class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very Rare*	*Frequency not known*
disorders						stia, Galactorrhea, Changes in libido[1]
Cardiac disorders				QT prolongation, Ventricular arrhythmias such as torsades de pointes, Ventricular tachycardia, Ventricular fibrillation, Cardiac arrest[2]	Sudden death[2]	
Vascular disorders						Thromboembolism (including cases of pulmonary embolism and deep venous thrombosis) (see section 4.4)[2]
Pregnancy, puerperium and perinatal conditions						Neonatal withdrawal syndrome, Extrapyramidal

System Organ Class	*Very common*	*Common*	*Uncommon*	*Rare*	*Very Rare*	*Frequency not known*
						symptoms (see section 4.6)
Investigations						Hyperprolactinaemia[1]

[1]Observed in special cases, due to prolonged administration and due to a reversible effect of levosulpiride on the functionality of the hypothalamic-pituitary-gonadal axis, similar to that known for many neuroleptics.

[2]Observed with other drugs of the same therapeutic class.

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 the national reporting system listed in Appendix V*.

4.9 Overdose

The medicine can induce extrapyramidal effects and sleep disorders,at higher doses and in patients sensitive to neuroleptics.

In these cases it will be advisable to reduce the dosage or discontinue the treatment, according to the physician decision.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Psycholeptics, antipsychotics, ATC code: N05AL07.

5.1 Pharmacodynamic properties

Biochemical, pharmacological and clinical data obtained with the two isomers of sulpiride, indicate that the antidopaminergic activity, both at central and local levels, is due to levo- rotatory enantiomer.

5.2 Pharmacokinetic properties

When levosulpiride is administered orally at a dose of 50 mg, the peak plasma concentration is reached in 3 hours, in an average of 94.183 ng/ml.
The t½ of elimination calculated after administration of 50 mg iv of levosulpiride is 4.305 hours.
The elimination of the medicine occurs mainly via the urine.

5.3 Preclinical safety data

The values expressed as LD50 acute toxicity after oral administration in mice, rats and rabbits were 2450 mg / kg, 2600 mg / kg and greater than 1500 mg / kg.
LD 50 values:

- in the mouse : 210 mg / kg, via i.p,
- in the rat via i.p. and i.v. :to 270 mg / kg and 53 mg / kg, respectively,
- in the rabbit via i.v.: to 42 mg / kg.

Subacute toxicity tests were conducted by administering the active ingredient in rat, rabbit and dog,daily, for 12-13 weeks. The appearance of any toxic symptoms was not observed at doses of:

- 25 mg / kg sc and 300 mg / kg p.o. in the rat,
- 250 mg / kg p.o. and 12.5 mg / kg i.m. in rabbits,
- 50 and 100 mg / kg p.o. in the dog.

To evidentiatethe chronic toxicity after administration of the drug for 180-190 days, the following doses were well tolerated:

- 100 mg / kg p.o. and 20 mg / kg s.c. in the rat,
- 10 mg / kg i.m. in rabbits and
- 20 mg / kg p.o. in the dog.

Studies performed in rats and mice, administering the medicine at a dose higher than that expected for man, have shown that levosulpiride do not possess carcinogenic properties.
Studies carried out in rats and rabbits have shown that the medicine is not teratogenic.
In vitro tests have ruled out that the medicine possesses mutagenic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)
lactose monohydrate
sodium starch glycolate type A
magnesium stearate (E572).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

6.5 Nature and contents of container

Packs of 20, 30, 60 and 100 tablets packed in blisters (PVC/PVDC/Alu or PVC/PCTFE/Alu).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT