1. TRADE NAME OF THE MEDICINAL PRODUCT
ORAP FORTE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

4 mg pimozide per tablet.

For excipients, see Section 6.1

3. PHARMACEUTICAL FORM
Tablets.

Tablet appearance:
Green, circular, biconvex tablet with the inscription “JANSSEN” on one side and cross-scored on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Orap is mainly indicated in chronic psychoses, responsive to the specific antipsychotic effects of neuroleptics and as basic medication for long-term antipsychotic maintenance therapy aimed at promoting, restoring, or maintaining optimum social integration.

Orap is also indicated as an initial therapy in outpatients and in newly or re-admitted patients, provided psychomotor agitation, aggressiveness, or severe anxiety do not constitute the predominant symptoms.

Orap is, moreover, indicated in patients with borderline psychosis, causing unadapted social behavior and requiring improvement or stabilization of their social integration.

4.2. Posology and method of administration

A single morning dose is recommended for all patients.
Since individual response to anti-psychotic drugs is variable, dosage should be individually determined and is best initiated and titrated under close clinical supervision.

Adults

The initial recommended dose in patients with chronic schizophrenia is 2 to 4 mg once daily, with weekly increments of 2 to 4 mg until a satisfactory level of therapeutic effect is attained or excessive adverse effects occur. The average maintenance dose is 6 mg daily with the usual range of 2 to 12 mg per day. The maximum daily dose is 20 mg.
The patients should be reviewed regularly to ensure the minimum effective dose is being used.
Elderly patients
The maintenance dose is the same as in adults but it is recommended to start with half of the adult starting dose.
Children
The recommended dose is half that of the adult dose. Experience in children below the age of 12 years is very limited.

4.3. Contraindications

Orap is contraindicated in central nervous system depression, comatose states, and in individuals who have previously displayed hypersensitivity to the drug. It should not be used in depressive disorders or Parkinson's syndrome.

Orap is contraindicated in patients with congenitally long QT syndrome or with a family history of this syndrome, and in patients with a history of cardiac arrhythmias or Torsade de Pointes. A pre-treatment ECG is thus recommended to exclude these conditions.

Orap should not be used in cases of acquired long QT interval, such as associated with concomitant use of drugs known to prolong the QT interval (see section 4.5)known hypokalaemia or hypomagnesaemia,or clinically significant bradycardia.
The concomitant use of CYP 3A4 inhibiting drugs such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone is contraindicated. The concomitant use of CYP 2D6 inhibiting drugs such as quinidine is also contraindicated. The inhibition of either or both of these cytochrome P450 systems, may result in the elevation of pimozide blood concentration and increase the possibility of QT-prolongation.

Orap is contraindicated with concomitant use of serotonin reuptake inhibitors, such as, sertraline, paroxetine, citalopram and escitalopram (see Section 4.5).

4.4. Special warnings and special precautions for use

Increased mortality in elderly patients with dementia-related psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the

placebo group. Although the causes of death 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.

Cardiac monitoring (See also Section 4.3 Contraindications)

There have been very rare reports of QT prolongation, ventricular arrhythmias, and Torsade de Pointes in patients without risk factors for QT prolongation administered therapeutic doses of pimozide, and in the setting of overdose. Ventricular tachycardia and ventricular fibrillation (in some cases with fatal outcomes) have also been reported, in addition to very rare reports of sudden death and cardiac arrest.

As with other neuroleptics, cases of sudden unexpected death have been reported with pimozide at recommended doses and in the setting of overdose. An ECG should be performed prior to initiation of treatment with pimozide, as well as periodically during treatment. If repolarization changes (prolongation of QT interval, T-wave changes or U-wave development) appear or arrhythmias develop, the need for treatment with pimozide in these patients should be reviewed. They should be closely monitored and their dose of pimozide should be reduced or the drug discontinued. If QT or QTc exceeds 500 msec, pimozide should be discontinued.

Neuroleptic malignant syndrome

In common with other antipsychotic drugs, ORAP has been associated with neuroleptic malignant syndrome: an idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dosage

is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.

Seizures

As with other antipsychotic drugs, ORAP should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. In addition, grand mal convulsions have been reported in association with ORAP.

Extrapyramidal symptoms

In common with all neuroleptics, extrapyramidal symptoms may occur (see Section 4.8). Antiparkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure.

Liver

Caution is advised in patients with liver disease because pimozide is metabolized in the liver.

Kinetics of response/withdrawal

In schizophrenia, the response to antipsychotic drug treatment may be delayed. If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months. Acute withdrawal symptoms, including nausea, vomiting, transient dyskinetic signs, and insomnia, have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Gradual withdrawal is advisable.

There is limited information available on the use of ORAP in children under 12 years of age.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing pimozide to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity or being subject to dehydration.

Increased psychomotor activity

Clinical trials with pimozide indicate that it is not or only poorly effective in the management of agitation, excitement and severe anxiey.

Endocrine Effects

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia, oligomenorrhoea or amenorrhoea, and erectile dysfunction.

Pimozide should only be used with great caution in patients with thyrotoxicosis.

Other

Caution is also advised in patients with renal failure, Parkinson's disease and phaeochromocytoma.
Concomitant use of pimozide with other neuroleptics should be avoided.

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

Pimozide is metabolised mainly via the cytochrome P450 subtype 3A4 (CYP3A4) enzyme system and more discreetly via the CYP 2D6 subtype. In-vitro data indicate that especially potent inhibitors of CYP 3A4 enzyme system such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone will inhibit the metabolism of pimozide, resulting in markedly elevated plasma levels of pimozide. In-vitro data also indicated that quinidine diminishes the CYP 2D6 dependent metabolism of pimozide. Elevated pimozide levels may enhance the risk of QT-prolongation.

Concomitant use of pimozide with drugs known to be inhibitors of cytochrome P450 CYP 3A4 or CYP 2D6 is contraindicated (see Section 4.3).

Concomitant use of pimozide with drugs known to prolong the QT interval is contraindicated (see Section 4.3). Examples include certain antiarrhythmics, such as those of Class IA (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone and sotalol), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), certain other antipsychotic medications (such as phenothiazines, and sertindole),

certain antihistamines (such as astemizole and terfenadine), cisapride, bepridil, halofantrine and sparfloxacin. This list is only indicative and not exhaustive.

Do not administer in combination with drugs causing electrolyte alteration. Concomitant use with diuretics should be avoided, in particular those causing hypokalemia.

As grapefruit juice is known to inhibit the metabolism of CYP3A4 metabolised drugs, concomitant use of grapefruit juice with Orap should be avoided.

An in vivo study of pimozide added to steady state sertraline revealed a 40% increase in the pimozide AUC and Cmax (see Section 4.3).

An in vivo study of co-administered pimozide and citalopram resulted in a mean increase of QTc values of approximately 10 milliseconds. Citalopram did not alter the AUC and Cmax of pimozide (see Section 4.3).

An in vivo study of co-administered pimozide (a single 2 mg dose) and paroxetine (60 mg daily) was associated with mean increases of 151% in pimozide AUC and 62% in pimozide Cmax (see Section 4.3).

As CYP1A2 may also contribute to the metabolism of Orap, prescribers should be aware of the theoretical potential for drug interactions with inhibitors of this enzymatic system.

Orap may in a dose-related way impair the antiparkinson effect of levodopa.

4.6. Pregnancy and lactation

The safety of the use of pimozide in pregnancy has not been established. Therefore, it should not be administered to women of child-bearing potential, particularly during the first trimester of pregnancy, unless, in the opinion of the physician, the expected benefits of the drug to the patient outweigh the potential risk to the fetus.

Orap may be excreted in breast milk. If the use of Orap is considered essential, breast-feeding should be discontinued.

Animal data has shown some embryo-toxicity at dose levels similar to the maximum human use level (MHUL). Fetal growth retardation and fetal-toxicity was observed at dose levels of approximately 6 times the MHUL on an mg/kg basis. Teratogenic effects have not been observed.

Neonates exposed to antipsychotic drugs (including pimozide) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder

4.7. Effects on ability to drive and use machines

Orap may impair alertness, especially at the start of treatment. These effects may be potentiated by alcohol. Patients should be warned of the risks of sedation and advised not to drive or operate machinery during treatment until their susceptibility is known.

4.8. Undesirable effects

Clinical Trial Data

Placebo-Controlled Double-Blind Data – Adverse Drug Reactions Reported at ≥2% Incidence

The safety of Orap was evaluated in 299 subjects who participated in 7 placebo-controlled, double-blind clinical trials. The information presented in this section was derived from pooled data. The specific patient population in the different trials consisted of patients with schizophrenia, patients with borderline psychosis or with behavioural disorders.

Adverse Drug Reactions (ADRs) reported by ≥2% of Orap-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥2% of ORAP-treated Subjects in 7 Placebo-Controlled, Double-Blind Clinical Trials of Orap

System/Organ Class Preferred Term	**Orap (n=165) %**	**PLACEBO (n=134) %**
Metabolism and Nutrition Disorders		
Anorexia	6	1
Psychiatric Disorders		
Insomnia	7	2
Nervous System Disorders		
Dizziness	11	6
Somnolence	11	7
Headache	7	4
Tremor	4	1
Lethargy	3	1
Eye Disorders		
Vision blurred	2	0
Gastrointestinal Disorders		
Constipation	7	1
Dry Mouth	5	2
Vomiting	3	1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	13	7
Sebaceous glands overactivity	3	1
Renal and Urinary Disorders		
Nocturia	12	6
Pollakuria	7	2
Reproductive System and Breast Disorder		
Erectile dysfunction	2	1
General Disorders and Administration Site		
Prostration	2	1

Active Comparator-Controlled Data – Adverse Drug Reactions Reported at ≥2% Incidence

The safety of Orap was evaluated in 303 patients who participated in 11 double-blind comparator studies. The information presented in this section was derived from pooled data. The specific patient population in the different trials consisted of (chronic) patients with schizophrenia or patients with other psychosis.

Adverse Drug Reactions (ADRs) reported by ≥2% of Orap-treated subjects in these trials and not listed in Table 1 are shown in Table 2.

Table 2. Adverse Drug Reactions Reported by ≥2% of Orap-treated Subjects in 11 Clinical Trials (Double-Blind Comparator Studies) of Orap

System/Organ Class Preferred Term	Orap (n=303) %
Psychiatric Disorders	
Depression	2
Agitation	2
Restlessness	2
Nervous System Disorders	
Extrapyramidal disorder	9
Akathisia	3
Gastrointestinal Disorders	
Salivary hypersecretion	7
Musculoskeletal and Connective Tissue Disorders	
Muscle rigidity	9

Placebo- and Active Comparator-Controlled Data – Adverse Drug Reactions Reported at <2% Incidence

Additional ADRs that occurred in <2% of Orap-treated subjects in either of the above two clinical datasets are listed below in Table 3.

Table 3. Adverse Drug Reactions Reported by <2% of Orap-Treated Subjects in Clinical Trials (Double-blind Placebo and Comparator Studies) of Orap

System/Organ Class Preferred Term
Nervous System Disorders
Bradykinesia
Cogwheel rigidity
Dyskinesia
Dystonia
Dysarthria
Eye Disorders
Oculogyration
Musculoskeletal and connective tissue disorders
Muscle spasms
Reproductive System and Breast Disorders
Amenorrhoea
General Disorders and Administration Site Conditions
Face oedema

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with Orap are included in Tables 4. The frequencies are provided according to the following 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, including isolated reports

Table 4: Adverse Drug Reactions Identified During Postmarketing Experience with Orap by Frequency Category Estimated From Spontaneous Reporting Rates

Endocrine Disorders	
Very rare	hyperglycaemia (in patients with pre-existing diabetes), hyperprolactinemia, blood prolactin increased
Metabolism and Nutrition Disorders	
Very rare	Hyponatraemia
Psychiatric Disorders	
Very rare	libido decreased
Nervous System Disorder	
Very rare	neuroleptic malignant syndrome, grand mal convulsion, tardive dyskinesia
Cardiac disorders	
Very rare	torsade de pointes, ventricular fibrillation, ventricular tachycardia
Skin and Subcutaneous Tissue Disorders	
Very rare	urticaria, pruritus, rash
Musculoskeletal and Connective Tissue Disorders	
Very rare	nuchal rigidity
Renal and Urinary Disorders	
Very rare	glycosuria
Reproductive System and Breast Disorders	
Very rare	galactorrhoea, gynaecomastia
General Disorders and Administration Site Conditions	
Very rare	hypothermia
Investigations	
Very rare	electrocardiogram QT Interval prolonged, electroencephalogram abnormal
Very rare	Weight increased

4.9. Overdose

Symptoms

In general, the signs and symptoms of overdosage with Orap would be an exaggeration of known pharmacological effects, the most prominent of which would be extrapyramidal symptoms. The risk of cardiac arrhythmias, possibly associated with QT-prolongation and ventricular arrhythmias including Torsade de Pointes should be considered. If these arrhythmias are severe, they can be associated with hypotension and circulatory collapse.

Treatment

There is no specific antidote to pimozide. Gastric lavage, establishment of a patent airway and, if necessary, mechanically assisted respiration are advised. Continous Electrocardiographic monitoring should be performed due to the risk of QT interval prolongation and ventricular arrhythmias including Torsade de Pointes and continue until the ECG returns to normal. Severe arrhythmias should be treated with appropriate antiarrhythmic treatment. Associated hypotension and circulatory collapse can be counteracted by supportive measures such as intravenous fluids, plasma or concentrated albumin, and vasopressors such as dopamine or dobutamine.

In cases of severe extrapyramidal symptoms, antiparkinsonian medication should be administered.

Because of the long half-life of pimozide, patients who have taken an overdose should be observed for at least 4 days.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pimozide is a diphenylbutylpiperidine derivative with neuroleptic properties that has been found to be useful in the management of chronic schizophrenic patients. It is relatively non-sedating and can be administered in a single daily dosage.

Pimozide selectively improves disturbances of perception and ideation. It promotes social contact, interest, initiative and insight.

In experimental studies in emotionally unstable persons, pimozide has shown to produce emotional stabilization and to improve motivation, achievements, and feelings of well-being.

It is assumed that the basic mechanism of action of pimozide is related to its action on central aminergic receptors. It appears to have a selective ability to block central dopaminergic receptors, affecting noradrenaline turnover at higher doses only. The extrapyramidal effects typical of other neuroleptic agents are also seen with pimozide, but it appears to have fewer autonomic

effects. As with other neuroleptics, endocrine effects and ECG changes have also been reported with pimozide.

5.2. Pharmacokinetic properties

More than 50% of a dose of pimozide is absorbed after oral administration. Peak serum levels occur generally six to eight hours (range: 4-12 hours) after dosing. Pimozide appears to undergo significant first pass metabolism. Pimozide is extensively metabolized, primarily by N-dealkylation in the liver. Two major metabolites have been identified: 1-(4-piperidyl)-2-benzimidazolinone and 4,4-bis(4-fluorphenyl)butyric acid. These metabolites have no antipsychotic activity. Only a very small fraction of pimozide is excreted unchanged in the urine. The major route of elimination of the metabolites is through the kidney.

The mean elimination half-life of pimozide in schizophrenic patients was approximately 55 hours. There was a more than ten-fold interindividual difference in the area under the serum pimozide level time curve and an equivalent degree of variation in peak serum levels among patients studied. The significance of this is unclear, since there are few correlations between plasma levels and clinical findings.

5.3. Preclinical safety data

The results of mutagenic studies indicate no genotoxicity. Carcinogenicity studies revealed no treatment related tumors in rats or male mice, but increased incidences of pituitary adenomas and mammary gland adenocarcinomas in female mice. These histopathology changes in the mammary gland and pituitary are thought to be prolactin-mediated and have been shown in rodents following hyperprolactinaemia by a variety of neuroleptic drugs with the relevance to humans being questionable.

Pimozide has been shown in studies in vitro to block the cardiac hERG channel and to prolong the action potential duration in isolated perfused hearts. This effect on the hERG channel may be attenuated by pimozide's blocking effect on the cardiac calcium L channel. In a number of in vivo animal studies intravenous or oral administration of pimozide has been shown to cause significant QTc prolongation. The doses which prolonged QTc did not cause arrhythmias.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Calcium hydrogen phosphate dihydrate, maize starch, microcrystalline cellulose, polyvidone, talc, cottonseed oil hydrogenated, yellow ferric oxide, indigotindisulphonate sodium .

6.2. Incompatibilities

None known.

6.4. Special precautions for storage

Store below 25^0 C
Keep out of reach of children.

6.5. Nature and contents of container

Blister packs with twenty 4 mg tablets.

Manufacturer :

Lusomedicamenta-Sociedade Tecnica Farm, Portugal

License Holder :

J-C Health Care Ltd.
Kibbutz Shefayim 60990,
Israel