Professional Information for ORAP® 1 mg and 4 mg

SCHEDULING STATUS

S5

1. PROPRIETARY NAME AND DOSAGE FORM

ORAP® 1 mg tablets

ORAP® 4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each tablet contains 1 mg of the active ingredient, pimozide.

Each tablet contains 4 mg of the active ingredient, pimozide.

Sugar free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

1 mg: Orange, circular, biconvex tablet with the inscription "ORAP 1" on one side.

4 mg: Green, circular, biconvex tablet with the inscription "ORAP 4" on one side and single-scored on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ORAP tablets are indicated for the maintenance treatment of chronic schizophrenics who respond to the anti-hallucinatory and anti-delusional effects of classical neuroleptics but who do not need, or are handicapped by, the hypnosedative action of such neuroleptics.

ORAP tablets are suitable for the long-term antipsychotic maintenance therapy of psychically

compensated schizophrenic outpatients.

ORAP tablets are indicated for initial and maintenance therapy in outpatients and in newly or re-admitted patients in whom psychomotor agitation, aggressiveness and severe anxiety are not the predominant symptoms.

4.2 Posology and method of administration

A single morning dose is recommended for all patients.

Since individual response to ORAP is variable, dosage should be individually determined and is best initiated and titrated under close clinical supervision.

When patients are transferred from other neuroleptic medication to ORAP tablets, the former medication should be decreased gradually. This is particularly important for patients with signs of psychomotor agitation.

The combination of maintenance therapy with ORAP tablets and an additional psychotropic medicines (such as neuroleptic, tranquilliser or sedative antidepressant) may sometimes prove advantageous.

Safety in pregnancy and lactation has not been established.

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. 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 is recommended to start with half of the adult starting dose.

Method of Administration

Oral use.

4.3 Contraindications

Sensitivity to pimozide or other neuroleptics.

ORAP is contraindicated in central nervous system depression and comatose states. It should not be used in depressive disorders or Parkinson's syndrome. ORAP is contraindicated in epilepsy.

ORAP is contraindicated in patients with a congenitally long QT syndrome or with a family history of this syndrome, and in patients with a history of cardiac dysrhythmia or torsades 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 is associated with concomitant use of medicines known to prolong QT interval (see section 4.5), known hypokalaemia or hypomagnesaemia and clinically significant bradycardia.

The concomitant use of CYP3A4 inhibiting agents such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone is contraindicated. The concomitant use of CYP2D6 inhibiting agents such as quinidine is also contraindicated. The inhibition of either or both 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 precautions for use

Caution should be observed in cases of Parkinson's syndrome and epilepsy.

Caution should be exercised when pimozide, which may cause drowsiness and sedation, is taken with other central nervous system depressants.

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

There have been reports of QT prolongation, ventricular dysrhythmias, and torsades de pointes in patients without risk factors for QT prolongation administered therapeutic doses of ORAP, and in the setting of overdose. Ventricular tachycardia and ventricular fibrillation (in some cases with fatal outcomes) have also been reported, in addition to reports of sudden death and cardiac arrest. (see section 4.3).

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

Increased psychomotor activity

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

Liver disease

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

Kinetics of response/withdrawal

In schizophrenia, the response to antipsychotic drug treatment may be delayed. If medication is 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 been described after abrupt cessation of high doses of antipsychotic medicines. Gradual withdrawal is advisable.

Extrapyramidal symptoms

Extrapyramidal symptoms may occur (see section 4.8).

Antiparkinson medicine of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure.

Tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy or after discontinuation of ORAP. The syndrome is mainly characterised 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 re-instituted, when the dosage is increased or when a switch is made to different antipsychotic medicine. Treatment should be discontinued as soon as possible.

Neuroleptic malignant syndrome

ORAP has been associated with neuroleptic malignant syndrome: an idiosyncratic response characterised by hyperthermia, generalised muscle rigidity, autonomic instability, and 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.

Seizures

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.

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 ORAP 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.

Endocrine effects

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

4.5 Interaction with other medicines and other forms of interaction

Since ORAP is metabolised mainly via the cytochrome P450 CYP3A4 enzyme system, and more discretely via the CYP2D6 subtype, it should not be administered concomitantly with inhibitors of CYP3A4 enzyme system, such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone, which may inhibit the metabolism of pimozide, resulting in markedly elevated plasma levels of pimozide. *In vitro* data also indicated that quinidine diminishes the CYP2D6 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 CYP3A4 or CYP2D6 is contraindicated (see section 4.3).

Concomitant use of ORAP with medicines known to prolong QT interval are also contraindicated (see section 4.3). Examples include certain anti-dysrhythmics, such as 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 phenothiazine, 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 medicines causing electrolyte alteration. Concomitant use with diuretics should be avoided, in particular those causing hypokalaemia.

As grapefruit is known to inhibit the metabolism of CYP3A4 metabolised medicine, concomitant use of grapefruit with ORAP should be avoided.

An *in vivo* study of pimozide added to steady state sertraline revealed a 40 % increase in pimozide AUC and C_{max} (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 C_{max} 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 $C_{max.}$ (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 impair the antiparkinson effect of levodopa in a dose-related way.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

Animal data has shown embryo-toxicity at dose levels similar to the maximum human use level (MHUL). Foetal growth retardation and foetal toxicity was observed at dose levels of approximately 6 times the MHUL on 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.

Breastfeeding

Pimozide may be excreted in breast milk. If the use of ORAP is considered essential, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use of 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

System/organ class	**ORAP (n = 165) %**	**Placebo (n = 134) %**
Metabolism and nutrition disorder		
Anorexia	6	1
Psychiatric disorder		
Insomnia	7	2

Nervous system disorder		
Dizziness	11	6
Somnolence	11	7
Headache	7	4
Tremor	4	1
Lethargy	3	1
Eye disorders		
Blurred vision	2	0
Gastrointestinal disorders		
Constipation	7	1
Dry mouth	5	2
Vomiting	3	1
Skin and subcutaneous tissue disorder		
Hyperhidrosis	13	7
Sebaceous glands overactivity	3	1
Renal and urinary disorders		
Nocturia	12	6
Pollakiuria	7	2
Reproductive system and breast disorder		
Erectile dysfunction	2	1
General disorders and administration site conditions		
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 (ADRs) reported by ≥ 2 % of ORAP-treated subjects in 11 clinical trials (double-blind comparator studies) of ORAP	
System/Organ class	**ORAP (n = 303) %**
Psychiatric disorders	
Depression	2
Agitation	2
Restlessness	2
Nervous system disorders	
Extrapyramidal disorders	9
Akathisia	3
Gastrointestinal disorders	
Salivary hypersecretion	7
Musculoskeletal and connective 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
Nervous system disorders Bradykinesia Cogwheel rigidity Dyskinesia Dystonia Dysarthria
Eye disorders Oculogyration
Musculoskeletal and connective tissue disorder Muscle spasms
Reproductive system and breast disorders Amenorrhoea
General disorders and administration site conditions Facial oedema

Post-marketing data

Adverse events first identified as ADRs during post-marketing experience with ORAP are included in Table 4.

Table 4: Adverse drug reactions identified during post-marketing experience with ORAP	
Endocrine disorders	Hyperglycaemia (in patients with pre-existing diabetes), hyperprolactinaemia, blood prolactin increased.

Metabolism and nutrition disorders	Hyponatraemia
Psychiatric disorders	Libido decreased
Nervous system disorders	Neuroleptic malignant syndrome, grand mal convulsions, tardive dyskinesia
Cardiac disorders	Torsades de pointes, ventricular fibrillation, ventricular tachycardia
Skin and subcutaneous tissue disorder	Urticaria, pruritus, rash
Musculoskeletal and Connective Tissue Disorders	Nuchal rigidity
Renal and Urinary Disorders	Glycosuria
Reproductive System and Breast Disorders	Galactorrhoea, gynaecomastia
General Disorders and Administration Site Conditions	Hypothermia
Investigations	Electrocardiogram QT Interval prolonged, electroencephalogram abnormal, increased weight

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the

Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Manifestations:

In general, the signs and symptoms of overdosage of ORAP would be an exaggeration of known pharmacological effects, the most prominent of which would be extrapyramidal symptoms. The risk of cardiac dysrhythmias, possibly associated with QT prolongation and ventricular dysrhythmias including torsades de pointes should be considered. If these dysrhythmias are severe, they may be associated with hypotension and circulatory collapse.

Treatment:

There is no specific antidote to pimozide and treatment is primarily supportive.

Establishment of a patent airway and if necessary, mechanically assisted respiration is advised. Continuous electrocardiographic monitoring should be performed due to the risk of QT interval prolongation and ventricular dysrhythmias including torsades de pointes and continued until the ECG returns to normal. Severe dysrhythmias should be treated with appropriate antidysrhythmic treatment.

Associated hypotension and circulatory collapse can be counteracted by supportive measures such as intravenous fluids, plasma or concentrated albumin and vasopressors.

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

A 2.6.5 Central nervous system depressants. Tranquillisers. Miscellaneous structures.

5.1 Pharmacodynamic properties

Pimozide is a neuroleptic of the diphenylbutylpiperidine series. It is a potent long-acting antipsychotic. Pimozide selectively blocks the central dopaminergic receptors but has minimal effect on the noradrenergic receptors. Extrapyramidal effects are encountered. Endocrine effects and ECG changes have also been reported with pimozide.

The clinical effects of this pharmacological action are to control effectively hallucinations and delusions and to normalise incoherent thought processes and bizarre behaviour patterns. Pimozide rarely produces significant hypnosedation or hypnokinesis and does not impair motor ability.

5.2 Pharmacokinetic properties

More than 50 % of a dose of pimozide is absorbed after oral administration. Peak serum levels occur generally 6 – 8 hours (range: 4 – 12 hours) after dosing. Pimozide appears to undergo significant first-pass metabolism. Pimozide is extensively metabolised, primarily by N-dealkylation in the liver. The 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 via the kidney.

The mean elimination half-life of pimozide in schizophrenic patients is approximately 55 hours. There is more than a 10-fold interindividual difference in the area under the serum pimozide concentration-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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate

Maize starch

Microcrystalline cellulose

Polyvidone K30

Talc

Cottonseed Oil Hydrogenated

Ferric oxide (E172)

Orange yellow S (E110) – aluminium lake (1 mg only)

Indigotindisulfonate (E132) - aluminium lake (4 mg only)

Purified water*

* not in final product

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

Store at or below 30 ˚C.

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container

Cartons containing blister packs of 20 or 25 tablets each.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

LeBasi Pharmaceuticals (Pty) Ltd

San Domenico Building, Unit 6, Ground Floor

10 Church Street

Durbanville

7551

8. REGISTRATION NUMBERS

ORAP 1 MG: B/2.6.5/1017

ORAP 4 mg: K/2.6.5/137

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

11 June 1979

10. DATE OF REVISION OF TEXT

19 May 2026

Namibia: NS3 Orap 1 mg: 90/2.6.5/00633 Orap 4 mg: 90/2.6.5/00634
Manufacturer Lusomedicamenta Sociedade Tecnica Farmaceutica S.A. 69-B Queluz de Baixo, 2730-055 Barcarena, Portugal