Orap® / Orap® Forte

NAME OF THE MEDICINAL PRODUCT Tradename
ORAP®
ORAP® Forte
International Non-Proprietary Name (INN) pimozide

QUALITATIVE AND QUANTITATIVE COMPO-SITION
ORAP (pimozide) is available in 1 mg and 4 mg tablets for oral administration.
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Tablets.
1 mg oral tablets
Orange, circular, biconvex tablet with the inscription "JANSSEN" on one side and "O 1" on the other side.
4 mg oral tablets
Green, circular, biconvex tablet with the inscription "JANSSEN" on one side and cross-scored on the other side.

CLINICAL PARTICULARS
Therapeutic indications
Orap is mainly indicated in chronic psychotics, responsive to the specific antipsychotic effects of neuroleptics, 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 behaviour and requiring improvement or stabilisation of their social integration.

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.

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 recom-mended 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 Interactions with other medicaments and other forms of interaction), 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 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 Interactions).

Special warnings and special precautions for use
Cardiac monitoring
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.
As with other neuroleptics, caution is advised in patients with cardiovascular diseases, patients with a family history of QT prolongation, and in patients administered other QT prolonging drugs.
Hypotension may very rarely occur. *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 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.
Extrapyramidal symptoms
In common with all neuroleptics, extrapyramidal symptoms may occur (see Undesirable effects). Antiparkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure.
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.
Neuroleptic malignant syndrome

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.
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.
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.
Endocrine Effects
Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia, oligomenorrhoea or amenorrhoea, and erectile dysfunction.
Interaction with other medicinal products and other forms of interaction
Pimozide is metabolized mainly via the cytochrome P450 subtype 3A4 (CYP 3A4) 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 prolong the QT interval is contraindicated (see Contraindications). 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 metabolized 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 C_{max} (see Contraindications).
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 Contraindications).
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 Contraindications).
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. **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.
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. **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 Table 4. In the table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports

In Table 4, ADRs are presented by frequency category based on spontaneous reporting rates.

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
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

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. Continuous electrocardiographic monitoring should be performed due to the risk of QT interval prolongation and ventricular arrhythmias including Torsade de Pointes and continued 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.

PHARMACOLOGICAL PROPERTIES
ATC Code, Level 4: N5A9
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 stabilisation 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.
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.
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.

PHARMACEUTICAL PARTICULARS
List of excipients
1 mg tablet
Calcium hydrogen phosphate dihydrate, maize starch, microcrystalline cellulose, polyvidone K30, talc, cottonseed oil hydrogenated, yellow ferric oxide, orange yellow S aluminum lake.
4 mg tablet
Calcium hydrogen phosphate dihydrate, maize starch, microcrystalline cellulose, polyvidone K30, talc, cottonseed oil hydrogenated, yellow ferric oxide, indigotindisulphonate sodium aluminum lake.
Incompatibilities
Not applicable.
Shelf Life
Observe expiry date on the outer pack.
Special precautions for storage
Store between 15°C and 30°C.
Keep out of reach of children.
Nature and contents of container
Blisters: Polyvinylchloride (PVC) – foil and aluminum foil.
Bottles: Polypropylene container with LDPE cap.
Instructions for Use and Handling <and Disposal>
Not applicable

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JANSSEN-CILAG

Manufactured by: see outer pack
for Janssen Pharmaceutica N.V., Turnhoutse weg 30, B-2340 Beerse, Belgium