

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Orap 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pimozide 4 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Round, pale green, biconvex tablets impressed with a cross-score on one face and 'Janssen' on the other face.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Orap is indicated in the management of chronic schizophrenia and allied psychoses, including monosymptomatic hypochondriacal psychosis, mania and hypomania.

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

4.2 Posology and method of administration

For oral use. A single morning dose is recommended for all patients.

Adults and children over 12 years of age only

An ECG should be performed in all patients prior to treatment and in those patients receiving Orap in excess of 16 mg daily, regular periodic ECGs should be performed.

Since individual response to antipsychotic drugs is variable, dosage should be individually determined and is best initiated and titrated under close clinical supervision. In determining the initial dose, consideration should be given to the patient's age, severity of symptoms and previous response to other neuroleptic drugs.

The patients should be reviewed regularly to ensure the minimum effective dose is being used.

The recommended starting dose is 2 to 4 mg daily.

Increases in dosage should be made at weekly intervals or longer, with 2-4 mg per day. The maintenance dose is usually in the range of 2 to 12 mg daily, depending on the individual response. The maximum daily dose is 20 mg.

Use in elderly patients:

Half the usual starting dose should be used, and then slowly titrated.

Poor CYP2D6 metabolisers

Adult and elderly patient- it is recommended that CYP2D6 genotyping be performed at doses at or above 4 mg/day.

In poor CYP2D6 metabolisers, it is recommended that the dose does not exceed 4 mg/day, and that doses are not increased earlier than every 14 days (*see section 4.4*).

Paediatric patients- it is recommended that CYP2D6 genotyping be performed at doses at or above 0.05 mg/kg/day. In poor CYP2D6 metabolisers, it is recommended that the dose does not exceed 0.05 mg/kg/day (with a maximum of 4 mg/day), and that doses are not increased earlier than every 14 days (*see Section 4.4*).

4.3 Contraindications

As pimozone has been reported to prolong the QT-interval it is contraindicated for patients with a pre-existing congenital prolongation of QT or with a family history of this syndrome, and patients with a history of cardiac arrhythmias or a family history of Torsades de pointes. A pre-treatment ECG is thus recommended to exclude these conditions. Orap should not be used in the case of acquired long QT interval, such as that associated with the concomitant use of drugs known to prolong the QT interval (see Section 4.5 Interaction with other medicinal products and other forms of interaction), known uncorrected hypokalaemia or hypomagnesaemia, or clinically significant bradycardia.

Orap is also contraindicated in central nervous system depression, comatose states and in patients with known hypersensitivity to pimozone or other diphenylbutyl piperidine derivatives.

Orap should not be used in depressive disorders or Parkinson's syndrome.

The concomitant use of orally or parenterally administered cytochrome P450 CYP3A4 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 contra-indicated. The inhibition of either or both of these cytochrome P450 systems may result in the elevation of pimozone 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

Patients receiving treatment with pimozone 6.0 mg daily or over should carry a treatment card indicating dosage.

Increased Mortality in Elderly people with Dementia

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a 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. 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, including the two mentioned above 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.

Orap is not licensed for the treatment of dementia-related behavioural disturbances.

Cardiac monitoring (See also Section 4.3 Contraindications)

There have been very rare reports of QT prolongation, ventricular arrhythmias, and Torsades de pointes in patients without risk factors for QT prolongation administered therapeutic doses of pimozone, 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. Electrolyte disturbances should also be considered a risk factor in oral therapy (See Section 4.3 Contraindications and Section 4.5 Interaction with other medicinal products and other forms of interaction) and periodic electrolyte monitoring is recommended.

Venous Thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported 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 Orap and preventive measures undertaken.

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 drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months. Acute withdrawal symptoms including nausea, vomiting, transient dyskinesic signs and insomnia, have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Gradual withdrawal of Orap is advised.

Extrapyramidal symptoms

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

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 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 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.

In an attempt to minimise the possibility of the development of such a syndrome, major tranquilliser therapy should be reserved for these patients. For whom it is essential, the dosage used should be the lowest commensurate with optimal benefit, and duration of treatment should not extend beyond that necessary for the patient.

There is no known treatment for tardive dyskinesia. The antipsychotic drug may mask it, as may anticholinergic agents. Although the latter do not predispose to tardive dyskinesia, they should not be used routinely to mask the Parkinsonian effects of antipsychotic drugs as they may mask the early signs of tardive dyskinesia.

Neuroleptic malignant syndrome

In common with other antipsychotic drugs, pimozide has been associated with neuroleptic malignant syndrome: an idiosyncratic response characterised 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, pimozide should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold (e.g. alcohol withdrawal or brain damage). In addition, grand mal convulsions have been reported in association with pimozide.

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.

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

CYP2D6 genotyping

In a clinical study, individuals with genetic variations resulting in poor CYP2D6 metabolism (approximately 5 to 10% of the population) exhibited higher pimozide concentrations than extensive CYP2D6 metabolisers. The concentrations observed in poor CYP2D6 metabolisers were similar to those seen with strong CYP2D6 inhibitors such as paroxetine (*see Section 4.5*). The time to achieve steady state pimozide concentrations is expected to be longer (approximately 2 weeks) in poor CYP2D6 metabolisers because of the prolonged half-life. It is recommended that CYP2D6 genotyping be performed at doses at or above 4 mg/day (adult and elderly patients) or 0.05 mg/kg/day (paediatric patients), and alternative dosing strategies are recommended in patients who are genetically poor CYP2D6 metabolisers (*see Section 4.2*)

Other

Caution is also advised in patients with renal failure, Parkinson's disease and phaeochromocytoma.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of pimozide with drugs known to prolong the QT interval are contraindicated (see Section 4.3). Examples include certain anti-arrhythmics, such as those of Class 1A (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 is not exhaustive.

As with all neuroleptics, Orap will potentiate the effects of central nervous system depressants including alcohol, hypnotic sedatives or strong analgesics.

While anticholinergic drugs may sometimes be necessary, they should not be used routinely to mask the Parkinsonian effects of antipsychotic drugs, as they mask the early signs of tardive dyskinesia.

Orap may impair the anti-Parkinsonian effects of levodopa. The dosage of anticonvulsants may need to be increased to take account of lowered seizure threshold.

Concomitant use of drugs which may cause electrolyte disturbances should be avoided. Concomitant use with diuretics should be avoided, in particular those causing hypokalemia.

Pimozide metabolism is catalyzed mainly by cytochrome P450 3A4 (CYP3A4) and CYP2D6 and to a lesser extent by CYP1A2. Concomitant use of pimozide with drugs known to be inhibitors of cytochrome P450 CYP 3A4 or CYP 2D6 is contraindicated (see Section 4.3).

In vitro data indicate that highly potent inhibitors of CYP 3A4 enzyme system, such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone will inhibit the metabolism of pimozone, resulting in markedly elevated plasma levels of pimozone.

In vitro data also indicated that quinidine diminishes the CYP 2D6 dependent metabolism of pimozone. Elevated pimozone levels may enhance the risk of QT-prolongation.

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

An *in vivo* study of pimozone added to steady state sertraline revealed a 40% increase in the pimozone AUC and C_{max} (see Section 4.3).

An *in vivo* study of co-administered pimozone and citalopram resulted in a mean increase of QT_c values of approximately 10 milliseconds. Citalopram did not alter the AUC and C_{max} of pimozone (see Section 4.3).

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

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

4.6 Fertility, pregnancy and lactation

The safety of the use of pimozone 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 should not be used during pregnancy unless considered essential by the physician.

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 (see Section 5.3).

Neonates exposed to antipsychotic drugs (including pimozone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Pimozone is excreted in breast milk. If the use of Orap is considered essential, breast feeding should be discontinued. For further details see Section 5.3.

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

The safety of ORAP was evaluated in 165 pimozone-treated subjects who participated in seven placebo-controlled trials of patients with schizophrenia, or patients with anxiety or behavioural disorders, and in 303 pimozone-treated subjects who participated in eleven active-comparator controlled clinical trials in patients with schizophrenia (10 trials, including chronic schizophrenia) or psychic fatigability (1 trial). Based on pooled safety data from these clinical trials, the most commonly reported ($\geq 9\%$ incidence). Adverse Drug Reactions (ADRs) were (with % incidence): Nervous System Disorders: Dizziness (11) and Somnolence (11), Extrapyramidal Disorder (9); Muscle Rigidity (9); Hyperhidrosis (13); Nocturia (12).

Including the above-mentioned ADRs, the following table displays ADRs that have been reported with the use of ORAP from either clinical-trial or post-marketing experiences.

The displayed frequency categories use 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), not known (cannot be estimated form the available data).

Adverse Drug Reactions				
Frequency Category				
System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Not Known
Endocrine Disorders				Hyperglycaemia (in patients with pre-existing diabetes); Hyperprolactinaemia; Blood Prolactin Increased
Metabolism and Nutrition Disorders		Anorexia		Hyponatraemia
Psychiatric Disorders		Depression; Insomnia; Agitation; Restlessness		Libido Decreased
Nervous System Disorders	Dizziness; Somnolence;	Extrapyramidal Disorder; Akathisia; Headache; Tremor; Lethargy	Bradykinesia; Cogwheel Rigidity; Dyskinesia; Dystonia; Dysarthria	Neuroleptic Malignant Syndrome; Grand Mal Convulsion; Tardive Dyskinesia
Eye Disorders		Vision Blurred	Oculogyration	
Cardiac Disorders				Torsade de Pointes; Ventricular Tachycardia; Ventricular Fibrillation
Gastrointestinal Disorders		Constipation; Dry Mouth; Vomiting; Salivary Hypersecretion		
Skin and subcutaneous tissue disorders	Hyperhidrosis	Sebaceous Glands Overactivity	Pruritus; Rash	Urticaria
Musculoskeletal and Connective Tissue Disorders		Muscle Rigidity	Muscle Spasms	Nuchal Rigidity
Renal and urinary disorders	Nocturia	Pollakuria		Glycosuria
Pregnancy, Puerperium and Perinatal Conditions				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive System and Breast Disorders		Erectile Dysfunction	Amenorrhoea	Galactorrhoea; Gynaecomastia
General Disorders and Administration Site Conditions		Prostration	Face oedema	Hypothermia
Investigations		Weight increased		Electrocardiogram QT Interval Prolonged; Electroencephalogram Abnormal

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs (frequency unknown).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

In general, the signs and symptoms of overdosage with Orap may be an exaggeration of known pharmacological effects, the most prominent of which would be severe extrapyramidal symptoms, hypotension and sedation. The risk of cardiac arrhythmias possibly associated with QT prolongation and ventricular arrhythmias including Torsades de pointes should be considered. The patient may appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state.

Treatment

There is no specific antidote to pimozide. 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 Torsades de pointes and continued until the patient is clinically recovered or any abnormalities that may have shown have disappeared. Hypotension and circulatory collapse may be counteracted by the use of intravenous fluid, plasma or concentrated albumin, and vasopressor agents such as dopamine or dobutamine. In cases of severe extrapyramidal symptoms, anti-Parkinsonian medication should be administered. In view 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 have been found to be useful in the management of patients with chronic schizophrenia. It is relatively non-sedating and can be administered in a single daily dose. Pimozide selectively improves disturbances of perception and ideation. It promotes social contact, interest and insight.

Pimozide appears to selectively block central dopaminergic receptors, but only affects noradrenaline turnover at higher doses.

5.2 Pharmacokinetic properties

Absorption is greater than 50% after oral administration, with peak serum levels occurring 6-8 hours after dosing. Orap is extensively metabolised, primarily by N-dealkylation in the liver. The mean elimination half life in schizophrenic patients is approximately 55 hours. There was a more than 10-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.

Two major metabolites have been identified, but they are inactive. A small fraction of pimozide is excreted in the urine. The major route of elimination of the metabolites is through the kidney.

5.3 Preclinical safety data

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.

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
Povidone (E1201)
Talc
Cottonseed oil, hydrogenated
Ferric oxide (E172)
Indigotinedisulphate (E132) aluminium Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/aluminium foil blister packs, containing 28*, 100 or 250* tablets.

* Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Janssen-Cilag Limited
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0748/024/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 31 March 2008

10 DATE OF REVISION OF THE TEXT

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