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 the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Green, circular, biconvex, normally arched tablets, single-scored on one side and 'ORAP 4' on the other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Orap is an antipsychotic of the diphenylbutyl-piperidine series and is indicated in:

- Chronic schizophrenia, for the treatment of symptoms and prevention of relapse.
- Other psychoses, especially paranoid and monosymptomatic hypochondriacal psychoses (eg delusional parasitosis).

Orap is indicated in adults and children over 12 years old.

4.2 Posology and method of administration

Posology

Orap is intended for once daily oral administration in adults and children over 12 years of age. 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. Dose increases should be made at weekly intervals or longer, and by increments of 2-4 mg in the daily dose.
The patient should be reviewed regularly to ensure the minimum effective dose is being used.

Chronic schizophrenia:
The dose ranges between 2 and 20 mg daily, with 2 mg as a starting dose. This may be increased according to response and tolerance to achieve an optimum response.

Other psychoses, paranoid states and monosymptomatic hypochondriacal psychoses (MHP):
An initial dose of 4 mg daily which may then be gradually increased, if necessary, according to response, to a maximum of 16 mg daily.

Use in elderly:
Elderly patients require half the normal starting dose of pimozide.

Paediatric population (less than 12 years old)
No data are available

Method of Administration

Oral use.

4.3 Contraindications

In common with several other neuroleptics, pimozide has been reported to prolong the QT interval. It is, therefore, contra-indicated in patients with a pre-existing congenital prolongation of QT, or with a history or family history of this syndrome, and in patients with a history of cardiac arrhythmias and a history of Torsades de pointes. 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), known uncorrected hypokalaemia or hypomagnesaemia, or clinically significant cardiac disorders (eg recent acute myocardial infarction, uncompensated heart failure, arrhythmias treated with class IA and III antiarrhythmic medicinal products) or clinically significant bradycardia.
Orap is also contra-indicated in patients with severe central nervous system depression and in patients with a known hypersensitivity to pimozide or other diphenylbutyl-piperidine derivatives, or to any of the excipients listed in section 6.1. It should not be used in patients with depression or Parkinson's syndrome.
The concomitant use of orally or parenterally administered cytochrome P450 CYP 3A4 inhibiting drugs such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone is contra-indicated. 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 pimozide blood concentration and increase the possibility of QT-prolongation.
Orap is contraindicated with concomitant use of serotonin uptake inhibitors such as sertraline, paroxetine, citalopram and escitalopram (see Section 4.5).

4.4 Special warnings and precautions for use

Please also refer to Drug Interactions section.

Increased Mortality in Elderly people with Dementia

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.

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

Cardiac monitoring (See also Section 4.3)

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,

Electrolyte disturbances should also be considered a risk factor (see Section 4.3and Section 4.5) and periodic electrolyte monitoring is recommended.

Drugs which may cause electrolyte disturbances are not recommended in patients receiving long-term pimozide (please also refer to Section 4.5)

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 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, sweating and insomnia, have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

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 (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 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.

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 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, 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.

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

Please also refer to the Precautions and Warnings and Contra-indications sections.

As with other neuroleptics, Orap may increase the central nervous system depression produced by other CNS depressant drugs, including alcohol, hypnotics, sedatives or strong analgesics.

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

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 terfenadine), cisapride, bretylium and certain antimalarials such as quinine and mefloquine. This list is not comprehensive.

There is an increased risk of extrapyramidal effects with anti-emetics such as metoclopramide.

Avoid concomitant use with sibutramine due to an increased risk of CNS toxicity.

Concomitant use with calcium channel blockers may result in an enhanced hypotensive effect.

Concurrent treatment with neuroleptics should be kept to a minimum as they may predispose to the cardiotoxic effects of pimozide. Particular care should be exercised in patients who are using depot neuroleptics. Low potency neuroleptics such as chlorpromazine and thioridazine should not be used concomitantly with pimozide.

Pimozide is metabolised mainly via the cytochrome P450 subtype 3A4 (CYP 3A4) enzyme system and, to a lesser extent, via the CYP 2D6 subtype. 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 the 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.

As grapefruit juice is known to inhibit the metabolism of CYP3A4 metabolised drugs, concomitant use of grapefruit juice with pimozide 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 pimozide, prescribers should be aware of the theoretical potential for drug interactions with inhibitors of this enzymatic system.

Concurrent use of drugs causing electrolyte imbalance is not recommended. Diuretics, in particular those causing hypokalemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety 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 foetus.
Studies in animals have shown reproductive toxicity but no teratogenic effects have been demonstrated (see section 5.3).
Neonates exposed to antipsychotic drugs (including pimozide) during the third trimester of pregnancy are at risk of adverse effects including extrapyramidal and/or withdrawal symptoms that may 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.

Breastfeeding

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

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 pimozide-treated subjects who participated in seven placebo-controlled trials of patients with schizophrenia, or patients with anxiety or behavioural disorders, and in 303 pimozide-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 (≥ 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 (next page) 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); 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; Muscle Rigidity	Bradykinesia; Cogwheel Rigidity; Dyskinesia; Dystonia; Dysarthria	Neuroleptic Malignant Syndrome; Grand Mal Convulsion; Tardive Dyskinesia; Neck Rigidity
Eye Disorders		Vision Blurred	Oculogyric crisis	
Cardiac Disorders				Torsade de Pointes; Ventricular Tachycardia; Ventricular Fibrillation
Gastrointestinal Disorders		Constipation; Dry Mouth; Vomiting; Salivary Hypersecretion		
Skin and subcutaneous tissue disorders	Hyperhidrosis	Sebaceous Gland Overactivity	Pruritus; Rash,	Urticaria
Musculoskeletal and Connective			Muscle Spasms	

System Organ Class	Adverse Drug Reactions Frequency Category			
	Very Common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Not Known**
Tissue Disorders				
Renal and urinary disorders	Nocturia	Urinary frequency		Glycosuria
Pregnancy, puerperium and perinatal conditions.				Drug withdrawal syndrome neonatal (see 4.6)
Reproductive System and Breast Disorders		Erectile Dysfunction	Amenorrhoea	Galactorrhoea; Gynaecomastia
General Disorders and Administration Site Conditions		Extreme exhaustion	Face oedema	Body Temperature Dysregulation; Hypothermia
Investigations		Weight increased		Electrocardiogram QT Interval Prolonged; Electroencephalogram Abnormal

In addition to the above, cardiac arrest and sudden unexplained death have been reported with the use of pimozide. These events should be considered ADRs associated with the class of medicinal products, the D2, dopamine-antagonist neuroleptics.
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 Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

In general, the signs and symptoms of overdose with Orap would be an exaggeration of known pharmacological effects, the most prominent of which would be severe extrapyramidal symptoms, hypotension or sedation. The risk of cardiac arrhythmias, possibly associated with QT-prolongation and ventricular arrhythmias including Torsade 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 Torsade de Pointes and continued until the ECG returns to normal. Hypotension and circulatory collapse may be counteracted by the use of intravenous fluids, plasma or concentrated albumin, and vasopressor agents such as noradrenaline.

Adrenaline should not be used.

In cases of severe extrapyramidal symptoms, anti-Parkinson 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

ATC Code, Level 4: N5A9

Pimozide is an orally active neuroleptic drug which blocks central dopaminergic receptors. Pimozide antagonises many of the actions of amphetamine and apomorphine.

5.2 Pharmacokinetic properties

The mean serum elimination half-life in schizophrenic patients is approximately 55 hours. This is highly variable and may be as long as 150 hours in some individuals. There is a 13-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.

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 unknown. Due to

the lack of toxicokinetic data in rodents the safety margin cannot be determined. Animal data has shown some embryo-toxicity at dose levels similar to the maximum human use level (MHUL). Fetal growth retardation and fetaltoxicity was observed at dose levels of approximately 6 times the MHUL on an mg/kg basis. Teratogenic effects have not been observed.

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 K30
Talc
Cottonseed Oil Hydrogenated
Ferric oxide (E172)
Indigotindisulphonate (E132) - aluminium lake
Purified water*

* not in final product

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

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

** not marketed*

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Eumedica S.A.

Winston Churchill Avenue 67

BE-1180 Brussels

Belgium

8 MARKETING AUTHORISATION NUMBER(S)

PL 21772/0004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 June 1976
Date of latest renewal: 7 April 2002

10 DATE OF REVISION OF THE TEXT

01/07/2016