SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Entumin®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clotiapine 40 mg

Excipient with known effect:
Entumin 40 mg tablets contain lactose.
This medicinal product is contraindicated in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of severe mental and emotional disorders (neuroleptic)

4.2 Posology and method of administration

Posology

Initial treatment 3 to 5 tablets daily in 2 or 3 divided doses may prove sufficient.
The daily oral dose may be increased to a maximum of 360 mg in divided doses, especially in cases of agitation/excitation.
The initial dosage may be given for periods of weeks or even months.
Maintenance and long-term treatment: 20 to 160 mg daily per os in 2 to 3 divided doses.
Specific populations
In underweight patients, patients with liver or kidney disease and in elderly patients, lower initial doses and a gradual dosage increase are indicated.

Paediatric population
The safety and efficacy of Entumin in children aged less than 16 years have not yet been established.

Method of administration

Entumin 40 mg tablets are for oral use. Entumin 40 mg tablets should not be chewed, should be administered with a small amount of water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Comatose states, severe CNS depression and post-encephalitic syndrome.
- Marked predisposition to convulsions: especially epilepsy.
- Children under 16 years of age.
- Contraindications due to the anticholinergic action:
    - absolute: angle-closure glaucoma.

4.4 Special warnings and precautions for use

Caution should be exercised:
- in elderly patients, due to their high sensitivity (sedation and hypotension);
- in severe cardiovascular disorders, due to haemodynamic changes, especially hypotension;
- in patients with renal and/or hepatic impairment, due to the risk of overdose;
- in patients with prostatic hypertrophy, marked intestinal atony;
- in patients with Parkinson's disease.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medications.
Since patients treated with antipsychotic agents often have acquired risk factors for VTE, all possible risk factors for VTE must be identified before and during Entumin treatment and preventive measures must be taken.
During all antipsychotic treatments, intense initial sedation and several days of immobilisation may promote thrombus formation in predisposed patients.
In the event of hyperthermia, treatment must be suspended, since such hyperthermia may be one of the constituents of the malignant syndrome (pallor, hyperthermia, autonomic disorders) described with neuroleptics.
Discontinuation of treatment must be gradual; any concomitant antiparkinson medications must be administered for longer, in view of their generally shorter plasma half-life.
As with other neuroleptic agents, hyperprolactinaemia such as that induced by taking Entumin may worsen the prognosis of breast cancer, although no formal link has been established. Entumin should be administered with caution in such situations.

<u>Class effects</u>

An increased risk of adverse cerebrovascular reactions has been observed in patients with dementia treated with some atypical antipsychotic agents. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Caution is recommended when using Entumin in the treatment of patients with risk factors for stroke.

In elderly patients with dementia-related psychosis, the efficacy and safety of Entumin have not been studied. Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotics are at increased risk of mortality. In the literature, risks predisposing this patient population to an increased

risk of mortality when treated with antipsychotics are: anaesthesia, the presence of cardiac disorders (e.g. cardiac arrhythmia) or lung disorders (e.g. pneumonia, with or without aspiration). Caution is recommended when using Entumin in the treatment of dementia.

As with other antipsychotics, caution is recommended in patients with known cardiovascular disease or a family history of QT interval prolongation and caution is recommended when Entumin is prescribed at the same time as medicinal products known to prolong the QTc interval.

In clinical trials and/or in post-marketing experience, events of leukopenia/neutropenia have been reported temporarily associated with antipsychotic agents. Cases of agranulocytosis have also been reported. Risk factors for leukopenia/neutropenia include a pre-existing low white blood cell count and a history of drug-induced leukopenia/neutropenia. In patients with a history of a low and clinically significant white blood cell count or drug-induced leukopenia/neutropenia, a full blood count should be performed frequently during the first few months of therapy and discontinuation of Entumin treatment should be envisaged at the first sign of any clinically significant decrease in the number of white blood cells in the absence of any other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever and other symptoms or signs of infection and treated rapidly if such symptoms or signs occur. Treatment with Entumin must be discontinued in patients with severe neutropenia (absolute neutrophil count <1,000/mm^3) and their white blood cell count must be monitored until it returns to normal.

4.5 Interaction with other medicinal products and other forms of interaction

Entumin can potentiate the:
- CNS effects of alcohol, tranquillisers, anaesthetics, hypnotics, analgesics, MAOIs and antihistamines;
- hypotensive effect of antihypertensive agents;
- toxicity of lithium.

As with other antipsychotic agents, caution is recommended when Entumin is prescribed at the same time as medicinal products known to prolong the QTc interval or lead to an electrolyte imbalance.

4.6 Fertility, pregnancy and lactation

Pregnancy

Neonates exposed to antipsychotics (including Entumin) during the third trimester of pregnancy are at risk of adverse reactions, including extrapyramidal symptoms and/or withdrawal symptoms, which may vary in terms of severity and duration *post partum*. The following reactions have been reported: agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, feeding problems. As a result, neonates must be closely monitored.

Breastfeeding

The metabolites of Entumin are excreted in human milk. A decision must be made

whether to discontinue breastfeeding or to discontinue/abstain from Entumin therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. In the event of prolonged administration in the mother, neuroleptics can induce extrapyramidal disorders and hyperreflexia in the neonate.

4.7 Effects on ability to drive and use machines

Entumin can cause somnolence, especially at the start of treatment, and thus diminish the patient's ability to react. Sedation is greatly increased upon concomitant use of alcohol or other agents with a depressant effect on the CNS (hypnotics, tranquillisers, analgesics, antihistamines).

4.8 Undesirable effects

Autonomic: Particularly during the first few days of treatment,
Orthostatic hypotension which may cause syncope in elderly individuals.
Atropine-like effects: dry mouth, constipation, accommodation disturbances.

Neurological:
Effects on the CNS, comprising sedation, agitation and states of confusion, are rare.
Extrapyramidal disorders, such as dystonia, akathisia (fear of sitting down) and pseudoparkinsonism are usually mild and can easily be controlled by antiparkinson agents.
Rare but sometimes irreversible tardive dyskinesias may be observed during prolonged courses of treatment.
Neuroleptic malignant syndrome (catatonia, obnubilation; akinesia, rigidity, opisthotonus, dysregulation of the autonomic nervous system, hyperpyrexia) may occur in the first few days of treatment when treatment is combined with another medicinal product or when the dosage is increased.

Eye: Blurred vision (uncommon).

Miscellaneous:
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic medications – Frequency not known.
Very rare cases of QT interval prolongation, which might be associated with torsades de pointes, have been observed, although a causal link with the use of Entumin cannot be conclusively demonstrated. Cases of leukopenia/neutropenia have been reported in temporal relationship with antipsychotics. Cases of agranulocytosis have also been reported.
Hyperkinesia, EEG changes, oedema, rash, hyperpyrexia, sweating, acute pancreatitis, thrombocytopenia, gastroenteritis, paralytic ileus: isolated cases, with a possible relationship with Entumin, have been observed.

Pregnancy, puerperium and perinatal conditions:
Frequency not known: neonatal drug withdrawal syndrome.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

The danger of overdose is increased with concomitant use of CNS depressants.

Symptoms: somnolence, unconsciousness, coma, agitation, convulsions, thermolability, respiratory depression, hypotension, collapse, tachycardia, arrhythmias, Parkinson's syndrome.

Treatment: there is no specific antidote. Treatment is symptomatic and is performed in a specialised environment:
- Gastric lavage followed by administration of adsorbent charcoal (peritoneal dialysis and haemodialysis are not very effective).
- Monitoring of cardiac and respiratory functions: in the event of hypotension: plasma substitutes; if necessary, administration of a vasopressor (do not use adrenaline, as it has an inverse effect).
- In the event of convulsions: benzodiazepines.
- Correction of disturbances in electrolyte and acid-base metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, antipsychotics.
ATC code: N05AH06.

Entumin is a neuroleptic of the dibenzothiazepine group which acts by inhibiting the central dopaminergic receptors.
Its action manifests in three phases:
- A rapid symptomatic effect which may appear from the very first day and concerns anxiety.
- A predominant, progressive sedative action on psychomotor activity and vigilance.
- An antipsychotic action that sets in more slowly, in stages; improvements do not involve any secondary depressive reactions, even after long-term treatment.

5.2 Pharmacokinetic properties

Due to method-related difficulties, the pharmacokinetics and metabolism are not yet fully understood.
In animals, absorption of radioactively (tritium) labelled clotiapine is good and rapid, with elimination occurring within 24 to 140 hours, depending on the species, at a rate of 65 - 80% via the urine and faeces.
In humans, absorption of clotiapine after oral administration is good and its

biotransformation is almost complete. The metabolites are, for the vast majority, glucuronides highly soluble in water which are eliminated via the urine. The main metabolite is N-dimethyl sulphoxide; 25 - 40% of the administered dose is recovered in the urine as unchanged substance (approx. 10%) or known metabolites.

5.3 Preclinical safety data

No data supplied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, maize starch, microcrystalline cellulose, gelatin, colloidal anhydrous silica, liquid paraffin, talc, magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging material

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Pack of 30 or 500 scored tablets packed in blisters, PVC/PVDC with Alu heat seal lacquer.

Not all pack sized may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER

Delpharm L'aigle, Zone Industrielle 1, Route De Crulai, 61300 L'aigle, France

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Juvisé Pharmaceuticals SAS
149 boulevard Stalingrad
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8. MARKETING AUTHORISATION HOLDER

Taro International Ltd., 14 Hakitor St., Haifa Bay 2624761

9. MARKETING AUTHORISATION NUMBERS

023.40.21411.00

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