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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
Yellow-tinged white, circular, flat, beveled edged, with a score on one side, plain on the other side.

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, and should be administered with a small amount of water.

4.3 Contraindications

This medicinal product must not be used in the following cases:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Comatose states, severe CNS depression and post-encephalitic states.
- History of epilepsy and/or predisposing factors (e.g. brain injuries from various causes, concomitant use of other antipsychotics, withdrawal from alcohol or anti-seizure medication such as benzodiazepines).
- Children aged under 16 years.
- Contraindications due to the anticholinergic action:
  - absolute: angle closure glaucoma

4.4 Special warnings and precautions for use

Enhanced monitoring of clotiapine treatment is necessary:

- In elderly patients with:
  - increased susceptibility to orthostatic hypotension, sedation and extrapyramidal effects
  - chronic constipation (risk of paralytic ileus)
  - possible prostatic hyperplasia
- In patients with serious cardiovascular conditions, because of haemodynamic changes, particularly hypotension
- In cases of severe renal and/or hepatic impairment, because of the risk of overdose
- In patients with Parkinson's disease.

Thromboembolic events
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Given that patients treated with antipsychotics often have acquired risk factors for VTE, all possible VTE risk factors, such as a history of thrombosis and prolonged immobilisation, must be identified before and during Entumin treatment, and preventive measures must be put in place.

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome (NMS) is a potentially fatal syndrome associated with antipsychotic drugs. In the event of unexplained hyperthermia, treatment must be suspended, as this hyperthermia may be one of the features of the malignant syndrome described with neuroleptics (pallor, hyperthermia, muscle rigidity, autonomic instability, altered consciousness, instability of heart rate and blood rate, tachycardia, excessive sweating, and heart rhythm disorders). Signs such as elevated serum creatine phosphokinase levels, myoglobinuria (rhabdomyolysis), and acute kidney injury may additionally occur.
If a patient shows signs or symptoms suggesting NMS, or unexplained hyperthermia not accompanied by other signs of NMS, all antipsychotic drugs, including clotiapine, must be stopped immediately, and appropriate supportive treatment together with close monitoring must be instituted.

Hyperprolactinaemia
As with other neuroleptics, hyperprolactinaemia such as that induced by taking Entumin may worsen the prognosis of breast cancer, although a clear link has not been established. Entumin should be administered with caution in these situations. Long-term effects of hyperprolactinaemia that may be observed are amenorrhoea, galactorrhoea and gynaecomastia.

Seizures
Antipsychotics can lower the seizure threshold. The occurrence of seizures is dose-dependent. For this reason, the recommended total daily dose of Entumin must not be exceeded.

Hyperglycaemia, metabolic syndrome
Rare cases of impaired glucose tolerance and/or the development or exacerbation of diabetes have been reported on treatment with clotiapine. Regular monitoring is recommended in order to detect any blood glucose abnormality in diabetic patients or those with risk factors increasing the risk of developing diabetes (see section 4.8).
Deterioration in the metabolic situation associated with weight gain, elevated blood glucose and dyslipidaemia

has been observed on treatment with certain atypical antipsychotics. For this reason, regular checks should be conducted, particularly in patients with pre-existing changes in these parameters.

Cerebrovascular accident
In randomised, placebo-controlled clinical studies in elderly patients with dementia treated with certain atypical antipsychotics, a risk of cerebrovascular accident three times higher than with placebo was observed. The mechanism of such a risk increase is not known. An increase in the risk with other antipsychotics or in other patient populations cannot be ruled out. This medicinal product must be used with caution in patients with risk factors for cerebrovascular accident.

Increase in mortality in elderly patients with dementia
The mortality risk is increased in elderly patients with dementia-associated psychosis treated with antipsychotics. The analyses of 17 placebo-controlled studies (mean duration 10 weeks) conducted in patients taking mostly atypical antipsychotics showed a risk 1.6 to 1.7 times higher in patients treated with these medicinal products compared with placebo.
At the end of a treatment lasting an average of 10 weeks, the mortality risk was 4.5% in the treated group of patients compared with 2.6% in the placebo group.

Although the cause of death varied in the clinical trials with atypical antipsychotics, most of the deaths seemed to be either from cardiovascular causes (for example, heart failure, sudden cardiac death) or from infection (for example, pneumonia).
Data from two large-scale observational studies showed that elderly people with dementia treated with conventional antipsychotics have a slightly increased risk of death compared with those who are not treated. Sufficient data to provide a precise estimate of the magnitude of the risk are not available, and the cause of the increase in this risk is not known.

The respective roles played by the antipsychotic and the patients' characteristics in the mortality increase in the epidemiological studies are not clear.

Nervous system disorders
Sedation/drowsiness, confusional states, agitation and extrapyramidal symptoms are undesirable effects reported with clotiapine.

Tardive dyskinesia has been observed chiefly after prolonged administration. In the event of the appearance of signs and symptoms of tardive dyskinesia, a dose reduction or cessation of clotiapine treatment should be considered. These symptoms may temporarily worsen or even newly occur after cessation of the treatment.

Enhanced monitoring of clotiapine treatment is necessary in elderly patients with higher susceptibility to sedation and extrapyramidal effects.

Orthostatic hypotension
Hypotension (orthostatic) may occur, mainly during the gradual treatment introduction period, and may cause syncope in elderly people. A dose reduction should be considered if hypotension occurs. Blood pressure must be checked regularly in patients aged 65 years and over.

Prolonged QT interval
As with other antipsychotics, caution is recommended in the prescribing of Entumin to patients with known cardiovascular disease, a family history of prolonged QT interval, bradycardia or electrolyte imbalances (hypokalaemia, hypomagnesaemia), as they can increase the risk of heart rhythm disturbances; this also applies to the concomitant use of medicinal products known to prolong the QT interval (see section 4.5).

Concomitant use of neuroleptics
The concomitant use of neuroleptics (particularly those known to prolong the QTc interval) must be avoided.

Leucopenia, neutropenia and agranulocytosis
In clinical trials and/or postmarketing experience, cases of leucopenia/neutropenia have been reported in connection with antipsychotics. Cases of agranulocytosis have also been reported. The potential risk factors for leucopenia/neutropenia include a pre-existing low white blood cell count and a history of drug-induced leucopenia/neutropenia. In patients with a history of a clinically significant reduction in the white blood cell count or drug-induced leucopenia/neutropenia, a full blood count should be performed frequently during the first few months of treatment, and cessation of Entumin treatment should be considered at the first sign of a clinically significant reduction in the white blood cell count in the absence of other causal factors. Patients with clinically significant neutropenia should be carefully checked for fever or other signs or symptoms of infection and promptly treated if such signs or symptoms appear. Entumine treatment must be stopped in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and their white blood cell count must be monitored until it normalises.

Anticholinergic effects
Entumin has anticholinergic action, which can lead to undesirable effects. Careful monitoring is required if prostatic hyperplasia is present. Probably as a result of its anticholinergic properties, Entumin has been linked to variable disturbances of intestinal transit, from constipation to paralytic ileus (see section 4.8). Particular vigilance is necessary in patients concomitantly receiving medicinal products known to cause constipation (in particular, medicinal products with anticholinergic properties such as certain antipsychotics, certain antidepressants, and certain anti-Parkinson's drugs) and in patients with a history of colonic disease or lower abdominal surgery, which could risk aggravating the situation. Screening for and active treatment of constipation are recommended.

Excipients
Entumin tablets contain lactose.
Patients with galactose intolerance, total lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary disorders) must not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Entumin may potentiate
- the central effects of alcohol, tranquillisers, anaesthetics, hypnotics, analgesics and MAOIs;
- the hypotensive effect of antihypertensives;
- lithium toxicity.

Medicinal products known to prolong the QT interval
As with other antipsychotics, caution is recommended when Entumin is prescribed with medicinal products known to prolong the QT interval, such as anti-arrhythmics, tricyclic antidepressants, tetracyclic antidepressants, certain antihistamines, other antipsychotics, certain antimalarials, and certain medicinal products causing electrolyte imbalances (hypokalaemia, hypomagnesaemia), bradycardia.
This list is a guide and is not exhaustive.

Antimuscarinic drugs
It must be borne in mind that antimuscarinic substances may have additive undesirable effects and more readily cause urine retention, an acute attack of glaucoma, constipation, dry mouth, etc.
The various antimuscarinic drugs are represented by imipramine antidepressants, most antimuscarinic H1 antihistamines, anticholinergic anti-Parkinson's drugs, antimuscarinic antispasmodics, disopyramide, phenothiazine neuroleptics, and clozapine.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies have not revealed evidence of teratogenicity (see section 5.3). There are no clinical data on use in pregnant women. Caution is required in the case of use during pregnancy.
Entumin should not be administered during pregnancy unless it is absolutely necessary.

Newborn infants exposed to antipsychotics (including Entumin) during the third trimester of pregnancy have a risk of adverse reactions, including extrapyramidal symptoms and/or withdrawal symptoms, which can vary in terms of severity and duration after birth. The following reactions have been reported: agitation, hypertonia, hypotonia, tremors, drowsiness, respiratory distress, feeding difficulties. Consequently, newborn infants must be closely monitored (see section 4.8).

Breastfeeding
Entumin metabolites are excreted in breast milk. A decision must be made whether to stop breastfeeding or stop/refrain from Entumin treatment, weighing the benefit of breastfeeding to the newborn infant against the benefit of treatment to the woman. In the case of prolonged administration in the mother, neuroleptics can cause extrapyramidal disorders and hyperreflexia in the newborn infant.

Fertility
There are no clinical data on fertility. In a toxicity study in dogs, effects on the testes (seminiferous tubule changes with a reduction in the sperm count) were observed, but the clinical relevance of these results is not known (see section 5.3).

4.7 Effects on ability to drive and use machines

Entumin can cause drowsiness, especially at the start of treatment, and thus impair the patient's reaction speeds. Sedation is greatly increased when alcohol or other CNS depressants (hypnotics, tranquillisers, analgesics, antihistamines) are used at the same time.

4.8 Undesirable effects

All undesirable effects are listed by system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and frequency not known (cannot be estimated from the available data). Within each frequency group, undesirable effects are listed in descending order of seriousness.

The frequency of undesirable effects reported during postmarketing use cannot be determined, as they come from spontaneous reports. Consequently, the frequency of these undesirable effects is stated as "not known".

Blood and lymphatic system disorders
Frequency not known
Leucopenia
Neutropenia
Agranulocytosis
Thrombocytopenia

Immune system disorders
Frequency not known
Hypersensitivity

Endocrine disorders
Frequency not known
Hyperprolactinaemia (and associated symptoms such as gynaecomastia, menstrual disorders, amenorrhoea, anovulation, galactorrhoea, fertility problems, reduced libido, erectile dysfunction)

Metabolism and nutrition disorders
Frequency not known
Weight gain
Impaired glucose tolerance
Increase in blood glucose
Occurrence or exacerbation of diabetes (see section 4.4)
Dyslipidaemia

Psychiatric disorders
Uncommon
Agitation
Confusional states

Nervous system disorders
Uncommon
Akathisia
Dyskinesia
Tardive dyskinesia
Dystonia

Frequency not known
Sedation or drowsiness
Parkinsonism
Seizures
Neuroleptic malignant syndrome (see section 4.4)
Hyperkinesia, EEG changes

Eye disorders
Uncommon
Blurred vision

Frequency not known
Accommodation problems

Cardiac disorders
Uncommon
Prolonged QTc (see section 4.4)

Rare
Ventricular arrhythmias such as *torsade de pointes*, ventricular tachycardia, which can lead to ventricular fibrillation or cardiac arrest

Frequency not known
Sudden cardiac death

Vascular disorders
Uncommon
Orthostatic hypotension

Frequency not known
Cases of venous thromboembolism, including sometimes fatal pulmonary embolism, as well as deep vein thrombosis, have been reported with antipsychotics.
Syncope

Gastrointestinal disorders
Uncommon
Mild and transient anticholinergic effects such as constipation and dry mouth

Frequency not known
Paralytic ileus
Pancreatitis
Gastroenteritis

Skin and subcutaneous tissue disorders
Frequency not known
Rash
Photosensitivity reaction
Sweating

Renal and urinary disorders
Frequency not known
Urine retention connected with the anticholinergic effect of clotiapine

Pregnancy, puerperium and perinatal disorders
Frequency not known
Neonatal abstinence syndrome (see section 4.6)

General disorders and administration site conditions
Frequency not known
Hyperpyrexia
Oedema

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 risk of overdose is increased if CNS depressants are taken at the same time.

Symptoms: drowsiness, unconsciousness, coma, agitation, convulsions, temperature instability, respiratory depression, hypotension, collapse, tachycardia, arrhythmias, parkinsonism.

Treatment: There is no specific antidote. Treatment is symptomatic and will be administered in a specialist setting:
- Gastric lavage followed by the administration of activated charcoal (peritoneal dialysis and haemodialysis are not very effective).
- Monitoring of cardiac and respiratory function: if hypotension is present: plasma substitutes; if necessary,

vasopressor administration (do not use adrenaline, as this has an inverse effect).
- If seizures occur: benzodiazepines.
- Correction of metabolic disorders (electrolyte and acid-base imbalances).

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 inhibition of the central dopaminergic receptors.
Its action develops in three phases:
- A rapid symptomatic effect which can appear from the first day and focuses on anxiety.
- A progressive sedative action predominantly on psychomotor activity and vigilance.
- An antipsychotic action of slower onset, in stages; the improvements do not involve secondary depressive reactions, even after prolonged treatment.

5.2 Pharmacokinetic properties

Due to the methodological difficulties, the pharmacokinetics and metabolism are still only incompletely understood.
In animals, radiolabelled (tritium-labelled) clotiapine is well and rapidly absorbed, and it is eliminated within 24 to 140 hours, depending on the species, 65 to 80% of it in the urine and faeces.
In humans, clotiapine is well absorbed after oral administration, and is almost completely metabolised. The great majority of the metabolites are highly water-soluble glucuronides which are eliminated in the urine. The main metabolite is N-desmethylsulfoxide. 25 to 40% of the administered dose is recovered in the urine as unchanged substance (around 10%) or known metabolites.

5.3 Preclinical safety data

There was no malformation or constitutional anomalies (according to a detailed macroscopic examination) in the offspring or foetuses of mice, rats and rabbits which had received a dose of clotiapine throughout gestation.

In a toxicity study after oral administration of repeated doses for 13 weeks in dogs, microscopic examination of the testes showed changes in the seminiferous tubules with a decrease in the sperm count at a dose of 60 mg/kg/day, similar but less uniform changes at 30 mg/kg/day, and no change at 15 mg/kg/day. The clinical significance of these results is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose - maize starch - microcrystalline cellulose - gelatine - 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, L'Aigle, 61300, France

8. MARKETING AUTHORISATION HOLDER

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

9. MARKETING AUTHORISATION NUMBERS

023.40.21411.00

Revised in November 2024.