IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0711/044/002
Case No: 2035808

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Cedine 400 mg Film-Coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/05/2007** until **26/02/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cedine 400 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains Cimetidine 400.00 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-Coated Tablet
Pale green, oblong, biconvex, film-coated tablets with a score notch on each side and engraved “C400” on one side. The score notch is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

CEDINE is indicated in the treatment of benign ulceration of the oesophagus, stomach upper intestinal tract (including post operative stomal area) and in the management of Zollinger – Ellison Syndrome.
In the management of conditions benefiting from reduced gastric acid secretion.
In the long-term maintenance management of benign peptic ulcer disease under regular surveillance.

For the treatment of benign ulceration associated with long – term use of non-steroidal anti-inflammatory drugs.

4.2 Posology and method of administration

Route of Administration:
Oral.

Recommended Dosage Schedule

Adults:
The total daily dose should not normally exceed 2.4g. Dosage should be reduced in patients with impaired renal function (refer Section 4.4).
For patients with duodenal or benign gastric ulceration, a single daily dose of 800 mg at bedtime is recommended. Otherwise the usual dosage is 400 mg twice a day with breakfast and at bedtime. Other effective regimens are 200 mg three times a day with meals and 400 mg at bedtime [1.0 g/day] and if inadequate, 400 mg four times a day [1.6 g/day] also with meals and at bedtime.
Treatment should be given initially for at least four weeks [six weeks in benign gastric ulcer, eight weeks in ulcer associated with continued non-steroidal anti-inflammatory agents].

Treatment may be continued for longer periods in those patients who may benefit from reduction of gastric secretion and the dosage may be reduced as appropriate to 400 mg at bedtime or 400 mg in the morning and at bedtime.

In patients with benign peptic ulcer disease, relapse may be prevented by continued treatment, usually with 400 mg at bedtime, 400 mg in the morning and at bedtime has also been used.

Patients on prolonged treatment (particularly those treated for more than one year) should be kept under regular surveillance.

In oesophageal reflux disease, 400 mg four times a day, with meals and at bedtime, for four to eight weeks is recommended.

In patients with very high gastric acid secretion [e.g. Zollinger-Ellison syndrome] it may be necessary to increase the dose to 400 mg four times a day, or in occasional cases further.

Antacids can be made available to all patients until symptoms disappear.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients, doses of 200 - 400 mg can be given every four to six hours.

In patients thought to be at risk of acid aspiration syndrome, an oral dose of 400 mg can be given 90 - 120 minutes before induction of general anaesthesia or in obstetric practice, at the start of labour. While such a risk persists, a dose of up to 400 mg may be repeated at four-hourly intervals as required up to the usual daily maximum of 2.4 g.

To reduce degradation of pancreatic enzyme supplements, 800-1600 mg a day may be given according to response in four divided doses, one to one and a half hours before meals.

Elderly:
The normal adult dosage may be used unless renal function is markedly impaired. (refer Section 4.4 and Section 4.8)

Children:
Experience in children is less than that in adults. In children more than two years old, CEDINE 25-30 mg/kg body weight per day in divided doses. The use of CEDINE in children less than two years old is not fully evaluated.

4.3 Contraindications

CEDINE should not be taken by patients who are hypersensitive to Cimetidine or other ingredients of the formulation.

4.4 Special warnings and precautions for use

Dosage should be reduced in patients with impaired renal function according to creatinine clearance. The following dosages are suggested: creatinine clearance of 0 to 15 ml per minute, 200 mg twice a day; 15 to 30 ml per minute, 200 mg three times a day, 30 to 50 ml per minute, 200 mg four times a day; over 50 ml per minute, normal dosage. Cimetidine is removed by haemodialysis, but not to any significant extent by peritoneal dialysis.

Before initiation of CEDINE therapy for any gastric ulceration, malignancy should be excluded by endoscopy and biopsy if possible. Treatment with CEDINE can mask symptoms and allow transient healing of gastric cancer. The consequences of a potential delay in diagnosis should be kept in mind particularly in patients of middle age or over with new or recently changed dyspeptic symptoms.

Care should be taken that patients with a history of peptic ulcer, particularly the elderly, being treated with CEDINE and a non-steroidal anti-inflammatory agent are observed regularly.

In patients on drug treatment or with illnesses that could cause falls in blood cell count, the possibility that H_2-receptor antagonism could potentiate this effect should be borne in mind.

The safety of prolonged use is not fully established and care should be taken to keep patients on prolonged treatment (particularly those treated for greater than one year) under regular surveillance.

4.5 Interaction with other medicinal products and other forms of interaction

CEDINE can prolong the elimination of drugs metabolised by oxidation in the liver. Although pharmacological interactions with a number of drugs, e.g. diazepam, propranolol, have been demonstrated only those with oral anticoagulants, phenytoin, theophylline and intravenous lidocaine appear, to date, to be of clinical significance. Close monitoring of patients on CEDINE receiving oral anticoagulants, phenytoin or theophylline is recommended and a reduction in the dosage of these drugs may be necessary.

4.6 Pregnancy and lactation

Although tests in animals and clinical evidence have not revealed any hazards from the administration of CEDINE during pregnancy or lactation, both animal and human studies have shown that it does cross the placental barrier and is excreted in milk. As with most drugs, the use of CEDINE should be avoided during pregnancy and lactation unless essential.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

More than 56 million patients have been treated with Cimetidine world-wide and adverse reactions have been infrequent. Diarrhoea, dizziness or rash, usually mild and transient and tiredness have been reported. Gynaecomastia has been reported but is almost always reversible on discontinuing treatment. Biochemical or biopsy evidence of reversible liver damage has been reported occasionally. Reversible confusional states sometimes associated with mood and behavioural changes or insomnia, may occur, especially in elderly or very ill patients [e.g. those with renal failure] on high dosage. Thrombocytopenia and leucopenia including agranulocytosis (refer Section 4.4) reversible on withdrawal of treatment have been reported very rarely. There have been very rare reports of interstitial nephritis, acute pancreatitis, (refer Section 4.4) headache, myalgia, arthralgia, sinus bradycardia, tachycardia and heart block, all reversible on withdrawal of treatment. In common with other H_2-receptor antagonists there have been very rare reports of anaphylaxis. Reversible impotence has also been very rarely reported but no causal relationship has been established at usual therapeutic doses. Isolated increases in plasma creatinine have been of no clinical significance.

4.9 Overdose

Acute overdosage of up to 20 grams has been reported several times with no significant ill effects. Induction of vomiting and/or gastric lavage may be employed together with symptomatic and supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cimetidine is a histamine H_2-receptor antagonist which rapidly inhibits both basal and stimulated gastric secretion of acid and reduces pepsin output. Cimetidine may also have a mucosal protective effect independent of its anti-secretory action.

5.2 Pharmacokinetic properties

Cimetidine is readily absorbed from the gastro-intestinal tract and peak plasma concentrations are obtained about an hour after administration on an empty stomach. A second peak may be seen after about 3 hours. Food delays the rate of absorption with the peak plasma concentration occurring after about two hours.

The bioavailability of Cimetidine following oral administration is about 60 to 70% due to first pass metabolism. The elimination half-life from plasma is around 2 hours and is increased in renal impairment. Cimetidine is weakly bound,

about 20% to plasma proteins. Cimetidine is partially metabolised in the liver to the sulphoxide and to hydroxymethylcimetidine but most is excreted unchanged in the urine. Cimetidine crosses the placental barrier and is excreted into breast milk where concentrations are reported to be higher than those in plasma.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch
Povidone K25
Glycerol 85%
Sodium Laurilsulfate
Microcrystalline Cellulose
Sodium Starch Glycolate
Magnesium Stearate
Hypromellose
Macrogol 6000
Titanium Dioxide [E 171]
Yellow Iron Oxide [E 172]
Black Iron Oxide [E 172]

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

CEDINE 400 mg Tablets are packed in blisters of transparent, non-toxic polypropylene, welded on an internally film-coated aluminium semi-rigid support and are available in blister packs of 60 tablets.

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

Rowex Limited
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA 711/44/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 February 1991

Date of last renewal: 27 February 2006

10 DATE OF REVISION OF THE TEXT

August 2006