Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cimeldine 200 mg Film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Cimetidine 200mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets. (Short term: Tablets)
Pale green, circular, biconvex, film-coated tablet with the Clonmel logo on one face and the code '274' on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of benign ulceration of oesophagus, stomach, upper intestinal tract (including post-operative stomal area) and the 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.

4.2 Posology and method of administration

Route of administration

Oral

Adults: The usual dosage is 400mg twice a day with breakfast and at bedtime. Alternatively patients with duodenal or benign gastric ulceration may be treated with a single dose of 800 mg at bedtime. Regimes of 200 mg thrice daily with meals and 400 mg nocte or, if inadequate, 400 mg q.d.s. with meals and at bedtime may also be used.

In oesophageal reflux 400 mg q.d.s. with meals and at bedtime for 4 to 8 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 q.d.s. or occasionally higher.

Treatment should be given initially for at least 4 weeks (6 weeks in the case of benign ulcer). In patients who may benefit from a reduction of gastric secretion, dosage may be reduced to a maintenance of 400 mg at bedtime, or in the morning and at bedtime.

A similar maintenance regimen may be used to prevent relapse in patients with benign peptic ulceration. Patients on prolonged treatment (particularly those treated for more than one year) should be kept under regular surveillance. Antacids may be used concurrently if required.
In the prophylaxis of haemorrhage from stress ulceration, doses up to 2.4 g daily may be given in divided doses. 200 – 400 mg doses can be given every 4 to 6 hours.

In the prophylaxis of acid aspiration (Mendelson's syndrome), a single dose of 400 mg may be given 90 – 120 minutes before induction of general anaesthesia or, in obstetric patients, at the start of labour. While such a risk persists, a dose

of up to 400 mg may be repeated (parenterally if appropriate) at 4 hourly intervals as required, up to the usual maximum of 2.4 g/day.

In pancreatic insufficiency, for protection of pancreatic enzyme supplements, 800 – 1,600 mg/day may be given according to response in four divided doses, one to one and half hours before meals.

The total daily dose by any route should not exceed 2,400 mg.

Dosage should be reduced in patients with impaired renal function when creatinine clearance is below 50 ml/minute.

Creatinine Clearance	Daily Dosage
30 – 50 ml/minute	200 mg q.d.s.
15 – 30 ml/minute	200 mg t.d.s.
0 –15 ml/minute	200 mg b.d.

Cimetidine is removed by haemodialysis, but not to any significant extent by peritoneal dialysis.

Elderly: The normal adult dosage may be used unless renal function is markedly impaired.

Children: Experience in children is less than that in adults. In children more than 2 years old, cimetidine 25-30 mg/kg body weight per day in divided doses may be administered by either the oral or parenteral routes.

The use of cimetidine in children less than 2 years of age is not fully evaluated.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Confusional states, mood and behavioural changes and insomnia may occur especially in the elderly or very ill patients or those with renal failure. Those on high dosage are particularly at risk. These states are usually reversible.

Before initiation of cimetidine therapy for any gastric ulceration, malignancy should be excluded by endoscopy, and biopsy if possible. Treatment with cimetidine can mask symptoms and assist 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 or with new or recently changed dyspeptic symptoms.

Patients on prolonged cimetidine therapy (particularly those treated for more than one year) should be kept under regular surveillance with particular attention to the pathology of the gastrointestinal tract.

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

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

Close monitoring of prothrombin time is recommended when cimetidine is concurrently used with anticoagulants. Co-administration of therapeutic agents with a narrow therapeutic index, such as phenytoin or theophylline, may require dosage adjustment when starting or stopping concomitantly administered cimetidine (see Section 4.5).

In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia. A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H_2 receptor antagonists versus those who had

stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07-2.48).

4.5 Interaction with other medicinal products and other forms of interaction

Cimetidine can prolong the elimination of drugs metabolised by oxidation in the liver.

Pharmacological interactions with a number of drugs e.g. diazepam, propranolol have been demonstrated; only those with oral anticoagulants, phenytoin and theophylline and intravenous lignocaine appear to date to be of clinical significance. Close monitoring of patients on cimetidine receiving oral anticoagulants, phenytoin or theophylline is recommended. A reduction in their dosage may be necessary.

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.

Cimetidine has the potential to affect the absorption, metabolism or renal excretion of other drugs which is particularly important when drugs with a narrow therapeutic index are administered concurrently. The altered pharmokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment (see Section 4.4).

Interactions may occur by several mechanisms including:

1. Inhibition of certain cytochrome P450 enzymes (including CYP1A2, CYP2C9, CYP2D6 and CYP3A3/A4, and CYP2C18). Inhibition of these enzymes may result in increased plasma levels of certain drugs including wafarin-type coumarin anticoagulants (e.g. warfarin), tricyclic antidepressants (e.g. amitriptyline), class I antiarrhythmics (e.g. lidocaine), calcium channel blockers (e.g. nifedipine, diltiazem), oral sulfonylureas (e.g. glipizide), phenytoin, theophylline and metoprolol.
2. Competition for renal tubular secretion. This may result in increased plasma levels of certain drugs including procainamide, metformin, ciclosporin and tacrolimus.
3. Alteration of gastric pH. The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. atazanavir) or a decrease in absorption (e.g. some azole antifungals such as ketoconazole, itraconazole or posaconazole).
4. Unknown mechanisms. Cimetidine may potentiate the myelosuppressive effects (e.g. neutropenia, agranulocytosis) of chemotherapeutic agents such as carmustine, fluorouracil, epirbuicin, or therapies such as radiation. Isolated cases of clinically relevant interactions have been documented with narcotic analgesics (e.g. morphine).

4.6 Pregnancy and lactation

Cimetidine should not be administered during pregnancy or lactation in women breast-feeding infants unless considered essential by the physician. Animal studies of reproduction have shown no drug-related abnormality. Significant levels of drug reach breast milk.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Adverse experiences with cimetidine are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000), very rare (<1/10000).

Blood and lymphatic system disorders
Uncommon: Leucopenia
Rare: Thrombocytopenia, aplastic anaemia
Very rare: Pancytopenia, agranulocytosis

Immune system disorders
Very rare: Anaphylactic reaction is usually cleared on withdrawal of the drug.

Psychiatric disorders
Uncommon: Depression, hallucination. Confusional state, reversible within a few days of withdrawing cimetidine, has been reported, usually in elderly or ill patients.

Nervous system disorders
Common: Headache, dizziness

Cardiac disorders
Uncommon: Tachycardia
Rare: Sinus bradycardia
Very rare: Heart block

Gastrointestinal disorders
Common: Diarrhoea
Very rare: Pancreatitis. Pancreatitis cleared on withdrawal of the drug.

Hepatobiliary disorders
Uncommon: Hepatitis
Rare: Increased serum transaminase levels. Hepatitis and increased serum transaminase levels cleared on withdrawal of the drug.

Skin and subcutaneous tissue disorders
Common: Rash
Very rare: Alopecia and hypersensitivity vasculitis. Hypersensitivity vasculitis usually cleared on withdrawal of the drug.

Musculoskeletal and connective tissue disorders
Common: Myalgia
Very rare: Arthralgia

Renal and urinary disorders
Uncommon: Blood creatinine increased.
Rare: Interstitial nephritis. Interstitial nephritis cleared on withdrawal of the drug. Small increases in blood creatinine have been reported, unassociated with changes in glomerular filtration rate. The increases do not progress with continued therapy and disappear at the end of therapy.

Reproductive system and breast disorders
Uncommon: Gynaecomastia and reversible impotence. Gynaecomastia is usually reversible upon discontinuation of cimetidine therapy. Reversible impotence has been reported particularly in patients receiving high doses (e.g. in Zollinger-Ellison Syndrome). However, at regular dosage, the incidence is similar to that in the general population.
Very rare: Galactorrhoea

General disorders and administration site conditions
Common: Fatigue
Very rare: Fever. Fever cleared on withdrawal of the drug.

4.9 Overdose

Overdosage of up to 20g has been reported 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

Pharmacotherapeutic group: H2 - receptor antagonists
ATC code A02BA01

Cimetidine is a H_2 antagonist. It is highly selective and acts by antagonising the effects of histamine and other H_2 agonists at H_2 receptors present on parietal cells. This action of cimetidine is competitive and results in inhibition of gastric acid secretion in a dose-dependent manner. The degree of inhibition parallels the plasma concentration of the drug over a wide range.

Cimetidine inhibits basal and nocturnal secretion as well as stimulated secretion. It reduces both the volume of gastric juice secreted and its hydrogen ion concentration (pH). Output of pepsin, which is secreted by the chief cells of the gastric glands, generally falls in parallel with the reduction in volume of the gastric juice. Concentrations of gastrin in the plasma are not significantly altered during fasting conditions, however, the normal prandial elevation of gastrin in the plasma may be augmented.

5.2 Pharmacokinetic properties

Cimetidine is rapidly and almost completely absorbed. Hepatic first-pass metabolism results in bioavailability of about 70%. Absorption is little impaired by food. Peak plasma concentrations are attained in about 1 to 2 hours. Equilibrium dialysis has shown 13 to 25 percent of cimetidine to be protein bound in ulcer patients. The elimination half-life is about 2 – 3 hours. Cimetidine is eliminated primarily by the kidneys, and 60% or more may appear in the urine unchanged with much of the rest as oxidation products. There are three known metabolic products: cimetidine sulphoxide, hydroxymethyl cimetidine, and guanylurea cimetidine which may be formed non-enzymatically in vitro. Small amounts of cimetidine are recovered in the stool.

5.3 Preclinical safety data

No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Laurilsulfate
Microcrystalline Cellulose
Colloidal Anhydrous Silica
Sodium Starch Glycolate Type A
Magnesium Stearate
Povidone

<u>Film Coat</u>

Opadry OY-5912 - {Hypromellose
Titanium Dioxide (E171)
Macrogol
Quinoline Yellow Aluminium Lake (E104)
Iron Oxide yellow (E172)
FD & C Blue # 2/Indigo Carmine Aluminium Lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Blisters
Store below 25^{o}C
Store in the original package in order to protect from moisture.
Keep the blister in the outer carton.

6.5 Nature and contents of container

Blister packs consisting of 250µm clear PVC and 20µm hard temper aluminum foil contained in a carton.

Pack sizes:
100, 120 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

Clonmel Healthcare Limited,
Waterford Road,
Clonmel,
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0126/077/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 November 1989

Date of last renewal: 06 November 2009

10 DATE OF REVISION OF THE TEXT

October 2010