Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cimetidine 800 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800mg of cimetidine.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Cimetidine 800 mg tablets are film coated, pale green, oval shaped biconvex tablets marked ‘S49’ on one side and ‘Sterwin’ 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 of benign peptic ulcer disease under regular surveillance.

4.2 Posology and method of administration

The total daily dose by any route should not normally exceed 2.4g. Dosage should be reduced in patients with impaired renal function (see section 4.4).

Adults
For patients with duodenal or benign gastric ulceration a single daily dose of 800 mg at bedtime is recommended. Otherwise the usual dosage is 400mg twice a day with breakfast at bedtime. Regimens of 200 mg thrice daily with meals and 400 mg *nocte* (night) (1.0g/day) or, if inadequate, 400 mg *q.d.s* (four times a day) (1.6g/day) 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, 8 weeks in ulcer associated with continued non-steroid anti-flammatory agents). Most ulcers will have healed by that stage, but those which have not will usually do so after a further course of treatment. Treatment may be continued for longer periods in those patients who may benefit from a reduction of gastric secretion and the dosage may be reduced as appropriate to 400 mg at bedtime, or 400mg in the morning and at bedtime.

In patients with benign peptic ulcer disease, relapse may be prevented by continued treatment, usually with 400mg at

bedtime; 400mg 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.
Antacids may be used concurrently if required.

In the prophylaxis of haemorrhage from 'stress' ulceration doses up to a maximum of 2.4 g daily may be given in divided doses. 200 – 400 mg doses can be given every 4 to 6 hours by oral, nasogastric or parenteral routes (NB by direct intravenous injection a dose of 200 mg should not be exceeded – see parenteral dosage recommendations).

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 practice, 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 the short bowel syndrome, e.g. following substantial resection for Crohn's disease, the usual dosage range (see above) can be used according to individual response.

In pancreatic insufficiency, for protection of pancreatic enzyme supplements, 800 – 1600 mg daily 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 (see section 4.4).

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

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

4.3 Contraindications

Hypersensitivity to cimetidine or its excipients.

4.4 Special warnings and precautions for use

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

Creatinine Clearance	**Daily Dosage**
30-50 ml/minute	200 mg q.d.s (four times a day)
15-30 ml/minute	200 mg t.d.s (three times a day)
0-15 ml/minute	200 mg b.d. (twice a day)

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

Clinical trials of over six years continuous treatment and more than 15 years widespread use have not revealed unexpected adverse reactions related to long term therapy. The safety of prolonged use is not, however, fully established and care should be taken to keep patients on prolonged treatment (particularly those treated for greater than one year) under regular surveillance

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.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 lidocaine appear to date to be of clinical significance. Close monitoring of patients on cimetidine receiving oral anticoagulants, phenytoin, theophylline is recommended. A reduction in their dosage may be necessary.

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

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

If dizziness, headache or tiredness occurs, care should be taken regarding driving and use of machinery.

4.8 Undesirable effects

Adverse reactions: More than 56 million patients have been treated with cimetidine worldwide and adverse reactions have been infrequent.

<u>Uncommonly reported adverse events:</u>
Gastrointestinal disorders: diarrhoea.
Nervous system disorders: dizziness.
Skin and subcutaneous tissue disorders: rash, usually mild and transient.
General disorders and administration site conditions: tiredness.
Reproductive system and breast disorders: gynaecomastia, which is almost always reversible upon discontinuing treatment.

<u>Rarely reported adverse events:</u>
Blood and the lymphatic system disorders:-thrombocytopenia; leucopenia; agranulocytosis, (see section 4.4) which are reversible on withdrawal of treatment.
Immune system disorders: hypersensitivity vasculitis, which is reversible on withdrawal of treatment.
Psychiatric disorders: reversible confusional states, usually in elderly or already very ill patients e.g. those with renal failure; depression.

Hepato-biliary disorders: biochemical or biopsy evidence of reversible liver damage.

<u>Very rarely reported adverse events:</u>
The following adverse events are usually reversible upon withdrawal of treatment:

Immune system disorders: hypersensitivity reactions including anaphylaxis.
Psychiatric disorders: hallucinations.

Blood and the lymphatic system disorders: pancytopenia and aplastic anaemia.
Nervous system disorders: headache.
Cardiac disorders: sinus bradycardia; tachycardia, heart block.
Gastrointestinal disorders: acute pancreatitis.
Musculoskeletal, connective tissue and bone disorders: myalgia; arthralgia.
Renal and urinary disorders: interstitial nephritis.
General disorders and administration site conditions: fever.

Alopecia has been reported but no causal relationship has been established. Reversible impotence has also been very rarely reported but no causal relationship has been established at usual therapeutic doses. Isolated increases of 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

Pharmacotherapeutic category: H_2-Receptor antagonists, ATC Code: A02B A01.

An H_2 receptor antagonist well absorbed after oral dosing, metabolised in the liver and excreted mainly through the kidney with a T½ of about 3-4 hours. The effects on acid secretion are of longer duration.

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 and about 2 hours after administration with food. The bioavailability of cimetidine following oral administration is about 60-70% compared to an intravenous dose due to first pass metabolism. The elimination half life from plasma is around 2 hours and cimetidine is weakly bound, about 20%, to plasma proteins. Cimetidine is partially metabolised in the liver to the sulphoxide and to hydroxymethyl cimetidine but most is excreted unchanged in the urine. Cimetidine crosses the placental barrier and is excreted in breast milk when concentrations are reported to be higher than those in plasma. It does not readily cross the blood-brain barrier.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone
Dalfcol Green 3203
- patent blue V (E131)
- quinoline yellow (E104)
Sodium laurilsulfate
Purified talc
Magnesium stearate

Croscarmellose sodium
Hypromellose
Macrogol 400
Mastercote FA1507
- patent blue V aluminium lake (E131)
- quinoline yellow aluminium lake (E104)
- titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date for this product shall not exceed 3 years from the date of its manufacture.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC aluminium foil blisters contained in cardboard cartons containing 30, 50, 56, 112 and 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

Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey GU1 4YS
U.K

8 MARKETING AUTHORISATION NUMBER

PA 1046/9/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 March 1995

Date of last renewal: 14 March 2005

10 DATE OF REVISION OF THE TEXT

December 2005