SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Axid capsules 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nizatidine 150 mg

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

Hard gelatin capsule with dark yellow caps and pale yellow bodies coded FLYNN 3144, containing an off-white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of the following diseases where reduction of gastric acid is indicated:

Duodenal ulcer
Benign gastric ulcer
Prevention of duodenal or benign gastric ulcer recurrence
Gastric and/or duodenal ulcer associated with concomitant use of non-steroidal anti-inflammatory drugs.

4.2 Posology and method of administration

Adults: For treatment of duodenal ulcer, the recommended daily dose is 300 mg in the evening. Treatment should continue for four weeks, although this period may be reduced if healing is confirmed earlier by endoscopy. Most ulcers will heal within four weeks, but if complete ulcer healing has not occurred after four weeks therapy, patients should continue therapy for a further four weeks.

For the treatment of benign gastric ulcer, the recommended daily dose is 300 mg in the evening for four or, if necessary, eight weeks. Prior to treatment with nizatidine, care should be taken to exclude the possibility of gastric cancer.

If preferred, the 300 mg daily dose for the treatment of duodenal or benign gastric ulcer may be given as two divided doses of 150 mg in the morning and evening.

For the prevention of duodenal and/or benign gastric ulcer recurrence (prophylactic maintenance therapy) the recommended daily dose is 150 mg in the evening. Patients should be kept under regular surveillance.

Treatment should not be for more than one year without medical review to determine the need for continued treatment.

For the treatment of gastric and/or duodenal ulcer associated with concomitant use of non-steroidal anti-inflammatory drugs, the recommended daily dose is 300 mg daily (either 300 mg at bedtime or 150 mg twice daily, in the morning and in the evening) for up to 8 weeks. In most patients, the ulcers will heal within 4 weeks. During treatment, the use of non-steroidal anti-inflammatory drugs may continue.

The elderly: Age does not significantly influence efficacy or safety. Normally dosage modification is not required, except in patients who have moderate to severe renal impairment (creatinine clearance less than 50 ml/min).

Children: Not recommended, as safety and efficacy have not been established.

Patients with impaired renal function: Nizatidine is principally excreted via the kidneys.

For patients who have moderate renal impairment (creatinine clearance less than 50 ml/min) or patients who have severe renal impairment (creatinine clearance less than 20 ml/min), the dosage should be reduced as follows:

DOSAGE RECOMMENDED		
No Renal Impairment	**Moderate Renal Impairment (creatinine clearance: 20-50 ml/min)**	**Severe Renal Impairment (creatinine clearance: <20 ml/min)**
300 mg daily dose 150 mg daily dose	150 mg in the evening 150 mg on alternate days	150 mg on alternate days 150 mg every third day

4.3 Contraindications

Known hypersensitivity to H_2-receptor antagonists.

4.4 Special warnings and precautions for use

As nizatidine is partially metabolised by the liver and principally excreted by the kidneys, patients with impaired liver or kidney function should be treated with caution (see 'Posology and Method of Administration' Section).

Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

Patients receiving prophylactic maintenance therapy should be kept under regular surveillance by the prescribing physician. Treatment should not be for more than one year without medical review to determine the need for continued treatment.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction has been observed between nizatidine and aminophylline, theophylline, chlordiazepoxide, diazepam, lignocaine, phenytoin, ibuprofen, metoprolol, warfarin or lorazepam. Nizatidine does not inhibit the hepatic cytochrome P450-linked drug metabolising enzyme system but may increase absorption of salicylates when they are used in very high dosage. However, nizatidine and other histamine H_2-receptor antagonists can reduce the gastric absorption of drugs whose absorption is dependent on an acidic gastric pH. Approximately 35% of nizatidine is bound to plasma protein. Warfarin, diazepam, paracetamol, propantheline, phenobarbitone and propranolol did not effect plasma protein binding of nizatidine *in vitro*.

Nizatidine has no significant effect on the serum concentrations of gonadotrophins, prolactin, growth hormone, antidiuretic hormone, cortisol, tri-iodothyronine, thyroxine, testosterone, 5 alpha-dihydrotestosterone, androstenedione or oestradiol.

Experience in clinical trials indicates that nizatidine has no greater potential than placebo for antiandrogenic effects.

Absorption of nizatidine is not clinically significantly affected by food intake, anticholinergic agents or antacids. Charcoal administration may reduce absorption up to 20 per cent.

4.6 Pregnancy and lactation

Usage in pregnancy: The safety of nizatidine for use during pregnancy has not been established. Animal studies have shown no evidence of impaired fertility or teratogenicity attributable to nizatidine. Nizatidine should only be used in pregnant women, or in those planning pregnancy, if considered absolutely necessary, and then with caution.

Usage in lactation: Studies conducted in lactating women have shown that 0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Because of the growth depression in pups reared by lactating rats treated with nizatidine, Axid should be administered to nursing mothers only if considered absolutely necessary.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

In large scale clinical trials, sweating and urticaria were significantly more common in nizatidine treated patients when compared with placebo.

In the same trials, patients treated with both nizatidine and placebo had mild, transient, asymptomatic elevations of transaminases or alkaline phosphatase; rare instances of marked elevations (>500 iu/l) occurred in nizatidine treated patients. The overall rate of occurrences of elevated liver enzymes and elevations to 3 times the upper limit of normal, however, did not differ significantly from placebo. All abnormalities were reversible after discontinuation of nizatidine. Since introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported, with reversal of abnormalities after discontinuation.

The following effects have also been rarely reported, although a causal relationship has not always been established: thrombocytopenic purpura, fatal thrombocytopenia, exfoliative dermatitis, vasculitis, arthralgia, myalgia, gynaecomastia, impotence, hyperuricaemia, fever, nausea and reversible mental confusion.

Rare episodes of hypersensitivity reactions (e.g. bronchospasm, laryngeal oedema, rash, pruritus and eosinophilia), serum sickness and anaphylaxis have been reported.

4.9 Overdose

There is little experience of overdose in humans. Tested at very high doses in animals, nizatidine has been shown to be relatively non-toxic. Animal studies suggest that cholinergic-type effects, including lacrimation, salivation, emesis, miosis and diarrhoea, may occur following very large oral doses.

Treatment: Symptomatic and supportive therapy is recommended. Activated charcoal may reduce nizatidine absorption. The ability of haemodialysis to remove nizatidine from the body has not been conclusively demonstrated. However, this method is not expected to be efficient, since nizatidine has a large volume of distribution.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Nizatidine is a potent, selective, competitive and fully reversible histamine H_2-receptor antagonist with a rapid onset of action. It significantly decreases acid and pepsin concentration, together with the volume of basal and stimulated gastric secretion. In clinical trials, nizatidine usually abolished ulcer pain within the first week of therapy. Nizatidine 300 mg at bedtime significantly reduced overnight gastric secretion, but did not increase subsequent basal or meal stimulated gastrin production. Intrinsic factor is not decreased in subjects administered nizatidine.

5.2 Pharmacokinetic properties

Bioavailability of orally administered nizatidine is not significantly influenced by food or antacids.

Absorption of nizatidine after oral administration is rapid and peak plasma concentrations (700-1800 µg/l after 150 mg dose; 1400-3600 µg/l after 300 mg dose) are achieved within 3 hours.
Oral bioavailability exceeds 70%, and the elimination half-life is 1 to 2 hours, while plasma clearance is 40 to 60 l/h. Approximately 35% of nizatidine is bound to plasma protein. The volume of distribution is 0.8 to 1.5 l/kg. Minor first pass hepatic metabolism occurs (6%), but nizatidine is principally excreted via the kidneys, about 60% as unchanged drug. The principal metabolite is desmethyl nizatidine, with smaller quantities of sulphoxide and n-oxide also being formed. Desmethyl nizatidine is an active metabolite, of limited potency. More than 90% of an oral dose of nizatidine (including metabolites) is excreted in the urine within 12 hours.
Moderate to severe renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine. In individuals who are functionally anephric, the half-life is 3.5 to 11 hours, and the plasma clearance is 7 to 14 l/h.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber in addition to that summarised in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Pregelatinised starch
Dimeticone
Magnesium stearate

Capsule shell:
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin
Black edible printing ink, including:
Shellac
Black iron oxide (E172)
Soya lecithin
Polydimethylsiloxane

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/aluminium foil blister packs containing 15, 28, 30 or 56 capsules.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Flynn Pharma Ltd
Alton House
4 Herbert Street
Dublin 2
Republic of Ireland

8. MARKETING AUTHORISATION NUMBER

PA 1226/4/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28th February 1988/28th February 2003

10. DATE OF REVISION OF THE TEXT

December 2005