IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0593/019/001
Case No: 2036382

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

Stada Arzneimittel AG

Stadastrasse 2-18, **D-61118 Bad Vilbel**, **Germany**

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

Famulco 20mg, 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 **14/06/2007** until **15/11/2008**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Famulco® 20 mg, film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Famotidine 20mg

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

Round, biconvex, white film-coated tablets, engraved “20” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Prevention of recurrent duodenal ulcers
- Duodenal ulcer
- Benign gastric ulcer
- Zollinger-Ellison-Syndrome
- Symptomatic treatment of mild reflux oesophagitis

4.2 Posology and method of administration

Dosing instructions:

Duodenal ulcers and benign gastric ulcers
40 mg of famotidine once before going to sleep

Prophylactic treatment for recurrent duodenal ulcers
20 mg of famotidine in the evening

Zollinger-Ellison syndrome
Providing there has not been previous therapy with antisecretory medications, Zollinger-Ellison syndrome therapy should start by administering 20 mg of famotidine (corresponding to one film-coated tablet of Famulco® 20 mg) every 6 hours. Depending on the acid secretion and the patient's clinical response, a dosage titration should be performed as treatment continues until the desired acid levels have been reached (e.g. < 10 mEq/h in the hour preceding the next dose of famotidine). If the desired inhibition of acid secretion cannot be attained with a daily dosage of 800 mg, alternative treatment should be considered to regulate acid secretion, since no long-term experience with dosages of more than 800 mg of famotidine/day have been recorded.
Treatment should be continued for as long as clinically necessary.
Patients who have previously undergone H_2 receptor antagonist treatment can begin famotidine treatment at a higher dosage than the initial dosage that is usually recommended. The dosage depends on the severity of the disease and the dosage of previous medications.

Symptomatic treating of mild reflux oesophagitis
A daily dosage of twice 20 mg of famotidine (corresponding to two film-coated tablets of Famulco® 20 mg) is recommended.

Famotidine is primarily eliminated via the kidneys. For patients with impaired renal function in whom creatinine clearance is less than 30 ml/min, the daily dosage of famotidine should be reduced to 50%.

Dialysis patients should also take dosages that are reduced to 50%. Famulco® 20 mg should be administered at the end of dialysis or thereafter since some of the active ingredient is removed via dialysis.

Mode and duration of administration:
Famulco® 20 mg should be swallowed whole with some liquid. It does not need to be taken at mealtimes.

Prophylactic treatment of recurrent duodenal ulcers
With regards to the maintenance therapy for preventing the recurrence of duodenal ulceration, the recommended maintenance dose of 20mg has been continued effectively in clinical studies of 12 months duration.

Duodenal ulcers and benign gastric ulcers
In treating duodenal ulcers and benign gastric ulcers, therapy should be conducted for 4 to 8 weeks. This period, however, may be shortened if endoscopy reveals that the ulcer has healed. If an endoscopic examination does not yield such findings, the treatment should be continued for another 4 weeks.

Zollinger-Ellison syndrome
Treatment should be continued for as long as clinically necessary.

Symptomatic treating of mild reflux oesophagitis
Generally, treatment should be conducted for 6 weeks, if necessary for 12 weeks.

4.3 Contraindications

Famulco® 20 mg may not be administered where there is known hypersensitivity to the active ingredient, famotidine, or to any of the other ingredients. If symptoms of hypersensitivity develop, Famulco® 20 mg should be discontinued.

There is not sufficient information about the safety and efficacy of famotidine in children. Therefore, children should not be treated with Famulco® 20 mg.

4.4 Special warnings and precautions for use

Malignancy cannot necessarily be ruled out when treatment with Famulco® 20 mg has a positive effect on the symptoms. Appropriate diagnostic measures should be used to determine the non-malignancy of an ulcer before famotidine treatment is undertaken.

Famotidine is primarily eliminated via the kidneys and partially broken down in the liver. Caution must therefore be exercised in patients with impaired renal function.

The daily dosage should be reduced for patients with impaired renal function (cf posology).

Do not administer Famulco® 20 mg in cases of minor gastrointestinal complaints.

In patients with duodenal ulcers and benign gastric ulcers the H. pylori status should be determined. Whenever possible, patients with H. pylori should undergo eradication therapy to eliminate the bacteria.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically important metabolic interactions with other drugs or substances have been recorded.

During concomitant use of substances whose absorption is affected by gastric acid levels, a possible change in the absorption of these substances should be considered. The absorption of ketoconazole or itraconazole can be reduced, ketoconazole should be administered two hours before administering famotidine.

Concomitant use of famotidine and antacids can reduce the famotidine absorption and lead to lower plasma levels of famotidine. Therefore, famotidine should be administered 1-2 hours before taking an antacid.

Concomitant use of sucralfate inhibits the absorption of famotidine. Therefore, sucralfate should as a rule not be administered within two hours of the famotidine dose.

The administration of probenecid can delay the elimination of famotidine. Concomitant use of probenecid and Famulco® 20 mg should be avoided.

4.6 Pregnancy and lactation

Data on a limited number of exposed pregnancies indicate no adverse effects of famotidine on pregnancy or on the health of the fetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3).

Famotidine should only be prescribed to pregnant women after a careful risk/benefit assessment has taken place.

Famotidine is eliminated via breast milk. Since there is a possibility of famotidine affecting the infant’s gastric acid secretion, women undergoing famotidine treatment should refrain from breastfeeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Blood and the lymphatic system disorders
Very rare (< 0.01%): Thrombocytopenia, leukopenia, agranulocytosis and pancytopenia.

Immune system disorders
Rare (> 0.01%, < 0.1%): Hypersensitivity reactions (anaphylaxis, angioneurotic edema, bronchospasm).

Psychiatric disorders
Very rare (< 0.01%): Reversible psychological disturbances (e.g. hallucinations, disorientation, confusion, anxiety, agitation, depression).

Nervous system disorders
Common (>1%): Headache, dizziness.
Very rare (< 0.01%): Paresthesia, drowsiness, sleeplessness, epileptic seizures (grand mal).

Gastrointestinal disorders
Common (> 1%): Constipation, diarrhea.
Uncommon (> 0.1%, < 1%): Dry mouth, nausea, vomiting, gastrointestinal complaints, flatulence, loss of appetite.

Hepato-biliary disorders
Rare (> 0.01%, < 0.1%): Intrahepatic cholestasis (visible sign: jaundice).

Skin and subcutaneous tissue disorders
Uncommon (> 0.1%, < 1%): Rash, pruritus.
Rare (> 0.01%, < 0.1%): Urticaria.
Very rare (< 0.01%): Hair loss, severe skin reactions (e.g. toxic epidermal necrolysis).

Musculoskeletal, connective tissue and bone disorders
Rare (> 0.01%, < 0.1%): Arthralgia.
Very rare (< 0.01%): Muscle cramps.

Reproductive system and breast disorders
Very rare (< 0.01%): Impotence, reduced libido.

General disorders and administration site conditions
Uncommon (> 0.1%, < 1%): Fatigue.
Very rare (< 0.01%): Feelings of tightness in the chest.

Investigations
Rare (> 0.01%, < 0.1%): Increase in laboratory values (transaminases, gamma GT, alkaline phosphatase, bilirubin).

4.9 Overdose

There are no reports of overdosing with famotidine.

If this should occur, efforts should be made to inhibit absorption and relieve symptoms.

The usual measures to remove unabsorbed material from gastro-intestinal tract should be employed together with clinical monitoring and supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: A02B A03
Pharmacotherapeutic group: Histamine H2 receptor antagonist/gastrointestinal medication

Famotidine is a competitive histamine H2 receptor antagonist which leads to the inhibition of gastric acid secretion mediated by the H2 receptors. In addition to the gastric acid levels, the pepsin level is also reduced. To a lesser extent there is also a decrease in the volume of the basal gastric juice and the gastric juice secreted on stimulation. Pharmacological effects on the CNS, immunological, cardiovascular or respiratory parameters have not been observed.

The drug takes effect within an hour of oral administration and reaches its peak efficacy within 1-3 hours.

Individual oral doses of 20 mg and 40 mg effectively inhibited the basal night-time secretion of gastric acid; mean gastric acid secretion was inhibited over a period of 10 hours by 86% and 94%, respectively. The same doses, administered in the morning, inhibited the gastric acid secretion stimulated by eating for 3-5 hours p.a. by a mean of 76% and 84%, respectively. 8-10 hours after administration, the levels were at 25% and 30%, respectively, although the effect of one 20 mg dose persisted for only 6-8 hours in some of the volunteers. Repeated administration did not lead to an accumulation of the active ingredient.

The basal night-time intragastral pH value was increased to a mean of 5 and 6.4 by evening doses of 20 mg and 40 mg of famotidine, respectively. When famotidine was administered after breakfast, the pH value in both the 20 mg and the 40 mg groups was increased to approximately 5 after 3 and 8 hours.

Famotidine had little or no effect on the fasting and postprandial serum gastrin levels. Gastric emptying and exocrine pancreas function were not affected by famotidine, nor were hepatic and portal blood flow. There was also no effect on

endocrine function. Hormone levels of prolactin, cortisone, thyroxin (T4) and testosterone remained unchanged under famotidine treatment.

5.2 Pharmacokinetic properties

Famotidine kinetics are linear.

Famotidine is quickly resorbed after oral administration.

Oral bioavailability is about 40%.

Peak plasma concentrations are achieved 1-3.5 hours after administration. Peak plasma concentrations are approximately 0.04-0.06 µg/ml after administration of 20 mg of famotidine and 0.075 to 0.1 µg/ml after administration of 40 mg of famotidine. Repeated administration does not lead to an accumulation of the active ingredient. Famotidine absorption is not influenced by concomitant food intake.

Famotidine is found in the cerebrospinal fluid only to a limited extent. The fluid/plasma ratio 4 hours after administering 40 mg of famotidine was a mean of 0.1.

Famotidine is excreted in maternal milk. 6 hours after oral administration, a milk/plasma concentration ratio of 1.78 was reached. The elimination half-life in the plasma is 2.6-4 hours.

Up to 30-35% of the active ingredient is metabolised in the liver; a sulfoxide metabolite is formed.

24 hours after oral administration, 25-30% of the active ingredient is excreted via the urine unchanged; after intravenous administration, 65-70% is excreted unchanged in urine. Renal clearance is 250-450 ml/min, which indicates tubular secretion. A slight amount can be eliminated as sulfoxide.

Renal insufficiency:
As renal function declines, renal and total clearance of famotidine decrease without there being an increase in non-renal elimination. The elimination half-life after intravenous injection of a single dose of 20 or 10 mg of famotidine is increased to 4.5-9 hours in moderate renal insufficiency (creatinine clearance 60-30 ml/min), to 10-12 hours in severe renal insufficiency (creatinine clearance < 30 ml/min) and to 18-27 hours in patients with terminal renal insufficiency or anuria. The amount of unchanged famotidine excreted with the urine is reduced to 60% in patients with moderate renal insufficiency. In cases of severe renal insufficiency it is only 25%.

Depending on the dialysis procedure (haemofiltration, 5-hour haemodialysis or continuous haemofiltration), dialysis patients have an elimination half-life of 7-14 hours after intravenous administration of 20 mg of famotidine; after oral administration of 20 mg of famotidine, it is 22.5 hours.

Liver function impairment:
The pharmacokinetics of famotidine are unchanged in patients with liver function impairment.

Kinetics among elderly patients:
Pharmacokinetic studies on elderly patients showed no signs of any clinically significant age-related changes; however, age-related impairment of renal function should be considered when determining the dosage.

5.3 Preclinical safety data

Preclinical data regarding famotidine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Microcrystalline cellulose, maize starch, pre-gelatinised maize starch, povidone, talc, magnesium stearate.
Tablet coat: Hypromellose, talc, titanium dioxide (E171), propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

The film-coated tablets are packed in PVC/PVDC-aluminium blister packs.
10, 15, 20, 28, 30, 50, 56, 60, 90, 100, 250, 500, 1000 film-coated 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

STADA Arzneimittel AG,
Stadastraße 2 – 18,
61118 Bad Vilbel,
Germany.

8 MARKETING AUTHORISATION NUMBER

PA 593/19/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th November 1999
Date of last renewal: 16th November 2003

10 DATE OF REVISION OF THE TEXT

April 2005