Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pepcid Duo Chewable Tablets Famotidine 10mg Magnesium Hydroxide 165mg Calcium Carbonate 800mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:
Famotidine 10.00 mg
Magnesium hydroxide 165.00 mg
Calcium carbonate 800.00 mg

Excipients with known effect:
Lactose monohydrate (62.31 mg/tablet), glucose monohydrate (642.61 mg/tablet) and benzyl alcohol (0.000238 mg/tablet).
Each tablet also contains maltodextrin (71.41mg/tablet) which contains glucose.

For the full list of excipients, see section 6.1.

Note: 165 mg of magnesium hydroxide means 69.3 mg of elemental magnesium and 800 mg of calcium carbonate means 320 mg of elemental calcium

3 PHARMACEUTICAL FORM

Chewable tablet.

Green coloured, mottled round chewable tablet with concave centre debossed with P.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pepcid Duo is indicated in short-term symptomatic treatment of heartburn and acid regurgitations in adults and adolescents 16 years & over.

4.2 Posology and method of administration

Posology
FOR ADULTS AND ADOLESCENTS (16 years & over).

Chew one tablet thoroughly when symptoms occur, and swallow preferably with a glass of water. Do not exceed 2 tablets per day.

Treatment duration is limited to 2 weeks (see section 4.4 Special warnings and Precautions for use).

Paediatric population
The safety and efficacy of Pepcid Duo in children under 16 years of age has not yet been established (no data are available).

Elderly
No dosage adjustment is required for the elderly.

Renal Impairment
This medicine is contraindicated in patients with severe renal failure (see section 4.3 Contraindications).
Patients with renal impairment should consult their physician before taking famotidine/antacid combination (Please refer to section 4.4 Special warnings and precautions for use).

Hepatic Impairment
No dosage adjustment is required for famotidine/antacid combination in hepatic impairment (see also section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Severe renal failure.
- Cross sensitivity in H2-receptor antagonists has been observed. Famotidine/antacid combination should not be administered to patients with a history of hypersensitivity to other H2-receptor antagonists.

4.4 Special warnings and precautions for use

Warnings:

- Patients should consult a physician or pharmacist before use with any other medication. Antacids may interact with certain medications (see section 4.5)
- Patients with renal or hepatic impairment should consult a physician before using Pepcid Duo Chewable Tablets. In case of renal failure, monitoring of serum magnesium and calcium should be undertaken.

- Pepcid Duo is contraindicated in patients with severe renal failure (see section 4.3).
- As some serious underlying conditions can have symptoms in common with simple indigestion, it is recommended patients seek medical advice in case of indigestion symptoms accompanied by unintentional weight loss, difficulty swallowing, persistent abdominal discomfort, heartburn occurring for the first time or if these symptoms have recently changed.
- Patients with pre-existing known hypercalcaemia, hypermagnesaemia, hypophosphataemia, hypercalcuria, a history of renal calculi or nephrocalcinosis should consult a physician before using famotidine/antacid combination.

- As this product contains lactose, glucose and benzyl alcohol:

- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Patients with rare glucose-galactose malabsorption should not take this medicine.
- This medicine contains 0.000238 mg benzyl alcohol in each tablet which is equivalent to 0.000129 mg/g. Benzyl alcohol may cause allergic reactions. High volumes of benzyl alcohol should be use with caution and only if necessary, especially in subjects pregnant or breastfeeding, or with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

- With long term use, especially during concomitant treatment with other calcium products and/or Vitamin D products, there is a risk of hypercalcaemia with subsequent kidney function impairment.
- Patients should stop use and consult a physician if new symptoms develop or if they experience dysphagia (difficulty swallowing) odynophagia (pain on swallowing), sever vomiting, melaena (black stools), choking or chest pain.

Precautions for use:
If symptoms persist after 2 weeks of continuous treatment or get worse, an etiologic survey must be done and the conduct of the treatment should be re-evaluated.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to antacid components (magnesium hydroxide, calcium carbonate)

Antacids interact with numerous other medicines taken orally. A decrease of the absorption of these medicines administered concomitantly has been observed. As a precaution, it is recommended to space out the dosing of antacids and any of the medications mentioned below at least 2 hours apart.

Antibiotics (clindamycine, cyclines, quinolones and fluoroquinolones, penicillamines, ethambutol, isoniazide), beta-blocking agents, bisphosphonates, glucocorticosteroids, integrase inhibitors (dolutegravir, elvitegravir), phenothiazine neuroleptics, thyroid hormones, salicylates, chloroquine, diflunisal, digoxin, estramustine, fexofenadine, fluor, indomethacin, iron, ledipasvir phosphore, proguanil, rosuvastatine, strontium, zinc, sodium and calcium polystyrene sulphonate resins, sulpiride, teriflunomide.

Bioavailability of antiretroviral medications (e.g. integrase inhibitors such as raltegravir, dolutegravir, elvitegravir) is significantly reduced by metal-cation containing antacids and dietary supplements.

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Interactions related to famotidine
Due to its H2-antagonist effect, famotidine may decrease the absorption of the following compounds:

- Atazanavir,
- Rilpivirine,
- Cyanocobalamine,
- Most of tyrosines kinase inhibitors (excluding vandetanib, imatinib): Co–administration of famotidine with the tyrosine kinase inhibitors (TKIs) dasatinib, erlotinib, gefitinib, pazopanib may decrease plasma concentrations of TKIs resulting in lower efficacy, therefore co-administration of famotidine with these TKIs is not recommended. For further specific recommendations please refer to the product information of individual TKI medicinal products.

Risk of loss of efficacy of calcium carbonate when co-administered as phosphate binder with famotidine in haemodialysis patients.

Interaction common to famotidine and antacids
Famotidine and antacids may decrease the absorption of the following compounds and co-administration should be avoided if possible:

- Azol antifungals (ketoconazole, itraconazole, posaconazole),
- Ulipristal.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Famotidine:
A large amount of data from pregnant women (more than 1000 exposed outcomes) indicated no malformative nor feto/neonatal toxicity.

Calcium carbonate and magnesium hydroxide:
In animals, only limited data are available.
In pregnant women, no malformative or foetotoxic effects was seen in the recommended posology but the data available on the pregnancies are too limited to exclude any risk.
It should be considered the presence of:

- Magnesium salts with the risk of diarrhoea,
- Calcium salts, which after a long-term treatment at high doses, can exposed to a risk of hypercalcaemia with a calcinosis of different organs, especially a nephrocalcinosis.

Famotidine, calcium carbonate and magnesium hydroxide:
There are no adequate, well-controlled clinical studies in pregnancy or breastfeeding women for the combination of calcium carbonate, famotidine, and magnesium hydroxide. This product should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs the possible risks to the developing foetus.

Breast-feeding
Famotidine has been identified in breastfed newborns/infants of treated mother. There is insufficient information on the effects of famotidine in newborns/infants.

A decision must be made whether to discontinue breast-feeding or to discontinue / abstain from therapy with famotidine / antacid combination taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

4.7 Effects on ability to drive and use machines

Some patients have experienced adverse reactions such as dizziness and somnolence while taking famotidine. Patients should be informed that they should avoid driving vehicles or operating machinery or doing activities which require prompt vigilance if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

The frequencies are provided according to the following convention:
Very common ≥ 1/10
Common ≥ 1/100 and ≤ 1/10
Uncommon ≥ 1/1,000 and ≤ 1/100
Rare ≥ 1/10,000 and ≤ 1/1,000
Very rare < 1/10,000
Not known (cannot be estimated from the available data).

Adverse Reactions By Body System (reported with famotidine / antacid combination)

SOC	Frequency	Adverse Event Preferred Term
Immune system disorders	Not known	Hypersensitivity Anaphylactic reaction
Nervous system disorders	Common	Headache
	Uncommon	Nervousness Paresthesia
		Dizziness
	Not known	Somnolence
Gastrointestinal disorders	Uncommon	Abdominal discomfort and pain
		Abdominal distension
		Nausea
		Diarrhoea
		Flatulence
		Dyspepsia
		Eructation
		Dysgeusia
		Oropharyngeal discomfort and pain
		Dry mouth, thirst
		Vomiting
	Not known	Abdominal pain upper
Skin and subcutaneous tissue disorders	Not known	Pruritus
		Rash
		Urticaria
		Angioedema
General disorders and administration site conditions	Not known	
		Asthenia, fatigue

Other side effects noted in isolated reports with higher dosages of famotidine in principle cannot be excluded.

There have been very rare reports of:

- Cutaneous: as with other H2 antagonists, severe skin reactions (toxic epidermal necrolysis).

- Hypersensitivity reactions: bronchospasm.

- Hepatic disorders including hepatic cholestasis and such as raised laboratory values for transaminases, gamma-GT, alkaline phosphatase and bilirubin.

- Neurological disorders such as hallucinations: disorientation, confusion and insomnia, epileptic seizures, drowsiness and agitation and depression related states. These have been reported to be reversible on stopping medication.

- Blood disorders such as thrombocytopenia, leucopenia, agranulocytosis and pancytopenia.

- Musculoskeletal disorders, such as muscle cramps.

- Others such as impotence, reduced libido, breast tension.

- Alopecia

- Malaise

The following side effects are generally attributed to antacids containing calcium and magnesium salts: change in stool frequency and consistence, bloating and fullness.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Patients have tolerated doses up to 800 mg/day of famotidine for more than a year without development of significant adverse effects.

No specific symptoms of overdose have been identified with this particular combination of substances.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: H_2 ANTAGONIST/ANTACID.
ATC code: A02BA53, famotidine, combinations

Famotidine reduces the acid and pepsin production, as well as the volume of basal, nocturnal and stimulated gastric secretion. Magnesium hydroxide and calcium carbonate have antacid properties by neutralisation mechanism.

Acid neutralisation capacity per tablet is evaluated at 21 mEq (USP method).

A study measuring gastric and oesophageal pH conducted on 23 patients demonstrated that the administration of the combination famotidine 10mg/antacid 21mEq with 60ml of water one hour after a high-fat evening meal produces an immediate increase of oesophageal pH.

The increase of the gastric pH, above the increase observed with placebo and antacid alone, remains for 12 hours.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of famotidine are not significantly modified when administered with magnesium hydroxide 165mg and calcium carbonate 800mg.

Famotidine:
Famotidine obeys linear kinetics.

Famotidine is rapidly absorbed with dose-related peak plasma concentration occurring at 1-3 hours after administration.

The mean bioavailability of an oral dose is 40-45 %. It is not modified when taken during meals. First-pass metabolism is minimal. Repeated doses do not lead to accumulation of the drug.

Protein binding in the plasma is relatively low (15-20 %). The plasma half-life after a single oral dose or multiple repeated doses (for 5 days) is approximately 3 hours.

Metabolism occurs in the liver, with formation of an inactive metabolite, the sulfoxide.

Following oral administration, the mean urinary excretion of famotidine is 65-70 % of the absorbed dose, 25 to 30 % as unchanged compound. Renal clearance is 250 to 450ml/min, indicating some tubular excretion. A small amount may be excreted as the sulfoxide.

The half-life is prolonged in patients with renal impairment.

Calcium carbonate and Magnesium hydroxide:
Calcium carbonate and magnesium hydroxide are converted to soluble chloride salts by gastric acid. Approximately 10% of the calcium and 15-20% of the magnesium is absorbed, and the remaining soluble chlorides are reconverted to insoluble salts, and are eliminated in the faeces. In individuals with normal kidney function the small amounts of calcium and magnesium that are absorbed are rapidly excreted by the kidneys.

5.3 Preclinical safety data

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

GENERAL TOXICOLOGY
Famotidine
Famotidine has low acute and repeated dose toxicity when administrated orally.

Magnesium hydroxide
Magnesium hydroxide low acute and repeated dose toxicity.

Calcium carbonate
Calcium Carbonate has low acute and repeated dose.

GENOTOXICITY
Famotidine
Famotidine was reported to be non-genotoxic in in-vitro and in-vivo assays.

Magnesium hydroxide
Magnesium hydroxide was reported to be non-genotoxic in in-vitro assays.

Calcium carbonate
Calcium Carbonate is reported to be non-genotoxic in in-vitro assays.

CARCINOGENICITY
Famotidine
Famotidine did not reveal carcinogenic potential in animal studies.

Magnesium hydroxide
No carcinogenic data on magnesium hydroxide was reported in published literature. However, mice fed magnesium chloride for 96 weeks showed no carcinogenic potential.

Calcium carbonate
There is no non-clinical data available. However, calcium carbonate is unlikely to have carcinogenic potential as both calcium and carbonate are natural constituents of cellular systems in humans.

Development and Reproductive Toxicity

teratogenicity

Famotidine
Famotidine did not reveal any teratogenic effects in rat and rabbit studies.

Magnesium hydroxide
Magnesium hydroxide did not cause any teratogenic effects in combined repeated dose and reproductive/developmental toxicity studies in rats.

Calcium carbonate
Calcium carbonate did not cause any developmental/teratogenicity in rats.

FERTILITY
Famotidine
Famotidine did not impair fertility in rat and rabbit reproductive toxicity studies.

Magnesium hydroxide
Magnesium hydroxide did not produce any effects on reproduction in combined repeated dose and reproductive/developmental toxicity studies in rats.

Calcium carbonate
Calcium carbonate did not impair fertility in combined repeated/reproductive/developmental toxicity studies in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Glucose monohydrate
- Sucralose (E955)
- Lactose monohydrate
- Crospovidone
- Cellulose acetate
- Maltodextrin (contains glucose)
- Liquid paraffin
- Magnesium stearate (E572)
- Hypromellose (E464)
- Hydroxypropylcellulose (E463)
- Cool Spearmint flavour (contains benzyl alcohol)
- Prosweet flavour (sugarless)
- FD&C Blue No. 1, Aluminium Lake, Certified
- Ferric oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

2 tablets in blister (PVC/ACLAR)
6 tablets in blister (PVC/ACLAR)
12 tablets in blister (PVC/ACLAR)
18 tablets in blister (PVC/ACLAR)
24 tablets in blister (PVC/ACLAR)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA23490/027/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th September 2000

Date of last renewal: 21st September 2009

10 DATE OF REVISION OF THE TEXT

March 2024