MODULE 2.4

NON-CLINICAL OVERVIEW

Famotidine/REMEDICA

(Film-coated tablets containing 20 mg or 40 mg famotidine)

Title:	**MODULE 2.4 - NON CLINICAL OVERVIEW** **Famotidine/REMEDICA** **(Film-coated tablets containing 20 mg or 40 mg famotidine)**
Signed by:	[redacted]
Signature:	
Date:	**18/07/2023**
Version:	**1.0**

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LIST OF ABBREVIATIONS

Ach: acetylcholine
ALDH-1: aldehyde dehydrogenase-1
ALP: alkaline phosphatase
ALT: alanine transaminase
ARA: acid-reducing agent
AST: aspartate transaminase
AUC: area under the curve
CCK2: cholecystokinin 2
CCl(4): tetrachloride
CIM: cimetidine
CL: total plasma clearance
C_{max}: maximum plasma concentration
C_{min}: minimum plasma concentration
CNS: central nervous system
COPD: chronic obstructive pulmonary disease
CSF: cerebrospinal fluid
Css: concentrations at steady-state
DPPH: 1,1-diphenyl-2-picryl hydrazyl
DU(s): duodenal ulcer(s)
ECG: electrocardiogram
ECL: enterochromaffin-like
ED_{50}: median effective dose
EEG: electroencephalogram
EMs: extensive metabolizers
FAM: famotidine
GU(s): gastric ulcer(s)
H. pylori: Helicobacter pylori
h.s.: at bedtime
H2RA(s): histamine-2 receptor antagonist(s)
HD-MTX: high-dose methotrexate
i.v.: intravenous
I/R: ischemia/reperfusion
LPS: lipopolysaccharide
LVP: left ventricular pressure
MPT: mean percentage time
MTX: methotrexate
NIZ: nizatidine
NSAID(s): nonsteroidal anti-inflammatory drug(s)
OATs: organic anion transporters
OCTs: organic cation transporter
OR: odds ratio
PCA: prothrombin complex activity
PGE2: prostaglandin E2
PMs: poor metalolizers
PPI(s): proton-pump inhibitor(s)
PUD: peptic ulcer disease
RAN: ranitidine
sSOL: subjective sleep onset latency

SUC: sucralfate
t_{max}: time of peak plasma concentration
TNF: tumor necrosis factor
TRH: thyrotropin-releasing hormone
Vd: volume of distribution
Vss: volume of distribution at steady-state
Vz: volume of distribution during the terminal log-linear phase
ZES: Zollinger-Ellison syndrome

2.4.1. OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

Peptic ulcer disease (PUD), a common disorder of the digestive system, is defined as digestive tract injury that results in a mucosal break greater than 3–5 mm, with a visible depth reaching the submucosa [redacted] PUD comprises both gastric (GU) and duodenal ulcers (DUs) defects that penetrate, respectively, beyond the muscularis mucosae of the gastric or duodenal mucosa-and its complications can include upper gastrointestinal bleeding, perforation and, rarely, gastric outlet obstruction [redacted] Bleeding, which manifests as melena or haematemesis, can occur without any warning symptoms in almost half of patients. Perforation typically presents with sudden onset of intense pain in the upper abdomen. Dependent on age and comorbidity, mortality can be as high as 20% [redacted]

PUD has various causes; however, *Helicobacter pylori (H. pylori)*-associated PUD and nonsteroidal anti-inflammatory drugs (NSAIDs)-associated PUD account for the majority of the disease etiology. More specifically, *H. pylori* is responsible for 90% of DUs and 70% to 90% of gastric ulcers (GUs) due to inflammation of the gastric mucosa. *H. pylori* infection is more prevalent among those with lower socioeconomic status and is commonly acquired during childhood. NSAIDs or aspirin use is the second most common cause of PUD after *H. pylori* infection, resulting in decreased gastric mucus and bicarbonate production and a decrease in mucosal blood flow. Apart from NSAIDs, corticosteroids, bisphosphonates, potassium chloride, and fluorouracil have been implicated in the etiology of PUD. Furthermore, smoking appears to play a role in DUs, but the correlation is not linear. Alcohol can irritate the gastric mucosa and induce acidity [redacted]

Gastroprotectant drugs, such as proton-pump inhibitors (PPIs), prostaglandin analogues, and histamine-2 receptor antagonists (H2RAs), have been developed for the protection of the mucosa, healing of mucosal damage, and stabilisation of gastrointestinal bleeding, and are prescribed for the prevention of PUD, to promote healing, and as treatment for bleeding complications [redacted] Although PPIs have a stronger acid suppression capacity than H2RAs, patients using H2RAs are at a lower risk of pneumonia and *Clostridium difficile* infection than PPIs users [redacted] Moreover, omeprazole could be considered as a treatment of choice with specific action on the proton pump and no side effects. However, with this drug the danger of permanent hypergastrinaemia being associated with fundic carcinoid induction should be appreciated [redacted]

H2RAs decrease gastric acid secretion by reversibly binding to histamine-2 receptors located on gastric parietal cells, functioning as competitive antagonists, thereby inhibiting the binding and activity of the endogenous ligand histamine. The effect of H2RAs is largely on basal and nocturnal acid secretion, which is important in peptic ulcer healing. Four H2RAs have been approved for clinical use: cimetidine (CIM), famotidine (FAM), ranitidine (RAN), and nizatidine (NIZ) [redacted]*).*

Focusing on FAM, an H2RA with a thiazole nucleus, data from the literature indicate that because of its chemical structure FAM has a much greater potency; approximately 8 and 20 times more potent than RAN and CIM, respectively, on an equimolar basis, and affinity for the histamine-2 receptor [redacted] Moreover, FAM has a longer duration of action than either RAN or CIM. Because FAM does not interact with cytochrome P450 of the hepatic enzyme system, it does not appear to affect the metabolism of drugs metabolized by this system, thus FAM has a notable lack of drug-drug interactions when compared with RAN and CIM [redacted]

The longer duration of action of FAM may reflect an H2-receptor interaction unique to FAM and would suggest that FAM may be of particular benefit in patients with gastric hypersecretion, including Zollinger-Ellison syndrome (ZES) patients. This is further supported because of its increased antisecretory potency and lack of antiandrogenic effects at higher FAM doses [redacted] ZES is a group of symptoms comprised of severe PUD, gastroesophageal reflux disease (GERD), and chronic diarrhoea caused by a gastrin-secreting tumor of the duodenum or pancreas (gastrinoma triangle) that results in increased stimulation of acid-secreting cells of the stomach [redacted] Because of the overlap between ZES and PUD, an accurate incidence cannot be determined for ZES, but gastrinomas are found in every 0.1 to 3 persons per million. There are more females than males developing ZES, and all age groups reported having ZES [redacted]

FAM is indicated for the treatment of the following conditions in which a reduction in gastric acid secretion is recommended:

- DUs
- Benign peptic ulcers (gastric ulcers)
- ZES [redacted]

FAM has been reviewed [redacted]

For the purpose of the current Non-Clinical Overview a thorough literature review was performed in the public domain, in order to adequately describe the pharmacology, pharmacokinetics, efficacy and toxicology profiles of FAM in the aforementioned indications in non-clinical studies.

The main search was performed in [redacted] and included the following query "famotidine[Title/abstract] AND english[Filter]" that resulted in 1982 items (14 June 2023).

All relevant review articles on famotidine were thoroughly reviewed and the included references were also assessed. The search strategy further involved queries in other web search engines (such as Google scholar) including the term "famotidine" in addition to the keywords: "pharmacology", "pharmacokinetics", "toxicology" and "safety pharmacology". Keywords related to each section of the overview were further applied. Other publicly available documents such as EPARs and SPC of the reference product were also reviewed and considered.

2.4.2. PHARMACOLOGY

2.4.2.1. PRIMARY PHARMACODYNAMICS

2.4.2.1.1. Mechanism of action

FAM is a competitive H2RA that binds to the H-receptors located on the basolateral membrane of the parietal cell in the stomach, effectively blocking histamine actions. Its pharmacologic activity results in the inhibition of gastric secretion by suppressing acid concentration and volume of gastric secretion. FAM inhibits both basal and nocturnal gastric acid secretion as well as reduces gastric volume, acidity, and secretion stimulated by food, caffeine, insulin, and pentagastrin [redacted]

Histamine receptor selectivity

In vitro and/or *in vivo*, FAM has demonstrated histamine H2-receptor, but neither antagonistic nor agonistic effects on muscarinic, nicotinic, histaminergic H1- or sympathetic

α- and β-receptors. The interaction between FAM and histamine H_2-receptors was tissue dependent, but in most *in vitro* models, FAM exhibited classic competitive inhibition at the H_2-receptor site, as evidenced by a shift in the histamine dose-response curve to the right without a reduction in maximal effect [redacted] However, some investigators report insurmountable inhibition when FAM in concentrations of 3×10^{-7} to 10^{-5} mol/L was assayed in guinea-pig atria [redacted] guinea-pig parietal cells [redacted] guinea-pig papillary muscle, rat gastric fundus and rat uterus [redacted] RAN consistently exhibited competitive inhibition. In the same studies, FAM but not RAN resisted washing from the tissue preparations, which is considered characteristic of a non-competitive receptor interaction. [redacted] dispute the conclusion drawn from these observations that FAM is a non-competitive H2RA, and argued that the potency of FAM causes a greater than 100-fold shift in the agonist concentration-response curve when assayed at the above concentrations, preventing valid comparisons and rendering the test results inapplicable to the clinical situation [redacted]

Other investigators observed only competitive inhibition when FAM was assayed in guinea-pig atria and mouse gastric mucosa [redacted] guinea-pig gastric mucosa [redacted] isolated rat parietal cells [redacted] and isolated rabbit gastric glands [redacted]

In vitro data from human gastric tissue are inconclusive; both FAM and RAN behaved as competitive inhibitors of histamine-stimulated cyclic adenosine monophosphate generation in normal human gastric epithelia, but inhibition was not completely reversed by serial washing of half maximal-inhibitory doses of either drug in HGT-1 human gastric cancer cells [redacted] Further investigation of the H_2-receptor in HGT-1 cells revealed that FAM had a slow onset of inhibition and dissociation from this receptor suggesting a potent, noncompetitive action on human gastric mucosa [redacted] Despite these results *in vitro*, FAM exhibits competitive antagonism of gastric acid secretion *in vivo* in both animals and humans [redacted]

Concentrations of FAM which inhibit histamine-stimulated acid secretion and adenylate cyclase activity in various animal gastric tissues are 24 to 124 times smaller than equally inhibitory concentrations of CIM [redacted] and 6 to 8 times smaller than equally inhibitory concentrations of RAN [redacted]

In human gastric tissue, FAM was 17 times more potent than RAN at inhibiting histamine-stimulated adenylate cyclase generation in normal fundic glands [redacted] and 3.5 times more potent in human gastric cancer HGT-1 cells [redacted] Furthermore, in rat brain, [redacted] demonstrated that histamine-induced cyclic AMP accumulation was inhibited by the addition of CIM or FAM [redacted]

Overall, FAM appears to be a highly specific H2RA. The concentration-response curve of guinea-pig ileum in response to histamine (an H1-receptor function), pentagastrin or methacholine (a muscarinic agonist) was not significantly altered by FAM [redacted] Neither did FAM affect the basal or phasic contractile activity of different animal gastrointestinal tract preparations (rat, guinea-pig and dog), suggesting no interference with the autonomic nervous system [redacted]

FAM had no antagonistic or agonistic effects during stimulation of muscarinic, nicotinic, histaminergic H1- or sympathetic α- or β-receptors in anaesthetised dogs or cats. FAM had no influence on receptor-adenylate cyclase systems sensitive to prostaglandin E2 (PGE2), isoprenaline (isoproterenol) or vasoactive peptide prepared from the purified plasma membranes of human fundic glands [redacted]

2.4.2.1.2. Effect on gastric acid secretion

In vitro studies

In vitro, in the isolated mouse whole stomach preparation, histamine (100 microM)-induced acid secretion was inhibited by CIM and FAM, and the doses of these drugs required for complete inhibition were 3 mM and 10 microM, respectively [redacted] Similarly, in isolated canine parietal cells, FAM inhibited the histamine-stimulated acid formation selectively [redacted] In another *in vitro* study on parietal cells in isolated mouse stomach, bethanechol (10-300 microM) produced a marked increase in acid output and this increase was completely blocked by FAM (10 microM). In the presence of FAM, bethanechol (1-30 microM) augmented the acid secretory response to dibutyryl AMP (200 microM) in a concentration-dependent manner. The augmentation was blocked by atropine (1 microM), 4-DAMP (0.1 microM), a muscarinic M3-selective antagonist, and by Ca^{2+} exclusion from the serosal nutrient solution. Pentagastrin (0.3-3 microM) also concentration-dependently stimulated gastric acid secretion, but the effect was completely inhibited by FAM. In the presence of FAM, pentagastrin (0.1-0.3 microM) elicited a definite potentiation of the acid secretory response to dibutyryl cyclic AMP (200 microM). This potentiation was inhibited by YM022 (1 microM), a cholecystokinin 2 (CCK2) receptor antagonist, and by exclusion of Ca^{2+} from the serosal nutrient solution. The present results suggested that gastric acid secretion via the activation of muscarinic M3 and CCK2 receptors on the parietal cells was induced by activation of the cyclic AMP-dependent secretory pathway [redacted]

Animal studies

The effectiveness of FAM in inhibiting gastric acid secretion has been investigated mainly in anaesthetised dogs [redacted] dogs with a Heidenhain pouch [redacted] dogs and rats with a gastric fistula [redacted] and in anaesthetised pylorus-ligated rats. In all studies, FAM, whether administered intravenously, orally or intraduodenally (pylorus-ligated rats), inhibited gastric acid secretion stimulated by histamine, pentagastrin, methacholine, dimaprit or a test meal. FAM was 7 to 20 times more potent than RAN and 40 to 150 times more potent than CIM on a molar basis depending on the experimental model, the secretory stimulant and the route of administration [redacted]

In rats

[redacted] studied the effects of FAM, administered orally in comparison with RAN, on gastric secretion and emptying as well as on experimentally-induced GUs and DUs in rats and demonstrated that FAM was an effective antisecretory and untiulcer compound. Its potency, but not its efficacy, was higher than that of RAN. Moreover, the duration of the antisecretory action was virtually the same for both drugs [redacted]

In chronic fistula rats, FAM at 1 mumol/kg completely inhibited not only the acid secretion induced by histamine, but also those by pentagastrin and carbachol [redacted] In pylorus-ligated rats, intravenous (i.v.) YM-14471 (an H2RA), FAM and CIM dose-dependently inhibited basal gastric secretion with median effective dose (ED_{50}) values of 0.04, 0.43 and 31.2 mg/kg, respectively. ED_{50} values for oral YM-14471, FAM, CIM and

omeprazole were 0.81, 0.42, 28.9 and 7.7 mg/kg when given at 1 hr before ligation, and 5.7, 26.7, 1639.5 and 18.6 mg/kg at 5 hr before ligation [redacted] On the other hand, [redacted] demonstrated that in pylorus-ligated rats, FAM partially inhibited acid secretion [redacted] Similarly, [redacted] showed that FAM only partially inhibited the acid secretion induced by 2-deoxy-D-glucose or stress, although it suppressed the acid secretion stimulated by other secretagogues [redacted]

In dogs

In dogs with a Heidenhain pouch, the secretory dose-response curve for dimaprit-stimulated gastric acid secretion was displaced to the right in a parallel fashion by FAM and CIM (competitive inhibition). Pentagastrin-stimulated and methacholine-stimulated gastric acid secretion were inhibited by FAM and CIM, although the inhibition was not of the surmountable type [redacted] At the i.v. doses which inhibited acid secretion by 50% (ED_{50}) FAM was 1.3 times longer-lasting ($p < 0.05$) than CIM in reducing the total acid output in response to histamine [redacted]

Moreover, in Heidenhain pouch dogs, both a substituted benzimidazole (AG-1749) and FAM potently inhibited histamine-, bethanechol-, pentagastrin- and peptone meal-stimulated acid secretion, but the inhibitory effect of FAM was short-lived in the case of bethanechol- and pentagastrin-stimulated acid secretion. These results suggest that the antisecretory effect of FAM depends on the nature of the stimuli [redacted]

In dogs with a chronic gastric fistula, the duration of antisecretory activity of equipotent oral doses of FAM and RAN were compared [redacted] Both drugs completely inhibited histamine-stimulated gastric acid secretion when the challenge was given 60 minutes after administration of the H2RA, and 4 hours after administration inhibition was 100% and 87% for FAM and RAN, respectively. However, FAM reduced secretion 59% and 18% in dogs pretreated 24 and 48 hours, respectively, before the challenge. In contrast, the antagonistic effect of RAN was significantly ($p < 0.05$) less (9%) at 24 hours. RAN-treated animals were not challenged at 48 hours [redacted]

In cats

[redacted] studied the antisecretory activity of omeprazole in comparison with FAM in the conscious gastric fistula cat and demonstrated that omeprazole caused a dose-dependent inhibition of the dimaprit-induced acid secretion, being approximately fivefold less potent than FAM. Conversely from FAM, the antisecretory effect of omeprazole was found to be dependent on the acid secretory state of the stomach, the effect being more evident when the compound was administered at the plateau of acid secretion. The inhibitory effect of omeprazole was very long lasting (25% inhibition was still present 24 h after administration of the drug) whereas that of FAM was overcome by dimaprit infusion within 3-4 h. The antisecretory effect of omeprazole concerned to the same extent the volume and the acid concentration of the gastric juice, whereas FAM reduced mainly the volume. When the stimulus was represented by pentagastrin the i.v. median infectious dose values were 0.57 +/- 0.03 and 0.088 +/- 0.015 mumol/kg for omeprazole and FAM. respectively. From the above data it may be concluded that the antisecretory profile of omeprazole differed markedly from that of FAM, independently from the potency and the efficacy of the two drugs [redacted]

Studies in humans

Studies in healthy volunteers

In healthy volunteers, single oral doses of FAM 5, 10 and 20 mg decrease pentagastrin-stimulated acid output in a dose-dependent manner [redacted] Similarly, pentagastrin-stimulated secretion was inhibited in a dose-dependent manner after three continuous 6-hour intravenous (i.v.) infusion rates of FAM, calculated to achieve steady-state plasma concentrations of 10, 30 and 90 ng ml^{-1} [redacted] Furthermore, acid output during pentagastrin stimulation in 10 healthy fasting subjects 12 hours after single doses of FAM 20 or 40 mg orally was still inhibited by 29 to 54% compared with placebo, and in 8 normal subjects FAM 10 and 20 mg administered intravenously at 21:00 h decreased the mean total basal acid output for the ensuing 12 hours from 105.3 mEq (placebo) to 8.3 and 2.3 mEq, respectively [redacted]

Moreover, in volunteers proven to be high (> 5 mEq/ h) basal acid secretors, 24 hours' treatment with FAM dosages of 10, 20 and 40mg twice daily at 0900h and 2100h or 40mg once daily at 2100h resulted in profound inhibition of nocturnal acid output and volume of nocturnal gastric secretions. On the other hand, meal-stimulated secretion was not similarly suppressed by all dosages, although 20 and 40 mg twice daily maintained statistically significant control of meal-stimulated acid output 8 to 10 hours after the morning dose [redacted]

In a placebo-controlled crossover study, FAM 40 mg orally was administered for 6 days either immediately after dinner or 3 hours later to 7 healthy volunteers, using 24-hour ambulatory pH-metry to record the results at the end of the treatment periods [redacted] Early and late FAM administration raised the median nocturnal (midnight to 07:00 h) intragastric pH from < 2 (placebo) to 5.9 and 6.3, respectively. An additional period of elevated (> 3.5) pH was measured through the evening after dinner time administration of FAM, extending the duration of relative anacidity from 7.1 hours with bedtime administration to 10.1 hours (p = 0.005) [redacted]

[redacted] evaluated the dose-response relationship of oral FAM at doses up to 10 mg in 10 healthy male subjects to assess the extent and duration of inhibition of meal-stimulated intragastric acid secretion and demonstrated that the mean intragastric pH was significantly higher after FAM doses 2.5, 5.0, and 10.0 mg than after placebo at times 2.5 to 3.0, 1.8 to 3.2, and 1.7 to 4.2 hours post-dose, respectively. There were no significant differences in mean pH seen between FAM 0.5 mg versus placebo. There was a statistically significant linear dose-response relationship between FAM dose and intragastric pH between 1.7 and 3.8 hours and from 6.3 to 8.7 hours after ingestion [redacted]

Furthermore, [redacted] found no statistically significant rise in nocturnal acidity after abrupt withdrawal of FAM in healthy subjects [redacted]

Studies in patients

[redacted] evaluated the antisecretory efficacy of a single bedtime dose of FAM in 20 patients with DUs and demonstrated that FAM relieves gastric acidity during the night and morning hours when administered as a single bedtime dose of 40 mg [redacted] Furthermore, 24 hours treatment with FAM 40 mg orally administered at either 18:00 h (dinner time) or 22:00 h (bedtime) was evaluated in a well-controlled trial of 9 patients with a history of DU. Both administration schedules suppressed gastric acid secretion equally between midnight and 04:00 h (median pH 7.1 and 7.2 vs 1.1 for placebo). Bedtime administration had a greater effect on intragastric pH in the early morning (04:00 to 08:00 h);

however, early administration of FAM maintained relative gastric anacidity during this period as well, with a median pH of 6.7. Moreover, administration of FAM with the evening meal increased the median intragastric pH from 1.2 (placebo) to 4.2 between 18:00h and midnight, whereas the bedtime dose had a negligible impact on the median pH over this interval [redacted] Normally the time between the evening meal and bedtime is characterised by high gastric acidity [redacted]

Furthermore, in DU patients in remission, there was no statistically significant rebound nocturnal acid hypersecretion after a 4-week course of FAM [redacted]

In 12 patients with healed DU, bolus injection of FAM 10mg and subsequent infusion of either 3.2 or 4 mg/h for 24 hours caused a highly significant ($p < 0.000$ I) increase in intragastric pH; 50% of pH measurements recorded over the 24-hour period exceeded pH 6 versus 1.3% of measurements during placebo treatment. Consumption of standard meals reduced the effect of FAM on pH despite continuous drug infusion; thus, the most profound effect on gastric pH occurred during the night when the median pH rose to 7.1 for both infusion rates versus 1.4 for placebo treatment [redacted]

Both daytime and night-time acid inhibition may be required for optimal therapeutic effect in patients with gastro-oesophageal reflux disease [redacted] 12 patients with normal oesophageal motility but daily complaints of heartburn associated with endoscopically proven erosive oesophagitis in 9 were treated for 24 hours with either oral FAM 40 mg at bedtime (h.s.), 20 mg twice daily, 40 mg twice daily or placebo. 24-Hour pH monitoring via probes placed 5 cm above the lower oesophageal sphincter revealed that all FAM treatments reduced the total number of reflux episodes (defined as an oesophageal $pH < 4$) and that twice daily administration of FAM was significantly ($p < 0.05$) more effective than once daily administration [redacted]

Only the twice daily regimens successfully reduced the percentage of acid contact time during the day and twice daily administration of FAM 40 mg was the only treatment to significantly ($p < 0.05$) reduce the number of reflux episodes lasting 5 or more minutes while in an upright posture; all treatments were equally effective regarding nocturnal acid exposure [redacted] investigated the effect of acid suppression on oesophageal sensitivity in patients with reflux disease but no oesophagitis and demonstrated that oesophageal sensitivity to acid was reduced by FAM independent of and effect on oesophagitis; the effect waned one to four weeks after the end of treatment and correlates with change in heartburn score [redacted]

In elderly patients

In the elderly (≥65 years), administration of 40 mg FAM was successful in elevating the gastric pH to > 5 in all subjects and maintained it at > 5 for at least 3 hr in all subjects tested [redacted]

In paediatric patients

In pediatric patients (aged 2-17 years), the administration of FAM on the morning of surgery significantly increased gastric pH (4.8 vs. 1.3) in comparison with placebo but failed to reduce gastric residual volume significantly [redacted]

Twice daily administration of 0.5 mg/kg FAM for 8 weeks appears to be a tolerated and effective treatment of children with gastroduodenal ulcers [redacted]

In patients with renal impairment

In patients with renal impairment, the pharmacodynamic investigation showed a two-fold prolongation in the duration of acid suppression as compared with patients with normal renal function [redacted]

Vs cimetidine

Compared with CIM, FAM is 20 to 50 times more potent on a weight basis in suppressing gastric acidity both in healthy volunteers and in patients with healed DU and possesses a longer duration of action [redacted]

Vs ranitidine

FAM is approximately 8 times more potent than RAN and may suppress gastric acid output for up to 3 hours longer, particularly in patients with high basal rates of gastric secretion [redacted] Generally, however, FAM 40 mg/day and RAN 300 mg/day in 1 or 2 divided doses have similar effects on gastric acid secretion [redacted] In asymptomatic men with DU disease, [redacted] demonstrated the equivalent effect of standard bed-time doses of FAM and RAN on intragastric pH, acid output and serum gastrin concentrations [redacted]

In healthy elderly subjects, FAM and RAN exhibited a similar duration of 24-hour antisecretory response [redacted]

Effect on parietal cell structure and H/K-ATPase levels

[redacted] determined the effect of inhibition of acid secretion on parietal cell morphology and the concentration of H,K-ATPase alpha-subunit protein in rabbit gastric mucosa *in vivo*. Omeprazole or FAM alone or in combination were used. Control animals showed a morphological stimulation index (0 = resting, 1.0 = fully stimulated) of 0.60; omeprazole treatment (1 mg/kg, twice a day) resulted a stimulation index of 0.63, FAM injection (20 mg/kg twice a day) an index of 0.11, FAM infusion (0.2 mg/hr) for five days an index of 0.38, and the combination of omeprazole and FAM injection twice a day gave an index of 0.02. No change in the frequency of degenerating or damaged parietal cells was observed in any of the groups. In control animals, the number of lysosomes was 0.9/cell, with FAM 1.8 and with omeprazole 5.6/cell. H/K-ATPase levels fell by about 25% with omeprazole and rose by about 23% with FAM [redacted]

2.4.2.1.3. Effect on pepsin

Single oral doses of FAM 5 to 20 mg suppressed basal and pentagastrin- or betazole-stimulated pepsin output in healthy subjects and in patients with PUD [redacted] Generally, no significant difference was found in the degree of suppression achieved by the various doses. Pepsin inhibition varied between approximately 30 and 90% of baseline values [redacted] FAM does not appear to change the concentration of pepsin in gastric secretions; rather, pepsin output is reduced by the decrease in volume of gastric secretions induced by FAM [redacted] This finding is in line with the results reported for CIM and RAN [redacted]

Because pepsin output is suppressed in association with decreased gastric acidity, pepsin activity might also be expected to change. At pH 4 the conversion of pepsinogen to pepsin is reduced; FAM 40 mg orally h.s. maintained gastric pH above 4 for almost half of a 24-hour period [redacted]

2.4.2.1.4. Effect on gastric and oesophageal mucosal protection

Effect on gastric mucosal protection

Animal studies

The influence of FAM on the production of gastric mucus was studied at experimental level. The authors measured the quantity of the intracellular mucus, the surface adherent mucus gel thickness, and the biosynthesis of prostaglandin E2 (PGE2) by the rat gastric mucosa, in pretreated animals. Both the intracellular mucus accumulation and the adherent mucus gel thickness revealed a highly statistically significant increase (P less than 0.0002). PGE2 assay showed that FAM also led to a statistically significant increase (P = 0.02) of PGE2 in treated versus control animals. These findings raise the question of whether despite its common antisecretory pathway of action this H2RA could play a role in the protection of gastric mucosa [redacted]

The elevated levels of gelatinolytic activities in the ulcerous tissues and ulcer index were significantly suppressed by treating rats with FAM [redacted]

The effect of FAM on gastric lesions induced by the decrease in mucosal defensive resistance was investigated in rats and compared with those of CIM, pirenzepine and cetraxate. FAM (0.03, 0.1 and 0.3 mg/kg, p.o.) inhibited dose-dependently the development of gastric lesions produced by taurocholate-histamine in doses that suppressed histamine-induced acid secretion in pylorus-ligated rats. The H2RA also prevented gastric mucosal lesions induced by taurocholate-serotonin, iodoacetamide, acidified aspirin and acidified ethanol. CIM, pirenzepine and cetraxate showed the inhibitory effects on almost all types of the gastric lesions, but their inhibitory effects were much less potent than those of FAM. On the other hand, FAM inhibited the decreases of gastric mucosal blood flow induced by acidified ethanol and the mucosal contents of glycoprotein induced by water immersion restraint stress. In addition, FAM increased the transgastric potential difference and promoted the recovery of decreased transgastric potential difference induced by acidified ethanol in rats. These results suggest that the preventive effect of FAM on gastric lesions is attributable not only to suppression of acid secretion but to activation of the gastric mucosal defensive mechanisms [redacted]

On indomethacin-induced gastric mucosa damage in the rat stomach, FAM and erythropoietin 2500 and 5000 IU/kg reduced the ulcer area by 98%, 31% and 58%, respectively, compared with the indomethacin group. Superoxide dismutase activity and glutathione level were decreased and myeloperoxidase activity increased in the indomethacin group compared with healthy rats. FAM and erythropoietin at all doses increased superoxide dismutase and glutathione levels significantly compared with the indomethacin group. Myeloperoxidase activity was decreased by erythropoietin and FAM [redacted]

Studies in humans

The integrity of the gastric mucosa is normally maintained by factors which protect against autodigestion by pepsin and acid. The effect of FAM on gastric protective factors

(gastric mucus, non-parietal secretions and the mucosal prostaglandins) is therefore of considerable interest

studied the composition of gastric mucus in 20 patients with DU before and after 4 weeks treatment with either RAN 300 mg h.s. or FAM 40 mg h.s. Based on an index developed by the investigators which correlates the constituents of gastric mucus to the viscoprotective properties of the gastric mucus coating, FAM caused a significant ($p < 0.01$) decrease in mucoprotection A similar result was reported for CIM however, RAN had no effect. Despite this difference, endoscopically confirmed healing was present in 70% of RAN-treated and 70% of FAM-treated patients, and healing was independent of the decline in the mucoprotective index

In a study of 10 healthy volunteers, non-parietal (bicarbonate) secretion was calculated from basal and pentagastrin-stimulated secretions collected 1 to 2.5 hours after oral administration of FAM 5, 10 and 20 mg While parietal (acid) secretion decreased in a dose-dependent manner from 146 ml/h following placebo to 23.5 ml/h ($p < 0.00$ I) following FAM 20mg, the mean non-parietal volume was not significantly decreased by any dose of FAM (mean basal volume 30.6 ml/h and mean stimulated volume 31 ml/h vs mean placebo basal volume of 33.8 ml/h).

In an inadequately controlled study of 20 patients with endoscopically proven DU, fundic and duodenal mucosa were biopsied for determination *ex vivo* of PGE2 production before and after treatment with either FAM 40 mg once daily or RAN 150 mg twice daily. After either treatment significant ($p < 0.01$) increases in PGE2 production were observed in the oxintic area and duodenal mucosa samples. Although the study design precludes ascribing this effect directly to the drugs, this investigation suggests that healing of DUs with H2RAs may be associated with increasing production of prostaglandins. The relationship between H2RAs and mucosal prostaglandin production warrants further study, particularly in regard to ulcer prophylaxis in individuals stressed by critical illness.

Although not correlated to a specific pharmacodynamic effect, FAM 20 mg significantly reduced gastric mucosal injury in healthy volunteers given the combination of FAM and aspirin 900 mg 5 times over a 48-hour period. Aspirin alone induced petechiae on the antral surface and bleeding, both of which were ameliorated by FAM 20mg. In contrast, low dose (2 mg) FAM had no influence on gastric pH or aspirin-induced gastric injury countering suggestions that lower doses of H2RAs are protective

compared the effects of omeprazole and FAM on ulcer healing and fibroblast growth factor-2 levels in GUs induced by endoscopic mucosal resection and demonstrated that ulcer healing rates under endoscopy were not different between the two treatment groups. In both groups, levels of fibroblast growth factor-2 slightly increased on day 4, but the values were not different at any time point. There were no differences in histological variables on days 4 and 7, but fibromuscular hyperplasia was significantly greater in the omeprazole group than in the FAM group on day 28 ($P < 0.05$). Omeprazole and FAM had an equivalent value for the treatment of ulcers induced by endoscopic mucosal resection

In a study of 20 healthy Japanese volunteers, FAM alleviated anti-platelet drug-induced gastric injury (by dual therapy with low-dose aspirin and clopidogrel) without attenuation of anti-platelet functions, irrespective of *H. pylori* and CYP2C19 genotypes

Effect on oesophageal mucosal injury

A study of 15 healthy Japanese volunteers, demonstrated that acid inhibition achieved with a half-dose of a PPI (lansoprazole and rabeprazole) effectively prevented development of aspirin-induced oesophageal mucosal injury, whereas a standard dose of FAM failed to achieve the same results[redacted]

Prevention of experimental gastric mucosal damage

FAM administered intraduodenally or orally inhibited the formation of aspirin-, indomethacin-, prednisolone- and histamine-induced GUs in rats (ED_{50} of 0.25, 0.6, 56.0 and 0.17 mg/kg, respectively). FAM also inhibited the formation of mepirizole-induced DUs (ED_{50} of 0.62 mg/kg) and water immersion stress-induced GUs in rats, and significantly ($p < 0.05$) accelerated the healing of the former[redacted]

In comparative studies, FAM was markedly more potent than CIM in suppressing indomethacin- and aspirin-induced GUs in rats. Neither FAM nor CIM inhibited the formation of GUs due to intragastric infusion of HCI, but on a weight-for-weight basis i.v. FAM was 30 times more potent than i.v. CIM in inhibiting GUs induced by the combination of histamine and intragastric taurocholate during haemorrhagic shock in rats [redacted]

Furthermore, in rats, it has been suggested that both FAM and omeprazole may be protective against gastric mucosal damage induced by ASA, although they were not as efficient as melatonin as an antioxidant. On the other hand, the antisecretory effect of omeprazole and FAM may also be contributing to their antiulcer effect [redacted].

FAM prevented deep histologic lesions induced by 0.6N HCl in rat gastric mucosa [redacted]

2.4.2.1.5. Effect on gastrin concentration

Clinically healthy dogs treated with FAM for 14 days had only transient increases in serum gastrin concentrations [redacted]

A number of investigators have noted an increase in serum gastrin concentrations during administration of FAM for 1 to 8 weeks; in some studies, this reached statistical significance [redacted] but in others it did not [redacted] Among studies demonstrating statistical significance, treatment with FAM 40 mg at night for 7 days in patients with healed DU produced an increase in the fasting serum gastrin concentration of 56% ($p < 0.05$) compared with placebo. A significant difference in integrated serum gastrin concentration was noted between 21:00 and 19:00h daily in healthy subjects given the same treatment. The median serum gastrin concentration was 59% higher than the placebo value [redacted]

Moreover, in patients with previous DU treatment with FAM 40 mg nocte or CIM 800 mg nocte (at 22:00 h) had no effect on fasting serum gastrin measured 12 h after dosing, since it was not significantly altered by either drug [redacted] However, in healthy volunteers, 4 hours after single oral doses of FAM 20 and 40mg serum gastrin concentrations were significantly ($p < 0.05$) higher than after placebo but remained within normal limits [redacted]

RAN, in clinical use, has not produced an increased incidence of gastric epithelial changes [redacted] and RAN produces equivalent or greater elevations in serum gastrin concentrations than does FAM [redacted]

2.4.2.1.6. Animal models of efficacy

In gastric ulcer rat models

In indomethacin-, histamine- and prednisolone-induced gastric ulcer rat models

FAM inhibited the formation of histamine- and prednisolone-induced GUs in rats.

Furthermore, FAM inhibited the formation of indomethacin-induced GUs in rats and was markedly more potent than CIM in suppressing the aforementioned ulcers [redacted] Indomethacin delayed ulcer healing but transforming growth factor-beta and FAM improved ulcer healing and reversed the effects of indomethacin. Maximal differences were observed on day 8. FAM induced a profound inhibition of gastric secretion and increased collagen secretion but it did not affect cell proliferation. Thus, transforming growth factor-beta and FAM accelerate ulcer healing delayed by indomethacin [redacted]

However, in refed rats, CIM (30 mg/kg, p.o.) and FAM (1 mg/kg, p.o.) had no significant effect on indomethacin-induced antral ulcer [redacted]

Further, on indomethacin-induced gastric mucosa damage in the rat stomach, FAM and erythropoietin 2500 and 5000 IU/kg reduced the ulcer area by 98%, 31% and 58%, respectively, compared with the indomethacin group [redacted]

The anti-ulcer activity of licorice was found to be similar to that of FAM in indomethacin-induced ulceration technique in rat stomach. Combination therapy of both FAM and licorice showed higher anti-ulcer activity than either of them alone [redacted]

Phytic acid and FAM produced significant reduction in ulcer number, size and index compared with control rats in ethanol-induced ulcers. FAM produced a gastroprotection of 77.86%, while phytic acid produced a protection of 85.9% [redacted]

Aspirin and pylorus ligation-induced gastric ulcer rat models

FAM inhibited the formation of aspirin-induced GUs in rats and was markedly more potent than CIM in suppressing the aforementioned ulcers [redacted]

In aspirin- and pylorus ligation-induced GU models, FAM formulation reduced gastric volume, total acidity and ulcer index thus, showing the anti-secretory mechanism involved in the antiulcerogenic activity through H2 receptors [redacted]

The combination of gallic acid and FAM showed synergistic effect in the protection of rat gastric mucosa in aspirin- and pylorus ligation-induced GU model [redacted]

In acetylsalicylic acid-induced gastric damage in rats, [redacted] demonstrated the protective effect of FAM [redacted]

Stress- and acetic acid-induced gastric ulcer rat models

FAM also inhibited the formation of stress-induced GUs in rats [redacted]

Phytic acid and FAM produced significant reduction in ulcer number, size and index compared with control rats in cold stress-induced ulcers. FAM was more potent in reducing mean ulcer index as compared to phytic acid and produced a gastroprotection of 92.7%, while phytic acid produced a protection of 70.5% [redacted]

[redacted] found that the synergistic action of FAM and chlorpheniramine on acetic acid-induced chronic GU in rats decreased the incidence of ulcer and also enhanced the healing of ulcer [redacted]

In duodenal ulcer rat models

FAM inhibited the formation of mepirizole-induced DUs in rats and significantly accelerated their healing [redacted]

[redacted] studied the combination of sucralfate (SUC) and FAM at subtherapeutic dose [200 mg/kg SUC and 0.2 mg/kg FAM (twice a day)] on cysteamine-induced DUs (3 x 250 mg/kg) in female rats and demonstrated that the effectiveness of their combination was confirmed by decreased number (from 1.3 to 0.5), length (from 5.5 mm to 1.9 mm), severity of DUs (from 3.4 to 1.2) and reduction of ulcerative index by 54.4% [redacted]

2.4.2.1.7. Other pharmacodynamic effects

Immunomodulatory effects

Animal studies

In rats and mice, FAM influenced neither the antigen-induced mediator release from mast cells nor the humoral and cell-mediated immune responses (IgE-mediated passive cutaneous anaphylaxis reaction, the peritoneal release of histamine and SRS-A, delayed type hypersensitivity reaction induced by picryl chloride, hapten specific IgE antibody response or plaque-forming cells formation) [redacted]

Studies in humans

FAM did not appear to modify T lymphocyte populations or lymphokine production in patients with DU treated for 6 weeks. FAM 40 mg orally did enhance lymphocyte responsiveness in the allogenic mixed reaction but had no effect on lymphocyte responsiveness to mitogens or in autologous mixed reactions. It is probable that immune modulation by H2RAs is a molecular rather than an H_2-receptor mediated effect [redacted]

In gastric cancer patients, [redacted] demonstrated that of the three H2RAs tested (FAM, RAN and CIM), CIM had the strongest and FAM the weakest immunomodulating effect. Only CIM augmented the cytotoxicity and proliferative response of lymphocyte to mitogen; neither RAN nor FAM had such an effect [redacted] Similarly, [redacted] compared the immunomodulative effect of each H2RA (CIM, RAN and FAM) on peripheral blood mononuclear cells in patients with gastric cancer and demonstrated that CIM was the most strongly modulative substance among H2RAs and FAM the least modulative drug [redacted]

A prospective, open-label, randomized, parallel-group study in patients with *H. pylori* infection that examined the effects of neutrophil activation after treatment with three different H2RAs (150 mg RAN, 20mg FAM, or 10 mg lafutidine b.d.), demonstrated that on the basis of the histological findings between before and after H2RA treatment, no significant differences were found in any groups. Similarly, there were no significant differences in myeloperoxidase activity or interleukin-8 levels. Therefore, in patients with *H. pylori*, when

used at clinical doses, any H2RAs can be used without concerning about inhibition of neutrophil activation [redacted]

Antioxidant effects

In vitro results showed beneficial effect of histamine H1 and H2-blockers, especially FAM, as antioxidants and/or metal chelators, which might be an additional explanation of their therapeutic action [redacted]

2.4.2.2. SECONDARY PHARMACODYNAMICS

Antioxidant, antinociceptive and hepatoprotective effects

The antioxidant, antinociceptive and hepatoprotective effects of H2RAs were examined with different experimental models. Antioxidant activities were determined by employing various *in vitro* assay systems such as 1,1-diphenyl-2-picryl hydrazyl (DPPH) radical-scavenging activity assays, reducing power determination assays, nitric oxide-scavenging activity assays and hydrogen peroxide-scavenging activity assays. Antinociceptive effects were determined using the hot plate test in mice. The hepatoprotective effects of CIM, RAN and FAM against hepatotoxicity induced by carbon tetrachloride (CCl(4)) were determined by measuring the levels of serum enzymes alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) activities in mice. The IC(50) values of CIM, RAN and FAM on DPPH radical-scavenging activity were 671±28, 538±21 and 955±43 μg/mL, respectively. FAM showed very strong nitric oxide-scavenging activity. All three compounds showed very weak hydrogen peroxide-scavenging activity. Moreover, the compounds did not exhibit any reducing power activity until concentrations of 1.6 mg/mL. All compounds also showed a dose-dependent and marked analgesic activity in mice relative to controls. Pretreatment of mice with CIM, RAN or FAM for three consecutive days reduced CCl(4)-induced hepatotoxicity in mice. Treatment with 200 mg/kg RAN reduced AST, AST and ALP serum levels, while 200 and 40 mg/kg of CIM and FAM, respectively, reduced AST and ALP serum levels. H2RAs exhibited varying levels of antioxidant activities in various assays. These results indicate that the antioxidant activities of H2RAs have an analgesic activity and protective effect on CCl(4)-induced hepatotoxicity in mice [redacted]

Prophylactic effects against histamine release

In ICR mice, FAM and RAN significantly inhibited the scratching behavior caused by histamine. The H2RAs did not affect the vascular permeability increase caused by histamine [redacted]

In mice, histamine H1 receptor antagonists such as chlorpheniramine and epinastine significantly inhibited nasal allergic symptoms caused by histamine, but the H2RAs CIM and FAM showed no effect. No additional effects were observed by combined use of chlorpheniramine and CIM or FAM compared with CIM or FAM alone. These results suggested that histamine H1 receptors play an important role in nasal allergy symptoms induced by histamine [redacted]

Cardioprotective effects

Reduction of cardiac hypertrophy and improvement in cardiac function of spontaneously hypertensive rats has been reported. In addition to being cardioprotective, FAM modulated cardiac stem cells characteristics. Restoration of stem cell efficiency by FAM is possibly mediated by reduction of oxidative stress as the expression of H2R was unaffected by the treatment. Maintenance of healthy stem cell population is suggested as a possible mechanism underlying the cardioprotective effect of FAM [redacted]

In functional dyspepsia

Gastroduodenal acidification has been reported to aggravate upper abdominal discomfort and pain that are symptoms suffered by functional dyspepsia (FD) patients. Delayed gastric emptying and hypersensitivity to gastric distension contribute importantly to the pathophysiology of FD. The results of an *in vivo* study showed that FAM ameliorated both delayed gastric emptying and gastric hypersensitivity, whereas mosapride only improved delayed gastric emptying [redacted]

Effect on the paclitaxel-induced plasma extravasation

In rats, FAM did not attenuate the paclitaxel-induced plasma extravasation [redacted]

Against ovary or testicular ischaemia-reperfusion injury

Biochemical and histological results show that FAM protects the ovarian tissue from ischemia-reperfusion (I/R) injury [redacted]

FAM prevented increases in oxidative stress markers and reductions of antioxidants during I/R injury in rats. Spermatogenesis was less affected and DNA injury was reduced in rats treated with FAM. The antioxidant characteristics of FAM and its protective effects have been shown in this study [redacted]

Radioprotective effects

Oral administration of FAM, vitamin C and CIM demonstrated reliable and similar radioprotective effects in mice. Additionally, the protective effect of single use of these drugs was similar to the combination form [redacted]

Potent radioprotective effects of combined regimens of FAM and vitamin C against radiation-induced micronuclei was demonstrated in mouse bone marrow erythrocytes [redacted]

Treatment with only 5 mg/kg FAM before 4 Gy irradiation led to almost 50% reduction in DNA damage when compared with those animals which received radiation alone. The radioprotective capability of FAM might be attributed to radical scavenging properties and an anti-oxidation mechanism [redacted]

2.4.2.3. SAFETY PHARMACOLOGY

2.4.2.3.1. Central nervous system effects

The effects of FAM on the central nervous system (CNS) were studied in squirrels, monkeys, mice, and cats. In monkeys, FAM had a bidirectional effect on lever pressing (avoidance response) causing an increase at the low dose (1.0 mg/kg p.o.) and a small decrease at 9 mg/kg. In mice following intraperitoneal administration of 6 to 150 mg/kg no overt behavioural signs or symptoms of CNS activity were observed. In mice FAM was not active as an antagonist of the CNS actions of thyrotropin-releasing hormone (TRH), neurotensin, substance P, or amphetamine. FAM was free of major or minor tranquillizing, anticonvulsant, anticholinergic, ganglionic blocking, or dopaminergic activity. In cats, FAM did not affect the electroencephalogram (EEG) or arousal response but did prolong the duration of hippocampal after-discharge. Only 4% of the plasma concentration of the drug was detected in the cerebrospinal fluid (CSF) [redacted]

FAM did not affect the ratio of food and water intake and ambulatory activity in rats [redacted]

2.4.2.3.2. Cardiovascular, bronchial and renal effects

Cardiovascular effects

In vitro and animal studies

The effects of FAM on the cardiac repolarization process were assessed using four different levels of test systems. In particular, a supratherapeutic concentration of FAM (10(-5) M), which is >8 times higher than maximum plasma concentration (C_{max}) obtained after its therapeutic dose, neither inhibited human ether-a-go-go-related gene (HERG) K(+) current expressed in human embryonic kidney 293 (HEK293) cells nor affected any of the action potential parameters of guinea pig papillary muscles. Therapeutic (0.3 mg/kg, i.v.) to supratherapeutic doses (3-10 mg/kg, i.v.) of FAM did not affect the repolarization process of the halothane-anesthetized canine model, while only supratherapeutic doses exerted the positive chronotropic, inotropic and dromotropic effects without affecting the mean blood pressure. Moreover, supratherapeutic doses of FAM (1-10 mg/kg, i.v.) neither induced torsades de pointes nor prolonged QT interval in the canine chronic atrioventricular conduction block model. These results suggest that FAM possesses no cardiovascular effects at a therapeutic dose, while it may exert cardiostimulatory actions after drug overdoses that might potentiate the proarrhythmic potential of co-administered cardiotonic agents by increasing the intracellular Ca(2+) concentration [redacted]

Animal studies

[redacted] demonstrated that in guinea pig atria, FAM and CIM produced a competitive dose-dependent displacement of histamine-induced tachycardia. In contrast, low concentrations of YM-14471 showed competitive inhibition of tachycardia, whereas high concentrations were irreversible or slowly dissociable [redacted]

Cardiovascular and bronchial effects

In vitro studies

In *in vitro* studies of guinea-pig tracheal smooth muscle, CIM, RAN and FAM ($\geq 10^{-5}$ mol/L) each enhanced histamine-induced smooth muscle contraction [redacted]

Animal studies

The effects of FAM on cardiovascular and bronchial functions were investigated in anesthetized dogs. FAM did not affect heart rate, blood pressure, left ventricular pressure (LVP), maximum dLVP/dt, cardiac output, or coronary blood flow at i.v. doses of 1 to 30 mg/kg in anesthetized dogs. FAM did not produce any remarkable change in the electrocardiogram (ECG) at doses up to 30 mg/kg in anesthetized dogs. The only exception was of a transient increase or decrease in the T-wave amplitude in the ECG at a dose of 30 mg/kg. No haemodynamic changes were observed after FAM administration to anesthetized dogs whose cardiac function was depressed by propranolol (1 mg/kg I.V.) [redacted]

Cardiorenal effects

Animal studies

The cardiorenal effects of FAM were studied in dogs and rats. Ten mg/kg of FAM administered orally were without effect on the blood pressure of spontaneously hypertensive rats. In anaesthetized dogs, i.v. administration of 1.0 and 4.0 mg/kg of FAM was without effect on cardiovascular parameters relating to the autonomic nervous system, blood pressure, heart rate, or respiratory function. In conscious dogs, an oral dose of 10 mg/kg was without diuretic effect [redacted]

Haemodynamic effects

In the rat, administration of FAM for 7 days had no effect on systemic, hepatic or portal haemodynamics [redacted]

2.4.2.3.3. Hepatic effects

In rats, lipopolysaccharide (LPS) administration caused an increase in circulating tumour necrosis factor (TNF) concentration. RAN cotreatment enhanced the LPS-induced TNF increase before the onset of hepatocellular injury, an effect that was not produced by FAM [redacted]

2.4.2.3.4. Endocrine effects

FAM neither displaces dihydrotestosterone from androgen binding sites nor decreases rat seminal vesicle or ventral prostate weights [redacted]

The effects of FAM on the thyroid of rats were evaluated after five weeks of oral administration at doses up to 2000 mg/kg/day. No evidence of treatment-related alterations of serum thyroid hormone levels, thyroid weight or the microscopic appearance were seen after administration of FAM [redacted]

2.4.2.3.5. Gastrointestinal effects

Gastric mucosal effects

After 1-year of oral administration, a treatment-related increased incidence and degree of eosinophilic cytoplasmic granularity of gastric chief cells due to an increase in electron density of the zymogen (secretory) granules was seen in rats administered FAM in dosage levels of 200 mg/kg daily or greater. Such changes were not noted in mice or dogs [redacted] Administration of the same dosages for up to 2 years did not produce neoplastic changes in the stomachs of rats ([redacted]). Gastric mucosal changes which have been observed with other antisecretory drugs, such as corpus mucosal hyperplasia (H2RAs), hyperplasia of endocrine enterochromaffin-like (ECL) cells or the formation of gastric tumours (loxtidine), formation of micronodules and occasional carcinoid proliferations into the submucosa (omeprazole) [redacted] have not been reported in rats administered FAM [redacted]

Contractile effects

[redacted] demonstrated that H2RAs possess a concentration-dependent contractile effect on the isolated smooth muscle strips from the rabbit stomach fundus and sigmoid colon and the order of potency was: RAN = NIZ > FAM > CIM [redacted]

Gastroprokinetic effect

In a model of delayed gastric emptying induced by clonidine in the dog and rat, neither CIM (3-30 mg/kg) nor FAM (0.3-3 mg/kg) affected the gastric emptying of a solid meal or delayed gastric emptying [redacted]

In vitro experiments in lower oesophageal sphincter rat tissues placed in a standard organ bath and contracted with carbachol, demonstrated that neither FAM nor RAN caused any direct significant change in lower oesophageal sphincter tone in the therapeutic dose range applied to the organ bath. However, the higher dose of FAM caused a significant relaxation in the lower oesophageal sphincter tone [redacted]

2.4.2.3.6. Effect on wound healing

In rats, in all the three wound models studied (i.e., resutured, incision, excision) FAM promoted wound healing, whereas omeprazole and SUC did not. Histopathological studies revealed increased collagen content and granulation tissue in FAM treated group compared to control [redacted]

2.4.2.3.7. Adverse effect on gastric mucosal protection

Rats were dosed with FAM, omeprazole, or buffer control for 4 weeks. Mucin synthesis, mucin histochemistry, mucin carbohydrate composition and prostaglandin E2 (PGE2) release were measured during and after drug treatment. PGE2 release was maximally inhibited after 2 weeks of omeprazole or 4 weeks of FAM. Total glycoprotein synthesis was inhibited at all times by omeprazole, but only after the cessation of dosing with FAM.

Sulphated glycoprotein synthesis was inhibited by both drugs at 2 weeks. PGE2 release and sulphated glycoprotein synthesis were restored to control values or more by the 5th day after the end of dosing, at which time total glycoprotein synthesis was significantly suppressed in both groups. Histologically, a reduction of PAS-positive surface mucus was observed after 2 weeks of dosing in both groups. Both FAM and omeprazole reduced the sialic acid content during and after treatment. Thus, long-term anti-secretory therapy also affects the production of factors involved in primary gastric mucosal defence [redacted]

FAM-induced suppression of gastric surface mucus cell function is prevented by combined treatment with methylmethionine sulfonium chloride [redacted]

Both the biosynthesis and the accumulation of gastric mucin were significantly decreased in the FAM-treated rats. Both the content and the immunoreactivity of surface mucus cell-derived mucin were reduced by FAM [redacted]

2.4.2.4. PHARMACODYNAMIC DRUG INTERACTIONS

Clopidogrel

In an *in vitro* assay system FAM showed little inhibition (no more than 20%) against the metabolic activation of clopidogrel by CYP2B6, CYP2C19 and CYP3A4. Thus, FAM is considered to be a safe alternative antiacid agent for both CYP2C19 extensive metabolizers (EMs) and poor metalolizers (PMs) patients receiving antiplatelet therapy with clopidogrel [redacted]

A double-blind, randomized study that compared the influence of esomeprazole and FAM on the platelet inhibitory effect of clopidogrel, demonstrated that neither esomeprazole nor FAM reduced the platelet inhibitory effect of clopidogrel [redacted]

Concomitant use of FAM had no effect on the antiplatelet effect of clopidogrel [redacted] Omeprazole therapy was associated with higher on- treatment platelet reactivity than FAM [redacted]

Suxamethonium

[redacted] examined the effect of preoperative i.v. administration of three different H2RAs (CIM 400 mg, RAN 80 mg and FAM 20 mg) or metoclopramide 10 mg i.v. on the duration of neuromuscular block produced by an intubating dose (1 mg kg^{-1}) of suxamethonium and demonstrated that the time from onset of 95% block to 25% recovery ("block time") was not significantly different between the groups receiving CIM, RAN, FAM and control [redacted]

Warfarin

In rats, the anticoagulant effect of a single bolus injection of warfarin was measured following no treatment (control) or equimolar doses of FAM or CIM. FAM had little effect on plasma prothrombin complex activity (PCA) and FAM-treated animals experienced a return to baseline plasma PCA in a manner similar to control. CIM induced a greater and a prolonged decline in plasma PCA [redacted]

Ten healthy volunteers were administered FAM 40 mg orally twice daily concurrently with warfarin, which was titrated to lengthen the prothrombin time to 1.5 times control. This study showed no statistical difference in mean prothrombin time ratios between warfarin-only days and warfarin-FAM days [redacted]

Ghrelin

[redacted] demonstrated that in rat stomach, FAM (0.33 mg/kg) completely inhibited the effects of ghrelin [redacted]

Vecuronium

The interaction between H2RAs and the neuromuscular blocking drug vecuronium was investigated in the rat phrenic nerve-hemidiaphragm preparation. FAM produced negligible and statistically insignificant (0-5%) neuromuscular paralysis at concentrations between 0.3 and 300 microM. CIM (800 microM) shifted the neuromuscular concentration-effect curve of vecuronium to the left in a parallel manner, while RAN (160 microM) shifted it to the right. The potentiation ratio was 1.90 +/- 0.14 for CIM and 0.62 +/- 0.05 for RAN. FAM (30 microM) did not alter the response to vecuronium [redacted]

2.4.3. PHARMACOKINETICS

2.4.3.1. ANIMAL PHARMACOKINETICS

Absorption and distribution

The absorption, distribution, metabolism and excretion of FAM were studied in two animal species. Absorption was 28% in the rat and 43% in the dog. The plasma half-life in dogs was 2.5 hours, which was unchanged after repeated doses, indicating no tendency for the drug to accumulate. In rats, the highest levels of radioactivity after an oral dose of FAM were found in the gastrointestinal tract, kidneys, liver, submandibular glands, arteries, epiphyseal membrane, fascia, and uvea. The distribution pattern was not affected on repeated dosing. FAM did not effectively cross the blood-brain [redacted]

Metabolism and excretion

The only metabolite of FAM in rat and dog urine was the sulfoxide derivative, which was present in minor amounts. Urinary and fecal excretion of radioactivity in rats accounted for 28% and 70%, respectively, of an oral dose, compared to 83% and 17% respectively, of an intravenous dose. About 2.4% of the dose in rats was excreted in the bile. Dogs excreted 45% of an oral dose in the urine, compared to 100% of an intravenous dose [redacted] studied the interaction of FAM with rat liver microsomes and its effect on drug metabolism *in vitro*. FAM interacted with liver microsomes obtained from untreated, phenobarbital-pretreated and 3-methylcholanthrene-pretreated rats to produce characteristic type II spectral changes with peaks at 423-426 nm and troughs at 387-390 nm. The spectral dissociation constants were in the range of 0.84-0.94 mM. FAM inhibited aminopyrine N-demethylase activity to a much lesser extent than did CIM. The extent of inhibition at a concentration of 5 mM of FAM was from 12 to 18% for the microsomes from the rats with different pretreatments. In contrast, 5 mM of CIM inhibited the activity 80, 59 and 80% in the microsomes from untreated, phenobarbital-pretreated and 3-methylcholanthrene-pretreated rats, respectively. Both FAM and CIM inhibited aminopyrine N-demethylase in a mixed-type manner for the microsomes from phenobarbital-pretreated rats, with inhibition constants of 4.7 and 0.7 mM, respectively. These results demonstrate that

FAM is an *in vitro* inhibitor of microsomal drug metabolism in rats but is much less inhibitory than CIM [redacted]

2.4.3.2. CLINICAL PHARMACOKINETICS

2.4.3.2.1. Absorption and bioavailability

Peak plasma concentrations are dose-dependent and are attained approximately 1 to 3.5 hours after dosing. Peak plasma concentrations are approximately 40-60 ng/ml after a 20 mg dose of FAM and 75-100 ng/ml after a 40 mg dose [redacted] FAM is not completely absorbed following oral administration and the bioavailability of both the tablet and suspension formulations is approximately 43% [redacted]

During repeated oral administration of FAM 20 mg 3 times daily, C_{max} and trough plasma concentrations (C_{min}) of the drug were largely constant (i.e., about 100 and 50 µg/L, respectively) over 8 weeks in heathy volunteers [redacted] No significant accumulation was observed in FAM C_{min} not only in healthy volunteers but also in cirrhotic patients with normal renal function during repeated oral administration of FAM 40 mg/day over 7 days [redacted]

Effect of food

In 17 healthy volunteers, oral administration of FAM 40 mg tablet with a standard breakfast was not associated with any change in the rate or extent of FAM absorption [redacted] Administration of FAM 40 mg with 10 ml of high-potency antacid (Mylanta II) in a fasted volunteer population resulted in a small but significant ($p < 0.05$) decrease in peak plasma concentration and a small non-significant decrease in area under the concentration-time curve and an increase in time to peak concentration [redacted]

A double-blind, placebo-controlled, multiple-step crossover study that compared the antisecretory efficacy of low-dose RAN and FAM in fasting and non-fasting volunteers, demonstrated that in non-fasting volunteers both low-dose H2-antagonists had comparable antisecretory effects and were superior to placebo over the first 8 h of therapy. Both drugs achieved a slightly higher antisecretory effect without food intake compared to with food intake [redacted]

2.4.3.2.2. Distribution and protein binding

The apparent volume of distribution at steady-state (Vss) and during the terminal log-linear phase (Vz) of FAM obtained from healthy adult volunteers range from 0.94 to 1.4 L/kg [redacted] The volume of distribution (Vd) values obtained from healthy subjects do not appear to differ significantly from those observed in patients with renal failure or liver cirrhosis. Although no systematic studies have been made, analysis of the cumulative data in the literature suggests that the Vd of FAM may decrease with aging. The mean apparent Vd for the central compartment (Vd is reported to be 0.34 L/kg in patients with normal renal function [redacted] the relatively small Vss and Vc for FAM may be associated with its rather high-water solubility [redacted]

FAM distributes into CSF at a mean CSF/plasma concentration ratio of 0.12 at 4 h after oral administration in patients with intact blood-brain barrier [redacted].

FAM is only weakly bound to plasma protein [redacted] Binding to plasma protein is relatively low (15-22%) ([redacted] As determined in vitro in pooled human plasma and in vivo in 5 healthy subjects given FAM 40 mg orally, the fraction of FAM bound to plasma proteins was approximately 16% ([redacted] Binding was not concentration-dependent over the range 0.05 to 0.5 mg/L. The fact that FAM binds weakly to plasma protein implies that it would have a low drug interaction potential at plasma protein binding site(s)[redacted]

2.4.3.2.3. Metabolism and elimination

FAM S-oxide is the only known metabolite of the drug in humans. After i.v. administration of FAM, about 2 to 8% of the dose was recovered in urine as FAM S-oxide in humans ([redacted] However, the biological activity of the sulphoxide metabolite is unknown ([redacted] Up to 30-35% of the active substance is metabolised in the liver ([redacted] Previous studies [redacted] have demonstrated that the nonrenal clearance (CL_{NR}) of FAM consisted of only 21 to 33% of the total plasma clearance (CL). Therefore, the hepatic metabolism of FAM would make only a minor contribution to the overall elimination of the drug [redacted]

The elimination half-life of FAM administered orally or intravenously was between 2.5 and 4 hours in healthy subjects ([redacted]

2.4.3.2.4. Excretion

FAM is excreted in the urine and faeces. The renal clearance of FAM in healthy subjects is 250-450 ml/min, indicating active tubular secretion of the drug [redacted] The percentage recovery of FAM in the urine is not dose dependent. Mean urinary recovery of unchanged FAM was from 25 to 30% of orally administered doses [redacted] and from 65 to 80% of intravenously administered doses [redacted] Unchanged drug accounted for 82% and 89% of urinary radioactivity in 2 of 4 healthy volunteers administered ^{14}C-FAM orally, but for only 53% and 68% in the remaining 2 volunteers [redacted]

The mean CL of FAM after i.v. administration has been reported as 25 and 29 L/h [redacted] Renal plasma clearance after i.v. and oral administration was 18 L/h [redacted] and 19 L/h, respectively [redacted]

[redacted] studied the biliary excretion of FAM using percutaneous biliary drainage in patients with complete extrahepatic biliary obstruction due to pancreatic carcinoma. Following single i.v. (20 mg) and oral (40 mg) doses of FAM (n = 2), even lower percentages (0.1% and 0.4%, respectively) were recovered in the 24 h bile. This negligible biliary excretion cannot account for the so-called second peak phenomenon observed in some individuals following a single dose of an H2RA [redacted]

2.4.3.2.5. Linearity

Following single oral doses of 5, 10, 20 and 40 mg the peak plasma concentrations increase proportionally, with the 20 and 40 mg tablets producing peak concentrations of 0.04 to 0.06 mg/L and 0.075 to 0.10 mg/L, respectively ([redacted]

2.4.3.3. PHARMACOKINETIC DRUG INTERACTIONS AND OTHER FORMS OF INTERACTION

No metabolism-related drug interactions are known to date [redacted] Among H2RAs, agents such as CIM or oxmetidine which possess an imidazole nucleus have been shown *in vitro* to bind to human cytochrome P450 enzymes, whereas neither furan analogues such as RAN nor thiazole analogues such as NIZ and FAM exhibit a strong ligand interaction [redacted]).

In liver microsomes prepared from normal human liver, FAM up to 2 mmol/L did not induce a significant change in the cytochrome P450-dependent O-de-ethylation of 7-ethoxycoumarin or the N-demethylation of benzphetamine [redacted]

In homogenates prepared with liver biopsy specimens taken from alcoholic or diabetic patients, FAM 0.63 mmol/L decreased the activity of aryl-hydrocarbon-hydroxylase to 35% of control, of 7-ethoxycoumarin-O-deethylase to 71% of control and of 7-ethoxyresorufin-O-deethylase to 83% of control. The respective enzyme activities observed with RAN 0.63 mmol/L were 86%, 95% and 77% of control values, and with oxmetidine 0.63 mmol/L were 10%, 46% and 39% of control values. These shifts in enzyme sensitivity *in vitro* suggest that the pool of cytochrome P450 enzyme species may be altered by disease or drugs, with resulting altered binding patterns for the various H2RA types [redacted]

In vitro spectral and kinetic studies of the potential interaction of FAM with the cytochrome P450 system, using CIM and RAN as active controls, were performed. In these studies, drug-induced disturbances of the P450 spectra and the inhibition of substrate metabolism were explored. Only CIM showed a pronounced different spectrum, indicative of a relatively strong ligand interaction with the ferriheme protein. No disturbances were noted with FAM or RAN. FAM, CIM, and RAN were examined for their effect on the cytochrome P450-catalyzed O-deethylation of 7-ethoxycoumarin and demethylation of benzphetamine. CIM caused a substantial concentration-dependent inhibition of both substrates, whereas little or no inhibition was shown for RAN and FAM [redacted]

FAM was found to only slightly affect cytochrome P-450 activities ([redacted]

2.4.3.3.1. Ketoconazole, dipyridamole or itraconazole

Animal studies

In vivo studies in dogs under control (no treatment), pentagastrin, and FAM treatments show marked differences in systemic ketoconazole and dipyridamole exposure. Area under the concentration-time curve (AUC) increased more than 4-fold as compared to control group, whereas it increased nearly 30-fold for ketoconazole and 9-fold for dipyridamole with pentagastrin (gastric pH approximately 2-3) as compared to FAM (gastric pH approximately 5-7.5) treatment [redacted]

Studies in humans

In patients undergoing chemotherapy, FAM decreases the plasma concentration of itraconazole. Close monitoring of the plasma concentration of itraconazole and dose adjustment are required for efficient prophylaxis ([redacted] Concomitant use of FAM and substances whose absorption is affected by stomach acidity are used at the same time, the possible change in absorption should be taken into account. In the case of

ketoconazole or itraconazole, absorption may be reduced. Ketoconazole should be taken 2 hours before FAM [redacted]

2.4.3.3.2. Antacids

[redacted] studied the effect of a high potency antacid on the bioavailability of FAM in 17 healthy volunteers and demonstrated that coadministration of the antacid caused a small but significant reduction in the C_{max} of FAM and a small decrease in the area under plasma concentration-time curve (AUC) [redacted] Similarly, [redacted] found that ingestion of the antacid concurrently with FAM resulted in a significant reduction of peak plasma FAM concentration (from 156 +/- 22 to 104 +/- 7, P less than 0.05) and area under the FAM plasma concentration curve (from 956 +/- 125 to 607 +/- 56, P less than 0.02). No significant interaction was observed when the antacid was ingested 2 hours after FAM administration [redacted]

Furthermore, the influence of concomitant antacid administration on the relative bioavailability of the H2Ras CIM, FAM, NIZ and RAN, was investigated in a panel of 21 healthy, adult male volunteers in an eight-way crossover trial. Administration with antacid reduced the bioavailability of all agents tested. The reduction in area under the serum concentration-time curve (AUC) was greatest for CIM (23%) and RAN (26%) and least for NIZ (12%) and FAM (19%). Reductions in peak serum concentration (C_{max}) followed a similar pattern. The times of peak serum concentrations were not affected by antacid [redacted]

Similarly, in healthy volunteers, antacid ingestion decreased significantly the bioavailability of FAM, RAN and CIM by 20-25%, and the bioavailability of NIZ by 12% [redacted]

Overall, concomitant use of FAM and antacids may decrease the absorption of FAM and result in lower plasma concentrations of FAM. FAM should therefore be taken 1-2 hours before an antacid [redacted]

2.4.3.3.3. Sucralfate

Concomitant use of SUC reduces the absorption of FAM. Therefore, SUC should always be taken 2 hours apart from FAM [redacted]

2.4.3.3.4. Probenecid

Probenecid, which is a classical inhibitor of renal tubular secretion of organic anions, inhibits the renal tubular secretion of FAM, which exists partly in a cationic form under physiological pH conditions [redacted] Concomitant use of FAM and probenecid may delay the excretion of FAM [redacted]

2.4.3.3.5. Antipyrine and aminopyrine

Animal studies

The effects of FAM, RAN, and CIM on the elimination kinetics of antipyrine were studied in rats. CIM was administered in a dose of 120mg/kg, FAM in a dose of 160mg/kg, and RAN in a dose of 160 mg/kg. CIM prolonged the half-life of antipyrine from a mean of 149 to 379min. Total clearance of antipyrine was decreased from 3.98 to 2.85 ml/min/kg.

These were statistically significant differences. After treatment with FAM or RAN, no changes in the elimination kinetics of antipyrine were noted [redacted]

Studies in humans

Antipyrine and aminopyrine clearance are considered classic models of the oxidative drug metabolising capacity of the liver. A number of investigators have noted that oral FAM 40 to 80 mg/day in 1 or 2 divided doses for 5 to 8 days did not significantly influence the pharmacokinetics of antipyrine in healthy volunteers (n = 15) [redacted] or in patients (n = 24) with various gastrointestinal diseases, including 4 patients with stable chronic liver disease [redacted] Similarly, a ^{14}C-aminopyrine breath test revealed no significant effect of FAM 40mg orally twice daily for 8 days on the half-life of aminopyrine in healthy volunteers [redacted]

Because clinically important drug interactions have been reported between CIM and a number of drugs, including warfarin, theophylline and phenytoin, which are metabolised in the liver by the mixed function oxidase system, similar interactions have been investigated for subsequent H2RAs. Based on the lack of interaction with antipyrine and aminopyrine, FAM is unlikely to induce clinically significant pharmacokinetic changes related to alterations in oxidative drug metabolism and, indeed, studies with a limited number of drugs in healthy volunteers have not demonstrated any such effect [redacted]

2.4.3.3.6. Diazepam

In vitro studies

FAM added in a concentration of 0.5 mmol, caused minimal inhibition of diazepam N-demethylase, whereas a 10-mmol concentration decreased diazepam N-demethylase activity by 55% [redacted]

Animal studies

The effect of FAM and CIM on plasma concentrations of diazepam was studied in dogs. Each animal received 20 mg FAM twice daily and 200 mg CIM three times daily for 7 days. On day 7, diazepam was administered. Plasma concentrations and the area under the curve (AUC) were higher in the animals receiving CIM than in the controls. The half-life of diazepam was prolonged after CIM treatment. In contrast, FAM did not affect the plasma concentration, AUC, or half-life of diazepam [redacted]

Studies in humans

The pharmacokinetics of diazepam and its major metabolite demethyldiazepam were measured in 11 healthy volunteers in a 3-way crossover study following a single i.v. dose of diazepam 10 mg. Participants received no other treatment (control), FAM 40 mg twice daily for 8 days beginning 24 hours before diazepam administration, or CIM 300 mg 4 times daily as described for FAM. FAM treatment did not change the terminal half-life or total clearance of diazepam compared with control; in contrast, CIM significantly ($p < 0.05$) prolonged both parameters. The AUC for demethyldiazepam was unaffected by FAM but was significantly ($p < 0.05$) increased by CIM [redacted]

In 2 similar studies in healthy volunteers administered a single dose of diazepam 1 mg/kg intravenously following 5 days pretreatment with FAM 40 mg orally at night, no

significant change in the terminal half-life or total clearance of diazepam was observed [redacted]

2.4.3.3.7. Theophylline

In contrast to CIM, FAM did not interfere with theophylline disposition in the rat [redacted]

In an open 2-way crossover study, 10 healthy volunteers were administered FAM 40 mg 12-hourly or CIM 300 mg 4 times daily for 4 days. On day 4, a single i.v. dose of aminophylline 5 mg/kg was administered and plasma and urine specimens collected for pharmacokinetic analysis. Compared with control, CIM significantly ($p < 0.01$) prolonged the elimination and decreased the clearance of theophylline whereas FAM had no effect. No change in urinary excretion of unchanged theophylline was associated with either drug [redacted] Similarly, in 26 patients with chronic obstructive pulmonary disease (COPD) the effect of FAM 40 mg orally per day for 4 days was indistinguishable from the effect of placebo on serum theophylline concentrations in patients on long term theophylline therapy and those given a single i.v. test dose. However, CIM 400 mg twice daily consistently prolonged the clearance of theophylline [redacted]. In line with this, in COPD patients, [redacted] and [redacted] demonstrated that FAM treatment had virtually no effect on any of theophylline's pharmacokinetic parameters. In contrast, CIM treatment significantly altered every pharmacokinetic parameter of theophylline [redacted]

2.4.3.3.8. Phenytoin

The effects of FAM and CIM on the disposition of oral phenytoin were assessed in 10 healthy volunteers in an open-label, randomized, two-way crossover study. FAM was given in a dosage of 40 mg h.s. and CIM in a dosage of 300 mg four times daily, each for 7 days. Phenytoin was given in single oral doses of 100 mg. When compared with results after phenytoin treatment alone, the concurrent administration of CIM significantly decreased the oral clearance (2.00 versus 2.361/h without CIM) and increased the initial Vd (1640 versus 1150/1 without CIM), of phenytoin. In contrast, these same measurements after concurrent administration with FAM were similar to baseline measurements obtained after phenytoin treatment alone [redacted]

Similarly, an open-label, randomized crossover study comparing the influence of FAM and CIM on phenytoin elimination and hepatic blood flow in healthy subjects, demonstrated that FAM did not alter either phenytoin or indocyanine green kinetics, whereas CIM decreased the plasma clearance of phenytoin by 16% +/- 14% (mean +/- s.d.), but was not found to have a significant influence on phenytoin Vd or terminal elimination rate constant nor on blood clearance of indocyanine green [redacted]

2.4.3.3.9. Warfarin

The effect of FAM and CIM on plasma concentrations of warfarin was studied in dogs. Each animal received 20 mg FAM twice daily and 200 mg CIM three times daily for 7 days. On day 7, warfarin was administered. Plasma concentrations and AUC were higher in the animals receiving CIM than in the controls. The half-life of warfarin was prolonged after CIM treatment. In contrast, FAM did not affect the plasma concentration, AUC, or half-life of warfarin [redacted]

2.4.3.3.10. Cationic drugs

CIM inhibits the renal elimination of various cationic drugs (e.g., procainamide) and creatinine by competing with these substances at the site of renal tubular secretion. Because FAM is a cationic drug and excreted into the urine via active renal tubular secretion, it is also assumed, on theoretical grounds, to interfere with the excretion of other cationic drugs or endogenous substances [redacted] However, it has been showed that FAM did not inhibit the renal elimination of procainamide, acecainide (N-acetylprocainamide) and creatinine [redacted] There remains, however, a possibility that FAM is excreted via a mechanism using a different cation transport system from that for CIM and other cationic drugs. It may also be plausible that plasma concentrations attained by a usual therapeutic dose (e.g., FAM 20mg twice daily) would be too low to cause significant competition with other drugs at the site of renal tubular secretion [redacted]

2.4.3.3.11. Dual orexin receptor antagonist

Daridorexant

In a prospective, single-centre, randomized, open-label study in 24 male subjects, when daridorexant administration was preceded by administration of FAM, daridorexant C_{max} decreased by 39%, geometric means ratio (90% confidence interval [90% CI]): 0.61 (0.50, 0.73) and $AUC_{0-\infty}$ remained unchanged [redacted]

Lemborexant

Lemborexant is a dual orexin receptor antagonist approved for treating insomnia. As the solubility of lemborexant is pH-sensitive, the impact of the gastric acid-reducing agent (ARA), FAM, on lemborexant pharmacokinetics was evaluated in a Phase 1 study. Additionally, post hoc analysis of data from Phase 3 studies examined the potential effect of concomitant ARAs on patient-reported/subjective sleep onset latency (sSOL) in subjects with insomnia. Coadministration of lemborexant 10 mg with FAM decreased the maximum observed concentration by 27% and delayed time of maximum observed concentration by 0.5 hours. FAM did not affect overall lemborexant exposure based on comparison of area under the concentration curves. Concomitant ARA use in the Phase 3 studies did not impact the effect of lemborexant on sSOL; the change from baseline during the last 7 nights of 1 month of treatment with lemborexant 10 mg was -17.1 minutes with vs -17.9 minutes without ARAs. Collectively, these results indicate that lemborexant can be coadministered with ARAs [redacted]

2.4.3.3.12. Filgotinib

Coadministration of filgotinib with FAM had no effect on filgotinib AUC_{∞} in a phase 1 study in healthy subjects [redacted]

2.4.3.3.13. Organic transporters

In vitro studies

Human organic cation transporters

In HEK293 cells that stably express human and rat organic cation transporters (hOCTs and rOCTs), the [(3)H]-1-methyl-4-phenylpydinium uptake by hOCT1/rOct1 and hOCT3/rOct3 was inhibited by FAM and RAN whereas that by hOCT2/rOct2 was not [redacted]

In vitro and human studies

Organic anion transporter 3

[redacted] investigated the potential drug-drug interactions between methotrexate (MTX) and gastric antisecretory drugs, such as PPIs and H2RAs (FAM), in high-dose methotrexate (HD-MTX) therapy. The impact of PPIs on the plasma MTX concentration on 73 cycles of HD-MTX therapy was analysed retrospectively in 43 patients with cancer. It was also investigated the involvement of OAT3 in PPI-MTX drug interaction in an in vitro study using human OAT3 expressing HEK293 cells. According to the results, patients who received a PPI had significantly higher MTX levels at 48 h (0.38 vs. 0.15 μmol l^{-1}, respectively, p = 0.000018) and 72 h (0.13 vs. 0.05 μmol l^{-1}, respectively, p = 0.0002) compared with patients who did not receive a PPI (but received FAM). Furthermore, the in vitro experiments demonstrated that PPIs (esomeprazole, lansoprazole, omeprazole and rabeprazole) inhibited hOAT3-mediated uptake of MTX in a concentration-dependent manner (IC_{50} values of 0.40-5.5 μm), with a rank order of lansoprazole > esomeprazole > rabeprazole > omeprazole. In contrast to PPIs, FAM showed little inhibitory effect on hOAT3-mediated MTX uptake. The authors concluded that co-administration of PPI, but not FAM, could result in a pharmacokinetic interaction that increases the plasma MTX levels, at least in part, via hOAT3 inhibition [redacted]

Animal studies

Organic cation transporters

CIM, RAN and FAM are organic bases that are cleared from the body by active renal tubular secretion involving the organic cation transporter in the proximal tubule. To determine the potential for competition for the transporter between these drugs and other drugs, their inhibitory potencies were assessed in-vitro, using rat renal brush-border membrane vesicles and tetraethylammonium as the substrate. The concentration-dependent effect of CIM, RAN and FAM on the 15-s proton-stimulated uptake of tetraethylammonium into the membrane vesicles was studied using five different rat kidneys. The order of inhibition potencies was: CIM (mean IC50 = 1.07 microM) > FAM (2.43 microM) < RAN (55.4 microM). The results indicate the potential for drug interactions in the kidney, especially for CIM and FAM [redacted]

[redacted] demonstrated that in the isolated perfused rat kidney model, FAM was a weaker inhibitor of the organic cation system compared with CIM and RAN [redacted]

In rats, I/R-induced acute kidney injury increased the plasma concentration of i.v. administrated FAM, a substrate for rOCT1 and rOCT2, or tetraethylammonium (TEA), a substrate for rOCT1, rOCT2, and rMATE1. The areas under the plasma concentration curves for FAM and TEA were 2- and 6-fold higher in I/R rats than in sham-operated rats, respectively [redacted]

2.4.3.3.14. Antiviral agents

Hepatitis C virus inhibitors (elbasvir/grazoprevir)

[redacted] found that gastric ARAs (FAM or pantoprazole) do not modify the pharmacokinetics of elbasvir or grazoprevir in a clinically relevant manner and may be coadministered with elbasvir/grazoprevir in HCV-infected patients without restriction [redacted]

Antiretroviral agents

In healthy subjects, FAM reduced exposures of atazanavir by 4-28% at doses of 20-40 mg twice daily. Similarly, in human immunodeficiency virus-infected patients coadministration of FAM 40 mg and atazanavir/ritonavir reduced exposures of atazanavir by approximately 20% [redacted]
[redacted] demonstrated that in healthy subjects there are no clinically relevant interactions between boosted elvitegravir, and thus elvitegravir/cobicistat/emtricitabine/tenofovir DF single-tablet regimen, and H2RAs (FAM); staggered antacid administration by ≥2 hours is recommended [redacted]

2.4.3.3.15. Antidiabetics

Saxagliptin

Coadministration of saxagliptin with FAM increased mean C_{max} by 14%, but AUC was almost unchanged in an open-label, randomized, 5-treatment, 5-period, 3-way crossover study in 15 healthy subjects [redacted]

Metformin

In healthy volunteers, FAM increased the estimated bioavailability of metformin without affecting its systemic exposure (AUC or C_{max}) as a result of a counteracting increase in metformin renal clearance. Moreover, metformin-FAM co-therapy caused a transient effect on oral glucose tolerance tests [redacted]

2.4.3.3.16. Anticancer agents

Paclitaxel

In women with advanced, platinum-refractory ovarian carcinoma, paclitaxel concentrations at steady-state (Css) were not significantly different in individual patients when either CIM or FAM preceded paclitaxel ($p = 0.16$). Mean paclitaxel clearance rates were 271 and 243 ml/min per m^2 following CIM and FAM, respectively. These clearance rates were not significantly different in paired analysis ($p = 0.30$) [redacted]

Ixabepilone

A phase I study that explored the effects of food and FAM on the PK of a single oral dose of ixabepilone in patients with advanced solid tumors, demonstrated that ixabepilone exposure was higher when administered 2 h after FAM [redacted]

Nilotinib

[redacted] demonstrated that in healthy subjects FAM did not significantly affected nilotinib pharmacokinetics. When concurrent use of an H2 blocker is necessary, the H2 blocker may be administered 10 h before and 2 h after nilotinib dose [redacted]

Dasatinib

A phase I study that explored the effect of FAM on dasatinib pharmacokinetics in patients with chronic myeloid leukemia, demonstrated that when FAM is administered 2 hours after dasatinib, dasatinib exposure is similar to dasatinib administered alone. However, dasatinib exposure is reduced by approximately 60% when FAM is administered 10 hours before dasatinib dosing. Thus, FAM should not be coadministered with dasatinib [redacted]

Palbociclib

FAM had no impact on palbociclib exposure under fed conditions in healthy subjects [redacted]

2.4.3.3.17. Levothyroxine

In healthy volunteers, no difference was noted in levothyroxine absorption after gastric acid suppression with 1 week of FAM [redacted]

2.4.3.3.18. Vesnarinone

In healthy volunteers, a significant decrease in maximum concentration (C_{max}) and increase in time to C_{max} (t_{max}) was observed for the inotropic agent vesnarinone during treatment with FAM, whereas area under the concentration-time curve (AUC) was similar for both treatments [redacted]

2.4.3.3.19. Grepafloxacin

FAM treatment (infusion of 20 mg) had no significant effect on grepafloxacin pharmacokinetics in healthy volunteers [redacted]*).*

2.4.3.3.20. Ferrous sulfate

In healthy subjects, concurrent ingestion of FAM (40 mg) with a ferrous sulfate tablet (300 mg) did not result in significant reductions in serum FAM AUC or C_{max} [redacted] .

2.4.3.3.21. Cyclosporine

In healthy men, neither CIM nor FAM produced a significant change in the pharmacokinetics of single-dose oral cyclosporine [redacted].

2.4.3.3.22. Antibacterials

A possible reduction in the total clearance of ciprofloxacin, owing to inhibition of its renal tubular excretion by FAM was demonstrated in rats after intravenous (3.5 mg/kg) and oral (5 mg/kg) FAM ([redacted]).

In healthy volunteers, combination of cefpodoxime proxetil with FAM caused a reduction in the AUC from 14.0 +/- 3.9 to 8.36 +/- 2.0 mg. h/liter. Corresponding changes were registered for the maximum concentration of drug in serum, 24-h urine recovery, and the time to maximum concentration of drug serum ([redacted] .

2.4.3.3.23. Lignocaine

[redacted] investigated the effects of FAM and CIM on plasma levels of epidurally administered lignocaine in patients before surgery and found that the patients who received CIM showed significantly higher plasma concentrations of lignocaine compared with patients who received FAM at all investigation times (p less than 0.01) [redacted]

2.4.3.3.24. Nifedipine

In a randomized placebo-controlled study 12 healthy volunteers were treated for 1 wk each with 10 mg of nifedipine four times daily plus placebo or the same dose of nifedipine concurrently with 40 mg of FAM once a day. FAM did not significantly alter pharmacokinetic parameters of nifedipine [redacted]

2.4.3.3.25. Ethanol

Inhibition of gastric alcohol dehydrogenase (ADH) activity by CIM results in elevated blood levels of ethanol after moderate consumption. To search for alternative H2-blockers lacking such an effect, the authors compared CIM, RAN, NIZ, and FAM. They inhibited rat gastric ADH noncompetitively, with a Ki for ethanol oxidation of 0.68 mM for CIM, 0.5 mM for RAN, 1 mM for NIZ, and 4.5 mM for FAM. These concentrations are higher than therapeutic plasma levels, but intracellular concentrations in the gastric mucosa (assessed with [3H]CIM and [14C]FAM) were at least 10- and 2-fold greater than in the blood, respectively. These results suggests that, given at therapeutic doses in vivo, the degree of inhibition by CIM and RAN should be significant and comparable, that by NIZ should be smaller, and that by FAM should be negligible. These drugs also exerted either mixed or competitive inhibition of rat hepatic ADH, but the effects of CIM and FAM were observed at concentrations unlikely to occur in vivo ([redacted]

[redacted] reported the effects of FAM, CIM and placebo on the blood alcohol concentrations produced by 500ml of beer consumed over 5 minutes by 12 fasted volunteers 30 minutes after the test drug. Peak blood alcohol concentrations occurred 30 to 45 minutes after beer consumption and slowly declined during the 2-hour observation period. Compared with placebo, neither FAM nor CIM induced a significant change in the blood alcohol concentration-time curves [redacted]

Similarly, [redacted] investigated the effects of H2RAs (CIM, RAN, and FAM) on ethanol metabolism. Neither in aldehyde dehydrogenase (ALDH)-1 deficient subjects nor in those with normal ALDH-1, did the three H2RAs and placebo differ in their effects on the pharmacokinetic parameters of ethanol (i.e., t_{max}, metabolic rate (k0), peak serum concentration (C_{max}), Vd and area under the concentration-time curve (AUC). The AUC of acetaldehyde was slightly but significantly (P less than 0.05) larger only after treatment with CIM. C_{max} and t_{max} of acetaldehyde were unchanged [redacted]

In a randomized, placebo-controlled study of 10 healthy human subjects blood alcohol levels after consumption of beer, 24-h intragastric pH, and serum gastrin concentrations were serially measured during a 28-day therapy with FAM. FAM did not significantly alter either the peak or the 2-h integrated blood alcohol response to beer. The median intragastric pH on days 1, 7, and 28 was significantly ($p < 0.006$) increased by FAM. After 7 days of FAM therapy, however, the pH was significantly ($p < 0.03$) lower than on day 1 (4.0 versus 2.4); this effect persisted on day 28 (2.3). Whereas basal plasma levels of gastrin were not significantly altered by FAM, the 2-h integrated plasma gastrin response to beer was significantly ($p < 0.05$) higher with FAM than with placebo [redacted]

In a randomized open crossover study, oral ethanol pharmacokinetics were assessed after breakfast in the morning following a 3-day regimen of FAM, 40 mg/day, and following a no-drug control period. FAM increased the area under the plasma ethanol concentration-time curve (AUC0-t) by 29% and maximal plasma concentration (C_{max}) by 23% [redacted]

In healthy men, FAM (40 mg/d) had no significant effects on blood alcohol levels after ethanol ingestion (0.3 g/kg of body weight), whereas RAN (300 mg/d) and CIM (1000 mg/d) had greater effects ([redacted] Similarly, in healthy subjects, [redacted] demonstrated that post-prandial alcohol absorption after 0.3 g/kg of alcohol is not affected by RAN, CIM or FAM [redacted]

In a randomized 4-way cross-over study in 12 healthy subjects, inhibition of gastric alcohol dehydrogenase activity by histamine H2RAs [CIM (800 mg day-1), RAN (300 mg day-1) or FAM (40 mg day-1)] had no influence on the pharmacokinetics of ethanol after a moderate dose (0.3 g kg-1) [redacted]

In healthy male subjects, it was found that FAM (40 mg), RAN (300 mg) and CIM (800 mg) had no effect on post-prandial absorption of ethanol 0.8 g/kg taken after an evening meal [redacted] Similarly, [redacted] demonstrated that in healthy nonalcoholic men, the H2Ras [FAM (20 mg twice daily), CIM (400 mg twice daily), NIZ (150 mg twice daily), RAN (150 mg twice daily)] did not alter serum ethanol levels following moderate alcohol consumption after an evening meal [redacted]

[redacted] investigated the possibility of a pharmacokinetic interaction between H2RAs and alcohol consumed at lunchtime in 24 healthy non-alcoholic male subjects, each receiving RAN 150 mg four times daily, CIM 400 mg four times daily, FAM 20 mg four times daily and placebo in an open, four-way cross-over study and demonstrated that none of the H2RAs had any statistically significant effects on any of the pharmacokinetic parameters for alcohol [redacted]

A meta-analysis including a total of twenty-four trials, demonstrated that CIM and RAN, but not the other H2RAs (i.e., FAM or NIZ) can cause small elevations of serum alcohol level when alcohol and drug are administered concurrently [redacted]

2.4.3.3.26. Propanolol

The effect of FAM and CIM on plasma concentrations of propranolol was studied in dogs. Each animal received 20 mg FAM twice daily and 200 mg CIM three times daily for 7 days. On day 7, propranolol was administered. Plasma concentrations and AUC were higher in the animals receiving CIM than in the controls. In contrast, FAM did not affect the plasma concentration, AUC, or half-life of propranolol [redacted]

2.4.3.3.27. Midazolam

In the rat *in-situ* perfused liver model, midazolam disposition was impaired at 10, 50 and 60 min of the experimental period following the addition of CIM (8 mg), whereas RAN (3 mg) and FAM (0.4 mg) produced an effect at 10 min only; midazolam levels in bile were not affected by the presence of a H2RA [redacted]

2.4.4. TOXICOLOGY

2.4.4.1. SINGLE DOSE TOXICITY

Acute toxicity of FAM was assessed in mice, rats and dogs. The following values for median lethal doses (LD_{50}) were observed:

Table 1. LD_{50} values in mice, rats and dogs [redacted]

Species	Route	Sex	LD_{50} (mg/kg)
Mouse	Oral	Male	4,684
		Female	3,233
	Intravenous	Male	254
		Female	358
Rat	Oral	Male	4,907
		Female	4,049
	Intraperitoneal	Male	987
		Female	814
Dog	Intravenous		300

In particular, the oral LD_{50} of FAM in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. FAM did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and growth depression in rabbits starting with 200 mg/kg/day orally. The i.v. LD_{50} of FAM for mice and rats ranged from 254-563 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in intravenously treated dogs were emesis, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse [redacted]

2.4.4.2. REPEAT-DOSE TOXICITY

13-week, 6-month, and 1-year oral toxicity studies in rats

The main aim of this study was to evaluate the toxicity of FAM in rats after 13 weeks, 6 months, and 1-year oral administration. The study showed that rats receiving an oral dose of FAM 4000 mg/kg/day (2000 mg/kg/ b.i.d) for 13 weeks had no notable toxicological findings. Similarly, rats administered FAM orally for 6 months at doses up to 1000 mg/kg/day had only minimal changes (increased urine osmolarity). Likewise, rats receiving an oral dose of FAM up to 2000 mg/kg/day for 1 year had no changes of toxicological significance.

In all of these studies, a dose- and time-dependent cytoplasmic granularity was observed in gastric chief cells compared to controls, in rats. Minimal evidence of eosinophilic cytoplasmic granularity was seen after 3 months, when given orally at dose levels of 4000 mg/kg/day. In case of doses given orally for 6 months at levels of 50 to 1000 mg/kg/day, the incidence was not dose dependent. In 2 other studies, in which doses between 20 and 2000 mg/kg/day were administered for 1 year, there was a doserelated increase in the incidence and extent of eosinophilic granularity at doses of 200 mg/kg/day and higher. The appearance of eosinophilic cytoplasmic granularity in control rats was also time-dependent. There was little evidence of the change in animal studies of 3 months, a minimal incidence (about 10%) after 6 months of treatment, and up to 50% incidence in control after 1 year of study.

In conclusion, oral administration of FAM up to 2000 mg/kg/day in rats for a period of 1 year was well tolerated. Dose- and time-dependent eosinophilic cytoplasmic granularity in gastric chief cells was noticed in treatment and control groups.

Intravenous administration of FAM was well tolerated by rats for 13 weeks at dosage levels of up to 20 mg/kg/day [redacted]

30-day, 13-week and 1-year oral toxicity studies in dogs

The main aim of this study was to evaluate the toxicity of FAM in dogs after 30 days, 13 weeks, and 1-year oral administration. Details regarding the methods were not reported in the article by the authors.

The study showed that high doses (dose not indicated) of FAM administered orally were well tolerated in beagle dogs. However, minimal changes like slight weight loss, slight increase in serum albumin, and reduced serum globulin were noticed in dogs that received FAM at a dose level of 1000 mg/kg/day for 13 weeks. Slight weight loss was also noted in dogs that received up to 4000 mg/kg/day of FAM for 30 days, and for 1 year at a dose level of 500 mg/kg/day.

Intravenous administration of FAM was well tolerated by dogs, except for occasional emesis, at dosage levels of up to 10 mg/kg/day for 5 to 26 weeks [redacted]

2.4.4.3. GENOTOXICITY

FAM was tested in a reverse-mutation test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation and no mutagenic potential was observed. The same studies were performed with FAM/sodium, nitrite reaction mixture and C-nitroso derivatives of FAM and they were also negative. FAM and C-nitroso derivatives of FAM were tested in the rec-assay using *Bacillus subtilis* H17 and M45 and the tests were negative for DNA-damaging capacity of the compounds. In *in vivo* studies in mice, a

micronucleus test and a chromosomal aberration test showed no evidence of a mutagenic effect[redacted]

2.4.4.4. CARCINOGENICITY

Mice [redacted] and rats [redacted] received FAM orally at dosage levels of 20, 200, or 2,000 mg/kg/day for 92 and 106 weeks, respectively. In mice, only a slight increased incidence of distention of gastric glands was observed in females in the 2,000 mg/kg/day group. In rats, there was a slightly higher mortality in females given 2,000 mg/kg/day of FAM compared with controls. In addition, slight distention of gastric glands was present in females in the highest dosage group, and an increased incidence of eosinophilic cytoplasmic granularity was seen in rats in the 200 and 2,000 mg/kg/day groups compared to controls. No evidence of a carcinogenic effect was seen in either species [redacted]

2.4.4.5. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

2.4.4.5.1. Fertility and early embryonic development

In fertility studies in rats, male and female animals were treated with oral doses of 100, 500 and 2000 mg/kg/day, with males being treated for 12 weeks before mating and during the mating period, while females were treated 14 days before mating to day 21 postpartum. No effects on fertility rates, general reproductive performance and early embryonic development were observed [redacted]

2.4.4.5.2. Embryo-foetal development

In animal studies of embryo-foetal developmental toxicity, female rats were administered oral doses of 100, 500 and 2000 mg/kg/day of FAM from gestation day 7 to 17. FAM administration did not result in teratogenicity, mortality or other embryo-foetal toxicities. In another study, female rabbits were treated orally with doses of 30, 200 and 500 mg/kg/day from gestation day 6 to 18. No teratogenic or toxic effects were observed in animals receiving the doses of 30 and 200 mg/kg/day, however, at the dose of 500 mg/kg/day mother food intake and body weight were suppressed, and abortions, related to decreased food consumption, were observed. Also, a delay in ossification and a decrease in the number of sacrocaudal vertebrae of fetuses were seen in the 500 mg/kg/day dose group. In conclusion, oral administration of FAM to pregnant rabbits during organogenesis, the maximum non-toxic dose was 200 mg/kg/day. There was no teratogenicity [redacted] FAM did not effectively cross the placental barrier of rats [redacted]

Only limited information is available on the tissue distribution of FAM in humans. Using an *ex vivo* placenta perfusion model, it was shown that FAM is transferred through the human placenta at a rate similar to that of other H2RAs (i.e., CIM, RAN and NIZ) [redacted]

2.4.4.5.3. Prenatal and postnatal development, including maternal function

The aim of this study was to assess the effects of oral administration of FAM on peri- and post-natal development in rats. FAM was administered orally to groups of 20-25 pregnant female Sprague-Dawley rats at doses of 0 (0.5% methylcellulose), 100, 500, and 2000 mg/kg/day during the period of organogenesis from gestation day 15 to postnatal day 21.

Following parameters were observed in all groups like general, delivery, and nursing conditions. Body weight and food consumption were measured on gestation days 0, 7, 10, 14, 15, 16, 17, 18, and 20, and on days 0, 4, 7, 10, 14, 17, and 22 after parturition. All dams were allowed to deliver naturally and wean their young. Dams were sacrificed and necropsied after weaning. The newborns (F1 generation) were observed for the number of live and dead pups, sex, weight at parturition and on days 4, 7, 10, 14, 17, and 22, external abnormalities at birth and during development, growth differentiation, and reflex function. At 22 days after parturition, 1 male and 1 female pup from each dam were evaluated further for reproductive function, and 1 male and 1 female pup from each of 10 dams were evaluated for behavioral function (e.g., open field, revolving wheel, rotarod test, T-maze test). The remaining pups were sacrificed, necropsied, and examined for skeletal abnormalities. The pups that have been weaned for the purpose of reproductive performance testing were weighed on a weekly basis, and mating between non-siblings took place 11 weeks after birth, reproductive functions were evaluated, and the pups were allowed to deliver naturally. Observations continued until 7 days after birth of the F2 generation, at which time all F1 dams and males used for mating and all F2 nurslings were sacrificed and necropsied.

There were no abnormalities in general conditions, delivery, or nursing conditions in the dams in any dose groups. Dams on high dose group (2000 mg/kg) had lower body weight once they entered the administration period; there was no difference in body weight during postnatal period. Food consumption was reduced in both the 500 and 2000 mg/kg/day dose groups, during the prenatal administration period. There was improvement after parturition. The autopsy examination at the time of weaning showed no abnormalities macroscopically. However, lower heart weight was observed in the 500 and 2000 mg/kg/day dose groups.

All pregnant dams gave birth to live offspring, and there were no abnormal values in the numbers of pups, stillborns, and weights of the live pups. In addition, no external abnormalities were found among the live pups. There were no treatment-related changes in survival rate during lactation period, number of fatalities during the peri-natal period, and the weaning rate. Pups at 500 and 2000 mg/kg/day dose groups showed reduced body weight following 10 days after birth, and a significant difference from the control group was noted between the age of 5 and 9 weeks. Autopsies of F1 pups at the time of weaning showed 4, 1, 2 and 1 cases of enlarged pylem in controls, 100, 500, and 2000 mg/kg/day dose groups, respectively. In addition, one pup showed unilateral poor development of the orchis in 500 mg/kg/day dose group and one mild case of diaphragmatic hernia was observed in 2000 mg/kg/day dose group. No treatment related changes in organ weight and skeletal abnormalities were observed. No abnormalities were found in growth differentiation, pupillary reflex, or behavioral function tests.

Reproductive performance test of F1 generation (at the age of 11 weeks) showed one case of unsuccessful mating out of 25 cases in the 500 mg/kg group and 2 cases out 20 cases in the 2000 mg/kg dose group. In addition, there were 2 cases of infertility in each group, including the control group. There were no variations in terms of delivery rate, number of pups, and number of stillborns. None of the pups (F2) showed signs of external abnormalities. The weights of the newborns were decreased in the 2000 mg/kg/day group, and the pups in the 500 and 2000 mg/kg/day groups had decreased body weight at 7 days of age. Although the 2000 mg/kg/day group had a slightly higher number of mortalities during the peri-natal period, there were no group differences in survival rate in the first 7 days after parturition. Necropsy did not reveal any abnormalities.

In conclusion, a transient depression of body weight gain and food intake was observed in dams after initiation of the treatment in case of higher dosages of FAM. No abnormalities were observed in delivery and nursing of pups. Newborns showed a slight

depression of body weight gains after birth, but there were no abnormalities in their physical and functional development and reproductive capacities [redacted]

FAM was present in rat milk [redacted]

FAM is excreted into human breast milk at a mean M/P ratio of 1.78 at 6 hours after a single oral dose of 40 mg in healthy puerperal women [redacted] The mean daily yield of milk ranged from 600 to 800 ml/day in Caucasian women [redacted] thus, assuming that the C_{max} of FAM attainable after an oral dose of 40 mg is about 100 µg/L, the maximum amount of the drug which could be ingested by a nursing infant less than 1 year old would be calculated to be about 0.14 mg/day or 0.015 to 0.04 mg/kg/day (i.e. equivalent to about 1 to 3 mg/day in a 70kg adult subject). If this assumptive estimate is correct, the excretion of FAM into human breast milk would be clinically insignificant [redacted]

Seven women were given oral FAM 40 mg daily in 2 or 4 divided doses for 3 days at 12 to 16 weeks postpartum. Average concentrations of FAM in breastmilk were 53 and 55 mcg/L at 3 and 6 hours after a dose, respectively [redacted]

2.4.4.6. OTHER TOXICITY STUDIES

In immunogenicity studies, no effect on the production of IgE antibodies was seen in the sera of mice which were injected, once intraperitoneally, with FAM alone (up to 2 mg/8 mL/kg) or coupled with either mouse serum albumin or ovalbumin. The sera were used to measure passive cutaneous anaphylaxis in rats which were then challenged with solutions of antigens similar to those antigens used for the initial dose in mice. Similarly, no evidence of an anaphylactic reaction was seen in guinea pigs challenged intravenously with FAM after initiating doses (three times, subcutaneously, at six-day intervals) of up to 10 mg/mL [redacted]

No evidence of local intramuscular or ocular irritation was observed in rabbits given 10 mg/ml of FAM [redacted]

2.4.4.7. DISCUSSION ON EXCIPIENTS

[redacted]

Table 2. Qualitative and quantitative composition of 'Famotidine 20 mg and 40 mg film-coated tablets/REMEDICA'.

Ingredients	Quantity (mg/tablet)		Function	Standard
Drug substance				
Famotidine[1]	[redacted]	[redacted]	Active ingredient	Ph. Eur.[2]
Excipients				
Cellulose, microcrystalline 101[1]	[redacted]	[redacted]	Diluent	Ph. Eur.[3]
Starch, pregelatinised	[redacted]	[redacted]	Diluent	Ph. Eur.
Hydroxypropyl cellulose	[redacted]	[redacted]	Binder	Ph. Eur.
Cellulose, microcrystalline 102	[redacted]	[redacted]	Diluent	Ph. Eur.
Magnesium stearate	[redacted]	[redacted]	Lubricant	Ph. Eur.

Water, purified[4]	[redacted]	[redacted]	Granulation solvent	Ph. Eur.
Tablet core weight:	[redacted]	[redacted]		
Coating material composition:				
Macrogol Poly(vinyl alcohol) Grafted Copolymer	[redacted]	[redacted]	Plasticizer	Ph. Eur.
Talc	[redacted]	[redacted]	Anti-caking agent	Ph. Eur.
Titanium dioxide	[redacted]	[redacted]	Opacifier	Ph. Eur.
Glycerol monocaprylocaprate Type I	[redacted]	[redacted]	Surfactant	Ph. Eur.
Poly(vinyl alcohol)	[redacted]	[redacted]	Film-forming agent	Ph. Eur.
Quinoline yellow aluminium lake E104	-	[redacted]	Colouring agent	EU 231/2012
Iron oxide red E172	[redacted]	-	Colouring agent	EU 231/2012
Iron oxide black E172	[redacted]	-	Colouring agent	EU 231/2012
Iron oxide yellow E172	[redacted]	-	Colouring agent	EU 231/2012
Water, purified[5]	[redacted]	[redacted]	Coating Solvent	Ph. Eur.
Total tablet weight:	[redacted]	[redacted]		

[redacted]

The excipients used in 'Famotidine 20 mg and 40 mg film-coated tablets/REMEDICA' are well known excipients, widely used in the pharmaceutical industry for oral preparations for decades. As such their safety profile is well established with no concern regarding toxicological issues.

Overall, the safety profile of all excipients is well established and no risk for humans is anticipated by the qualitative and quantitative composition of 'Famotidine 20 mg and 40 mg film-coated tablets/REMEDICA' described in the table above when used according to the product information.

2.4.4.8. DISCUSSION ON IMPURITIES

The impurities that may be present in the final products 'Famotidine 20 mg and 40 mg film-coated tablets/REMEDICA' and their limits as per the product's specifications are presented in table 3.

Table 3. Finished product specifications for impurities present in 'Famotidine 20 mg and 40 mg film-coated tablets/REMEDICA'.

Related substances [HPLC]	**At release and up to end of shelf-life**	
- Degradation impurity-3	NMT 0.2%	NMT 0.2%
- Impurity-C	NMT 0.3%	NMT 0.3%

Related substances [HPLC]	At release and up to end of shelf-life	
- Degradation impurity-2 (Impurity-D)	NMT 0.3%	NMT 0.3%
- Degradation impurity-1 (Impurity-F)	NMT 0.2%	NMT 0.2%
- Max unknown impurity	NMT 0.2%	NMT 0.2%
- Total impurities	NMT 2.5 %	NMT 2.5%

According to the product's SmPC, the maximum daily dose that may be administered is 800 mg. Therefore, and in accordance with ICH Guideline Q3B(R2) Impurities in New Drug Products, both the identification and qualification threshold is 0.2%.

The specification limit for Impurity-C and Degradation impurity-2 (Impurity-D) has been set to ≤ 0.3%% at both release and shelf-life according to the Ph. Eur. Monograph for Famotidine and as per the recommendations of the General Chapter Ph. Eur. 5.10.

Therefore, the specifications set by the manufacturer comply with the ICH Guideline Q3B(R2) Impurities in New Drug Products and Ph. Eur. Monograph for Famotidine and as per the recommendations of the General Chapter Ph. Eur. 5.10.

In conclusion, all specifications set for all impurities that may be potentially found in the drug products 'Famotidine 20 mg and 40 mg film-coated tablets/REMEDICA' are in accordance with the acceptance criteria set by the ICH Guideline Q3B(R2) Impurities in New Drug Products and Ph. Eur. Monograph for Famotidine and as per the recommendations of the General Chapter Ph. Eur. 5.10. Therefore, no risk for humans is anticipated by the presence of impurities in the drug products 'Famotidine 20 mg and 40 mg film-coated tablets/REMEDICA' at the levels set in the product's specifications.

2.4.5. INTEGRATED OVERVIEW AND CONCLUSIONS

PRIMARY PHARMACODYNAMICS

Mechanism of action

FAM is a competitive H_2RA that binds to the H-receptors located on the basolateral membrane of the parietal cell in the stomach, effectively blocking histamine actions. Its pharmacologic activity results in the inhibition of gastric secretion by suppressing acid concentration and volume of gastric secretion. FAM inhibits both basal and nocturnal gastric acid secretion as well as reduces gastric volume, acidity, and secretion stimulated by food, caffeine, insulin, and pentagastrin [redacted] .

Histamine receptor selectivity

In vitro and/or *in vivo*, FAM has demonstrated histamine H_2-receptor, but neither antagonistic nor agonistic effects on muscarinic, nicotinic, histaminergic H_1- or sympathetic α- and β-receptors. The interaction between FAM and histamine H_2-receptors was tissue dependent, but in most *in vitro* models, FAM exhibited classic competitive inhibition at the H_2-receptor site [redacted]

However, some investigators report insurmountable inhibition when FAM in concentrations of 3 x 10^{-7} to 10^{-5} mol/L was assayed in guinea-pig atria [redacted]

[redacted] guinea-pig parietal cells [redacted] guinea-pig papillary muscle, rat gastric fundus and rat uterus [redacted]

Other investigators observed only competitive inhibition when FAM was assayed in guinea-pig atria and mouse gastric mucosa [redacted] guinea-pig gastric mucosa [redacted] isolated rat parietal cells [redacted] and isolated rabbit gastric glands [redacted]

Concentrations of FAM which inhibit histamine-stimulated acid secretion and adenylate cyclase activity in various animal gastric tissues are 24 to 124 times smaller than equally inhibitory concentrations of CIM [redacted] and 6 to 8 times smaller than equally inhibitory concentrations of RAN [redacted]

In human gastric tissue, FAM was 17 times more potent than RAN at inhibiting histamine-stimulated adenylate cyclase generation in normal fundic glands [redacted] and 3.5 times more potent in human gastric cancer HGT-1 cells [redacted] Furthermore, in rat brain, [redacted] demonstrated that histamine-induced cyclic AMP accumulation was inhibited by the addition of CIM or FAM [redacted]

FAM had no antagonistic or agonistic effects during stimulation of muscarinic, nicotinic, histaminergic H_1- or sympathetic α- or β-receptors in anaesthetised dogs or cats. FAM had no influence on receptor-adenylate cyclase systems sensitive to prostaglandin E2 (PGE2), isoprenaline (isoproterenol) or vasoactive peptide prepared from the purified plasma membranes of human fundic glands [redacted]

Pharmacodynamic effects

Effect on gastric acid secretion

Animal studies

The effectiveness of FAM in inhibiting gastric acid secretion has been investigated in anaesthetised dogs [redacted]), dogs with a Heidenhain pouch [redacted] dogs, rats and cats with a gastric fistula [redacted] and in anaesthetised pylorus-ligated rats. In all studies, FAM, whether administered intravenously, orally or intraduodenally (pylorus-ligated rats), inhibited gastric acid secretion stimulated by histamine, pentagastrin, methacholine, dimaprit or a test meal. FAM was 7 to 20 times more potent than RAN and 40 to 150 times more potent than CIM on a molar basis depending on the experimental model, the secretory stimulant and the route of administration [redacted]

Studies in humans

In healthy volunteers, single oral doses of FAM 5, 10 and 20mg decrease pentagastrin-stimulated acid output in a dose-dependent manner [redacted]

Placebo-controlled studies using 24-hour pH-metry in patients with a history of DU revealed profound inhibition of nocturnal acidity but a decreased to negligible effect during the day for various therapeutic dosage schedules of oral or i.v. FAM [redacted]

Effect on pepsin

Single oral doses of FAM 5 to 20 mg suppressed basal and pentagastrin- or betazole-stimulated pepsin output in healthy subjects and in patients with PUD [redacted] Generally, no significant difference was found in the degree of suppression achieved by the various doses. Pepsin inhibition varied between approximately 30 and 90% of baseline values [redacted]

Effect on gastric and oesophageal mucosal protection

Effect on gastric mucosal protection

FAM inhibited dose-dependently the development of gastric lesions produced by taurocholate-histamine in doses that suppressed histamine-induced acid secretion in pylorus-ligated rats. The H_2-antagonist also prevented gastric mucosal lesions induced by taurocholate-serotonin, iodoacetamide, acidified aspirin and acidified ethanol [redacted]

On indometacin-induced gastric mucosa damage in the rat stomach, FAM and erythropoietin 2500 and 5000 IU/kg reduced the ulcer area by 98%, 31% and 58%, respectively, compared with the indometacin group [redacted]

Prevention of experimental gastric mucosal damage

FAM administered intraduodenally or orally inhibited the formation of aspirin-, indomethacin-, prednisolone- and histamine-induced GUs in rats. FAM also inhibited the formation of mepirizole-induced DUs and water immersion stress-induced GUs in rats, and significantly accelerated the healing of the former [redacted]

In comparative studies, FAM was markedly more potent than CIM in suppressing indomethacin- and aspirin-induced GUs in rats. Neither FAM nor CIM inhibited the formation of GUs due to intragastric infusion of HCI, but on a weight-for-weight basis intravenous FAM was 30 times more potent than intravenous CIM in inhibiting GUs induced by the combination of histamine and intragastric taurocholate during haemorrhagic shock in rats [redacted]

Effect on gastrin concentration

A number of investigators have noted an increase in serum gastrin concentrations during administration of FAM for 1 to 8 weeks; in some studies, this reached statistical significance [redacted] but in others it did not [redacted]

Animal models of efficacy

In gastric ulcer rat models

FAM inhibited the formation of histamine- and prednisolone-induced GUs in rats.

FAM inhibited the formation of indomethacin-induced GUs in rats. The drug was markedly more potent than CIM in suppressing indomethacin-induced GUs in rats [redacted]

FAM inhibited the formation of aspirin-induced GUs in rats and was markedly more potent than CIM in suppressing the aforementioned ulcers [redacted]

In aspirin- and pylorus ligation-induced GU models, FAM formulation reduced gastric volume, total acidity and ulcer index thus, showing the anti-secretory mechanism involved in the antiulcerogenic activity through H2 receptors [redacted]

FAM also inhibited the formation of stress-induced GUs in rats [redacted]

[redacted] found that the synergistic action of FAM and chlorpheniramine on acetic acid-induced chronic gastric ulcer in rats decreases the incidence of ulcer and also enhances the healing of ulcer [redacted]

In duodenal ulcer rat models

FAM inhibited the formation of mepirizole-induced DUs in rats and significantly accelerated their healing [redacted]

In the cysteamine-induced DU model in female rats, the combination of sucralfate and FAM (at subtherapeutic dose) was effective in decreasing the number, length, severity of DUs, as well as ulcerative index [redacted]

SAFETY PHARMACOLOGY

Central nervous system effects

The effects of FAM on the central nervous system (CNS) were studied in squirrels, monkeys, mice, and cats. In monkeys, FAM had a bidirectional effect on lever pressing (avoidance response) causing an increase at the low dose (1.0 mg/kg p.o.) and a small decrease at 9 mg/kg. In mice following intraperitoneal administration of 6 to 150 mg/kg no overt behavioural signs or symptoms of CNS activity were observed. In mice FAM was not active as an antagonist of the CNS actions of TRH, neurotensin, substance P, or amphetamine. FAM was free of major or minor tranquillizing, anticonvulsant, anticholinergic, ganglionic blocking, or dopaminergic activity. In cats, FAM did not affect the EEG or arousal response but did prolong the duration of hippocampal after-discharge [redacted]

Cardiovascular, bronchial and renal effects

Results from both *in vitro* in HEK293 cells and animal studies (halothane-anesthetized canine model and canine chronic atrioventricular conduction block model) have shown that FAM possesses no cardiovascular effects at a therapeutic dose, while it may exert cardiostimulatory actions after drug overdoses that might potentiate the proarrhythmic potential of co-administered cardiotonic agents by increasing the intracellular Ca(2+) concentration [redacted]

The effects of FAM on cardiovascular and bronchial functions were investigated in anesthetized dogs. FAM did not affect heart rate, blood pressure, LVP, maximum dLVP/dt, cardiac output, or coronary blood flow at i.v. doses of 1 to 30 mg/kg in anesthetized dogs. FAM did not produce any remarkable change in the ECG at doses up to 30 mg/kg in anesthetized dogs. The only exception was of a transient increase or decrease in the T-wave amplitude in the ECG at a dose of 30 mg/kg. No haemodynamic changes were observed after

FAM administration to anesthetized dogs whose cardiac function was depressed by propranolol (1 mg/kg I.V.) [redacted]

Ten mg/kg of FAM administered orally were without effect on the blood pressure of spontaneously hypertensive rats. In anaesthetized dogs, i.v. administration of 1.0 and 4.0 mg/kg of FAM was without effect on cardiovascular parameters relating to the autonomic nervous system, blood pressure, heart rate, or respiratory function. In conscious dogs, an oral dose of 10 mg/kg was without diuretic effect [redacted]

Endocrine effects

The effects of FAM on the thyroid of rats were evaluated after five weeks of oral administration at doses up to 2000 mg/kg/day. No evidence of treatment-related alterations of serum thyroid hormone levels, thyroid weight or the microscopic appearance were seen after administration of FAM [redacted]

PHARMACODYNAMIC DRUG INTERACTIONS

Clopidogrel

A double-blind, randomized study that compared the influence of esomeprazole and FAM on the platelet inhibitory effect of clopidogrel, demonstrated that neither esomeprazole nor FAM reduced the platelet inhibitory effect of clopidogrel [redacted]

Concomitant use of FAM had no effect on the antiplatelet effect of clopidogrel [redacted] Omeprazole therapy was associated with higher on- treatment platelet reactivity than FAM [redacted]

Suxamethonium

[redacted] examined the effect of preoperative i.v. administration of three different H_2RAs (CIM 400 mg, RAN 80 mg and FAM 20 mg) or metoclopramide 10 mg i.v. on the duration of neuromuscular block produced by an intubating dose (1 mg kg^{-1}) of suxamethonium and demonstrated that the time from onset of 95% block to 25% recovery ("block time") was not significantly different between the groups receiving CIM, RAN, FAM and control [redacted]

Warfarin

Ten healthy volunteers were administered FAM 40 mg orally twice daily concurrently with warfarin, which was titrated to lengthen the prothrombin time to 1.5 times control. This study showed no statistical difference in mean prothrombin time ratios between warfarin-only days and warfarin-FAM days [redacted]

PHARMACOKINETICS

Animal pharmacokinetics

The absorption, distribution, metabolism and excretion of FAM were studied in two animal species. Absorption was 28% in the rat and 43% in the dog. Absorption was 28% in the rat and 43% in the dog. The plasma half-life in dogs was 2.5 hours, which was unchanged after repeated doses, indicating no tendency for the drug to accumulate. In rats, the highest

levels of radioactivity after an oral dose of FAM were found in the gastrointestinal tract, kidneys, liver, submandibular glands, arteries, epiphyseal membrane, fascia, and uvea. The distribution pattern was not affected on repeated dosing. FAM did not effectively cross the blood-brain [redacted]

The only metabolite of FAM in rat and dog urine was the sulfoxide derivative, which was present in minor amounts. Urinary and fecal excretion of radioactivity in rats accounted for 28% and 70%, respectively, of an oral dose, compared to 83% and 17% respectively, of an intravenous dose. About 2.4% of the dose in rats was excreted in the bile. Dogs excreted 45% of an oral dose in the urine, compared to 100% of an intravenous dose [redacted]

Clinical pharmacokinetics

Absorption

Peak plasma concentrations are dose-dependent and are attained approximately 1 to 3.5 hours after dosing. Peak plasma concentrations are approximately 40-60 ng/ml after a 20 mg dose of FAM and 75-100 ng/ml after a 40 mg dose [redacted] FAM is not completely absorbed following oral administration and the bioavailability of both the tablet and suspension formulations is approximately 43% [redacted]

During repeated oral administration of FAM 20 mg 3 times daily, C_{max} and trough plasma concentrations (C_{min}) of the drug were largely constant (i.e., about 100 and 50 µg/L, respectively) over 8 weeks in heathy volunteers [redacted] No significant accumulation was observed in FAM C_{min} not only in healthy volunteers but also in cirrhotic patients with normal renal function during repeated oral administration of FAM 40 mg/day over 7 days [redacted]

Effect of food

In 17 healthy volunteers, oral administration of FAM 40mg tablet with a standard breakfast was not associated with any change in the rate or extent of FAM absorption [redacted] FAM alone, up to 80 mg/day, does not appear to delay gastric emptying [redacted] Administration of FAM 40 mg with 10ml of high-potency antacid (Mylanta II) in a fasted volunteer population resulted in a small but significant ($p < 0.05$) decrease in peak plasma concentration and a small non-significant decrease in area under the concentration-time curve and an increase in time to peak concentration [redacted]

Distribution and protein binding

The apparent volume of distribution at steady-state (V_{ss}) and during the terminal log-linear phase (V_z) of FAM obtained from healthy adult volunteers range from 0.94 to 1.33 L/kg [redacted] The volume of distribution (V_d) values obtained from healthy subjects do not appear to differ significantly from those observed in patients with renal failure or liver cirrhosis [redacted].

FAM distributes into CSF at a mean CSF/plasma concentration ratio of 0.12 at 4h after oral administration in patients with intact blood-brain barrier [redacted]

FAM is only weakly bound to plasma protein [redacted] Binding to plasma protein is relatively low (15-22%) [redacted]

Metabolism and elimination

FAM S-oxide is the only known metabolite of the drug in humans. After i.v. administration of FAM, about 2 to 8% of the dose was recovered in urine as FAM S-oxide in humans [redacted] Previous studies [redacted] have demonstrated that the CL_{NR} of FAM consisted of only 21 to 33% of the CL. Therefore, the hepatic metabolism of FAM would make only a minor contribution to the overall elimination of the drug [redacted]

The $t_{1/2}$ of FAM administered orally or intravenously was between 2.5 and 4 hours in healthy subjects [redacted]

Excretion

FAM is excreted in the urine and faeces. The CL_R of FAM in healthy subjects is 250-450 ml/min, indicating active tubular secretion of the drug [redacted] The percentage recovery of FAM in the urine is not dose dependent. Mean urinary recovery of unchanged FAM was from 25 to 30% of orally administered doses [redacted] and from 65 to 70% of intravenously administered doses.

The mean CL of FAM after i.v. administration has been reported as 25 and 29 L/h [redacted]

Linearity

Following single oral doses of 5, 10, 20 and 40 mg FAM the peak plasma concentrations increase proportionally, with the 20 and 40 mg tablets producing peak concentrations of 0.04 to 0.06 mg/L and 0.075 to 0.10 mg/L, respectively [redacted]

Pharmacokinetic drug interactions

No metabolism-related drug interactions are known to date [redacted]

Ketoconazole or itraconazole

Concomitant use of FAM and substances whose absorption is affected by stomach acidity are used at the same time, the possible change in absorption should be taken into account. In the case of ketoconazole or itraconazole, absorption may be reduced. Ketoconazole should be taken 2 hours before FAM [redacted]

Antacids

Concomitant use of FAM and antacids may decrease the absorption of FAM and result in lower plasma concentrations of FAM. FAM should therefore be taken 1-2 hours before an antacid [redacted]

Sucralfate

Concomitant use of sucralfate reduces the absorption of FAM. Therefore, sucralfate should always be taken 2 hours apart from FAM [redacted]

Probenecid

Concomitant use of FAM and probenecid may delay the excretion of FAM [redacted].

TOXICOLOGY

Single dose toxicity

The oral LD_{50} of FAM in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. The i.v. LD_{50} of FAM for mice and rats ranged from 254-563 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in intravenously treated dogs were emesis, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse [redacted]

Repeat-dose toxicity

Oral administration of FAM up to 2000 mg/kg/day in rats for a period of 1 year was well tolerated. Dose- and time-dependent eosinophilic cytoplasmic granularity in gastric chief cells was noticed in treatment and control groups.

Intravenous administration of FAM was well tolerated by rats for 13 weeks at dosage levels of up to 20 mg/kg/day.

Intravenous administration of FAM was well tolerated by dogs, except for occasional emesis, at dosage levels of up to 10 mg/kg/day for 5 to 26 weeks [redacted]

Genotoxicity

There was no evidence of a mutagenic effect of FAM in the Ames test, the mouse micronucleus test and the mouse chromosomal aberration test [redacted]

Carcinogenicity

No evidence of a carcinogenic effect was seen in mice and rats [redacted]

Reproductive and developmental toxicity

No effects on fertility rates, general reproductive performance and early embryonic development were observed.

FAM administration did not result in teratogenicity, mortality or other embryo-fetal toxicities [redacted]

FAM did not cross the placenta [redacted]

A transient depression of body weight gain and food intake was observed in dams after initiation of the treatment in case of higher dosages of FAM. No abnormalities were observed in delivery and nursing of pups. Newborns showed a slight depression of body weight gains after birth, but there were no abnormalities in their physical and functional development and reproductive capacities [redacted] FAM was present in rat milk [redacted]

Other toxicity studies

In immunogenicity studies, no effect on the production of IgE antibodies was seen in the sera of mice which were injected, once intraperitoneally, with FAM alone (up to 2 mg/kg) or coupled with either mouse serum albumin or ovalbumin. No evidence of an anaphylactic reaction was seen in guinea pigs challenged intravenously with FAM after initiating doses of up to 10 mg/mL [redacted]

2.4.6. LIST OF LITERATURE REFERENCES

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