PRODUCT MONOGRAPH

ACID REDUCER

(Ranitidine Tablets, USP)

75 mg

Histamine H_2-receptor antagonist

Mylan Pharmaceuticals ULC
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PRODUCT MONOGRAPH

ACID REDUCER

(Ranitidine Tablets, USP)

75 mg

THERAPEUTIC CLASSIFICATION

Histamine H_2-receptor antagonist

ACTION

Ranitidine is an antagonist of histamine at gastric H_2-receptor sites. Thus, ranitidine inhibits both basal gastric secretion and gastric acid secretion induced by histamine, pentagastrin and other secretagogues. Inhibition of gastric acid secretion has been observed following intravenous, intraduodenal and oral administration of ranitidine. This response is dose-related, a maximum response being achieved at an oral dose of 300 mg/day.

Pepsin secretion is also inhibited but secretion of gastric mucus is not affected. Ranitidine does not alter the secretion of bicarbonate or enzymes from the pancreas in response to secretin and pancerozymin.

Ranitidine is rapidly absorbed after oral administration, peak plasma concentrations being achieved within 2 to 3 hours. These plasma concentrations are not significantly influenced by the presence of food in the stomach at the time of the oral administration nor by regular doses of antacids.

Bioavailability of oral ranitidine is approximately 50%. Serum protein binding of ranitidine in man is in the range 10 to 19%. The elimination half-life is approximately 3 hours. The principal route of excretion is the urine (40% recovery of free and metabolized drug in 24 hours).

There is significant linear correlation between the dose administered and the inhibitory effect upon gastric acid secretion for single oral doses up to 300 mg. In healthy subjects a single 75 mg dose of ranitidine significantly reduced meal-stimulated intragastric acidity ([H+] AUC) compared with placebo. The effect of ranitidine on intragastric acidity and pH is also dose-related. A single 75 mg dose has an early onset of action, significantly elevating gastric pH (within one hour), and a long duration of action (up to 9 hours). In a large, multicentre, dose-ranging, placebo-controlled trial in patients with episodic heartburn, a single 75 mg dose relieved symptoms within 30 minutes and provided relief for the duration of the 4 hour evaluation period.

Volunteers treated with an oral dose of ranitidine have reported no significant gastrointestinal or central nervous system side effects; moreover pulse rate, blood pressure, electrocardiogram and electroencephalogram are not significantly affected in man following ranitidine administration.

In healthy human volunteers and patients, ranitidine, when administered orally did not influence plasma levels of the following hormones: cortisol, testosterone, oestrogens, growth hormone, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, aldosterone or gastrin; although like cimetidine, ranitidine reduced vasopressin output. Treatment for up to 6 weeks with ranitidine 150 mg twice daily by mouth did not affect the human hypothalamic pituitary-testicular-ovarian or -adrenal axes.

The safety and efficacy of 75 mg ranitidine for treatment of episodic heartburn were established in two large replicate Phase III studies involving 2,985 patients. These two pivotal studies showed that one ranitidine 75 mg tablet was statistically and clinically superior to placebo in providing relief of episodic heartburn beginning at 30 minutes.

INDICATIONS

ACID REDUCER (ranitidine hydrochloride) Tablets are indicated for fast and effective relief, day or night, of the burning and discomfort of acid indigestion

(dyspepsia), heartburn, hyperacidity, sour stomach, and upset stomach associated with excess stomach acid.

CONTRAINDICATIONS

ACID REDUCER (ranitidine hydrochloride) is contraindicated for patients known to have hypersensitivity to any component of the preparation.

WARNINGS

Gastric Carcinoma

Treatment with a histamine H_2-antagonist may mask symptoms associated with carcinoma of the stomach and, therefore, may delay diagnosis of that condition. Accordingly, patients should be advised to consult a physician if they have difficulty swallowing or persistent abdominal discomfort or if symptoms get worse or persist for more than 2 weeks.

Use in Patient with a History of Acute Porphyria

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Therefore, ranitidine should be avoided in patients with a history of acute porphyria.

Use in Pregnancy and Nursing Mothers

The safety of ACID REDUCER (ranitidine hydrochloride) in the treatment of conditions where a controlled reduction of gastric secretion is required during pregnancy has not been established. Reproduction studies performed in rats and

rabbits at higher doses have revealed no evidence of ranitidine induced impaired fertility or harm to the foetus. Nevertheless, if the administration of ranitidine is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the foetus.

Ranitidine is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated. Women who are breast-feeding are advised to speak with their doctor before taking ACID REDUCER 75 mg Tablets.

PRECAUTIONS

Use in Impaired Renal Function

Ranitidine is excreted via the kidneys and, in the presence of severe renal impairment, plasma levels of ranitidine are increased and elimination prolonged. Accordingly, ACID REDUCER (ranitidine hydrochloride) should be used under physician supervision for these patients.

Interaction with Other Drugs

Although ranitidine has been reported to bind weakly to cytochrome P_{450} *in vitro,* recommended doses of the drug do not inhibit the action of the hepatic cytochrome P_{450}-linked oxygenase enzymes. A review of selected publications of controlled clinical drug interaction studies, at the level of hepatic elimination has indicated ranitidine is unlikely to cause clinically significant potentiation of

actions of drugs which are inactivated by the hepatic Cytochrome P_{450} enzyme system; these drugs may include: diazepam, lignocaine, phenytoin, propranolol, theophylline, and warfarin. Sporadic cases (approximately 1 case per 4 million patient treatments) of drug interactions have been reported in elderly patients involving both hypoglycaemic drugs and theophylline. The significance of these reports cannot be determined at present, as controlled clinical trials have not shown interactions. These reports are based on use for prescription indications and dosage.

Antacids: concurrent administration of antacid of medium to high potency (75 mEq) with ranitidine is not recommended. The absorption of ranitidine may be decreased. Patients should be cautioned not to take antacids within l/2 -1 hour of ranitidine ingestion.

Ketoconazole: simultaneous administration of ketoconazole and ranitidine may result in reduction of the absorption of ketoconazole by some mechanism as yet unidentified (e.g. a pH dependent effect on absorption or a change of volume of distribution). Patients should be cautioned not to take ranitidine for at least 2 hours after ketoconazole. These reports are based on use of prescription indications and dosage.

Sucralfate: if high doses of sucralfate (two grams) are co-administered with Acid Reducer, the absorption of Acid Reducer may be reduced. This effect is not seen

if sucralfate is taken at least two hours after Acid Reducer administration. These reports are based on use of prescription indications and dosage.

Procainamide: some evidence of interactions with ranitidine at the level of renal elimination have been reported, but the clinical importance is unknown/questionable. These reports are based on use for prescription indications and dosage.

Ethanol: The co-administration of a single oral dose of ranitidine 75 mg and ethanol 0.15 g/Kg has no clinically relevant effect on ethanol pharmacokinetics as shown in a double-blind placebo-controlled, crossover study in 25 healthy subjects.

Use in the Elderly

Since malignancy is more common in the elderly, particular consideration must be given to this before therapy with Acid Reducer is instituted. Elderly patients receiving non-steroidal anti-inflammatory drugs concomitantly with Acid Reducer 75 mg should be closely supervised. As with all medication, in the elderly, consideration should be given to concurrent drug therapy.

ADVERSE REACTIONS

In clinical trials with Ranitidine the most frequently reported adverse events included: headache (4%), nausea and vomiting (3%), and diarrhea (2%). There

was no statistical difference in reported events between Ranitidine and placebo treated groups.

The following adverse reactions have been reported as events in clinical trials, in post-marketing surveillance, or in the routine management of patients treated with prescription doses of Ranitidine. The majority of these events have been observed following oral administration of higher prescription doses of ranitidine, and a cause and effect relationship to Ranitidine has not always been established.

Central Nervous System: headache, sometimes severe; malaise; dizziness; somnolence; insomnia; vertigo; and reversible blurred vision suggestive of a change in accommodation. Isolated cases of reversible mental confusion, agitation, depression, hallucinations have been reported, predominantly in severely ill elderly patients.

Cardiovascular: As with other H_2 receptor antagonists, there have been rare reports of tachycardia, premature ventricular beats, bradycardia, and atrioventricular block.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting and abdominal discomfort/pain.

Hepatic: Transient and reversible changes in liver function tests can occur (increase in SGPT and SGOT values). With oral administration, there have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed with or without jaundice. In such circumstances, ranitidine should be discontinued immediately. These are usually reversible, but in exceedingly rare circumstances, death has occurred.

Musculoskeletal: Rare reports of arthralgia and myalgia.

Haematologic: Blood count changes (leukopenia, thrombocytopenia) have occurred in a few patients. These are usually reversible. Rare cases of agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or aplasia have been reported.

Endocrine: No clinically significant interference with endocrine or gonadal function has been reported. There have been a few reports of breast symptoms in men taking ranitidine.

Dermatologic: Rash, including cases suggestive of mild erythema multiform.

Other: Rare cases of hypersensitivity reactions (including chest pain, bronchospasm, fever, rash, eosinophilia, anaphylaxis, urticaria, angioneurotic

edema, hypotension) and small increases in serum creatinine have occasionally occurred after a single dose. Acute pancreatitis has been reported rarely.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed drug from the gastrointestinal tract (including activated charcoal or syrup of ipecac), clinical monitoring and supportive therapy should be employed. Also, if need be, the drug can be removed from the plasma by haemodialysis. Up to 6 g per day has been administered without untoward effect.

DOSAGE AND ADMINISTRATION

ADULTS AND CHILDREN 16 YEARS OF AGE AND OLDER:

One ACID REDUCER 75 mg tablet should be taken when symptoms appear, day or night. If symptoms persist for more than 1 hour or return after 1 hour, a second tablet may be taken. The maximum dosage is 2 tablets in a 24-hour period. Patients are advised to consult their physician if symptoms get worse or continue after 14 days of treatment.

CHILDREN UNDER 16 YEARS

Children under 16 years of age should be supervised by a physician.

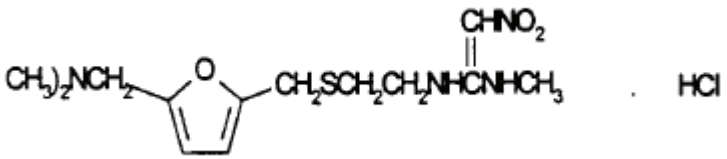
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper name: ranitidine hydrochloride

Chemical name: 1,2-Ethenediamine, N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-,monohydrochloride.

Structural formula:



Empirical formula: $C_{13}H_{22}N_4O_3S.HCl$

Molecular weight: 350.87 (as hydrochloride salt)

Description: Ranitidine hydrochloride is a white to pale yellow, crystalline, practically odourless powder. It is very soluble in water, moderately soluble in alcohol and sparingly soluble in chloroform. It melts at about 140°C, with decomposition. Ranitidine hydrochloride is sensitive to light and moisture.

Composition: Each Acid Reducer 75 mg tablet contains ranitidine hydrochloride 84 mg. Non-medicinal ingredients include: microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polydextrose, triethyl citrate, polyethylene glycol, FD & C yellow No. 6 aluminum lake, and synthetic yellow iron oxide.

Stability and Storage: Acid Reducer tablets should be stored in a dry place between 15°C and 30°C and protected from light.

AVAILABILITY

ACID REDUCER 75 mg Tablets are peach, round, biconvex, film-coated tablets with "G" on one side and “75” on the other side. Available in blister packs of 12’s, 24’s, and 30’s.

INFORMATION FOR THE CONSUMER

ACID REDUCER

(Ranitidine Tablets USP 75 mg)

What is ACID REDUCER?

ACID REDUCER is a new product which contains the nonprescription strength of ranitidine, the world's #1 selling acid reducer, prescribed by doctors more than 200 million times world-wide.

ACID REDUCER relieves and treats the burning and discomfort of heartburn, acid indigestion, upset and sour stomach, providing fast and effective relief. Acid Reducer reduces and controls stomach acid for up to 9 hours, day or night. ACID REDUCER works by reducing the production of excess stomach acid, which causes the burning and discomfort of heartburn and acid indigestion. This is what makes Acid Reducer different from antacids which only neutralise the acid in your stomach. Antacids do not reduce the production of excess stomach acid.

What symptoms does ACID REDUCER relieve and treat?

Acid Reducer provides fast relief and treatment, day or night, of the following symptoms:

- Heartburn
- Acid Indigestion

- Upset or Sour stomach

Should you take ACID REDUCER?

Please consult your doctor or pharmacist before taking ACID REDUCER:

* if you are allergic to ranitidine or any of the ingredients in Acid Reducer tablets,
* if you have a stomach or duodenal ulcer,
* if you have difficulty swallowing or persistent abdominal discomfort,
* if you are taking non-steroidal anti-inflammatory drugs (NSAIDs), because these medicines may be causing your symptoms,
* if you are pregnant, or breast-feeding,
* if you have kidney problems,
* if you suffer from porphyria (a rare blood disorder),
* if you experience unintended weight loss associated with acid indigestion,
* if you are over 40 years of age and are experiencing new or recently changed symptoms of heartburn or acid indigestion,
* if you have any other illness, and are taking any prescription medicines, seeing a doctor regularly,
* if you are under 16 years of age.

How should you take ACID REDUCER tablets?

Adults and children 16 years and older: take one tablet as needed. If symptoms return, take another tablet. Do not take more than 2 tablets during a 24-hour

period. If symptoms persist for more than 2 consecutive weeks consult your doctor. Acid Reducer and prescription doses of antacids should be taken one hour apart.

What can you do to help avoid symptoms?

* do not lie down soon after eating,
* if you are overweight, lose weight,
* if you smoke, stop or cut down,
* avoid or limit foods such as: caffeine (coffee, tea, or cola drinks), chocolate, spicy or fatty fried foods and alcohol.

How should you keep ACID REDUCER?

Keep in a safe place out of the reach of children.

Store at room temperature (15°C to 30°C).

What ingredients are in ACID REDUCER?

Each tablet contains 75 mg ranitidine, as ranitidine hydrochloride.

Nonmedicinal ingredients: microcrystalline cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polydextrose, triethyl citrate, polyethylene glycol, FD & C yellow No. 6 aluminum lake, and synthetic yellow iron oxide.

Acid Reducer 75 mg is sodium- and sugar-free.

Availability: Packages of 12, 24, and 30 tablets (12, 24, and 30 doses).

Questions?

Speak to your pharmacist, doctor or call if have any questions about ACID REDUCER: 1-800-575-1379.

Mylan Pharmaceuticals ULC, 85 Advance Road, Etobicoke, Ontario, M8Z 2S6.

PHARMACOLOGY

Animal Pharmacology

Ranitidine is a potent competitive reversible, selective antagonist of histamine at H_2-receptors in vitro and in vivo. Thus, ranitidine antagonised the actions of histamine at H_2-receptors in the rat-isolated uterus and in the guinea-pig isolated atrium. Ranitidine is not an anticholinergic agent. On a molar basis, ranitidine is 4 to 5 times more active than cimetidine with a pA_2 value of 7.2. In concentrations 1,000 times greater than those required to block H_2-receptors, it failed to block either H_1-receptors or muscarinic receptors in the guinea-pig isolated ileum. The beta-adrenoceptor responses of the rat uterus and guinea pig atrium to isoprenaline were also unaffected by ranitidine.

Blockade of histamine H_2-receptors in the stomach in vivo is the pharmacological action of ranitidine with greatest immediate clinical relevance. Ranitidine inhibits gastric secretion induced by various secretagogues in both the rat and dog.

In the conscious dog with a Heidenhain pouch, ranitidine given orally or intravenously antagonised gastric acid secretion induced by histamine, pentagastrin and bethanechol. Ranitidine was 5 to 10 times more active than cimetidine. However, both ranitidine and cimetidine had similar time curves of action. Ranitidine also inhibited the gastric secretory response to food in the conscious fistulated dog.

Ranitidine inhibited acid secretion in the perfused stomach of the anaesthetised rat, and aspirin induced gastric lesion formation in the conscious rat, both in the presence and absence of excess hydrochloric acid. Measurements of the ratio of mucosal blood flow to acid secretion show that the inhibitory action of ranitidine upon gastric acid secretion cannot be attributed to changes in blood flow.

There were no behavioural effects in the mouse and rat after oral administration of 800 mg/kg ranitidine. Cats and dogs dosed with ranitidine 80 mg/kg orally, exhibited no behavioural effects indicative of an action on the central nervous system, although at this high dose level in the dog there was an indication of peripheral vasodilation and skin irritation due to released histamine. Ranitidine, when coadministered with the following CNS modulating preparations; codeine, hexobarbitone, ethyl alcohol, chlordiazepoxide, chlorpromazine, imipramine, -methyldopa, reserpine, apomorphine or pentylenetetrazol, did not alter the pharmacological effects of either preparation.

At a dose level 45 times the antisecretory ED_{50}, intravenous infusion of ranitidine had no effect on the heart rate, blood pressure or electrocardiogram of the anaesthetised dog. The respiratory system was unaffected by ranitidine after oral doses in the mouse, rat, rabbit, cat and dog and after intravenous doses in the dog.

In the conscious dog, ranitidine had no appreciable effect on blood pressure or heart rate when administered orally at 10 mg/kg. There were short-lived falls in diastolic blood pressure after an intravenous dose of 10 mg/kg, 370 times the antisecretory dose level. There was no evidence of arrhythmia nor of any electrocardiographic abnormality.

Long-term toxicity studies have shown that ranitidine does not possess antiandrogenic activity nor does it displace dihydrotestosterone from the androgen binding sites.

Metoclopramide, atropine and aspirin in the rat produced no change in the antisecretory activity of ranitidine.

The effect of ranitidine on anti-inflammatory drugs was varied. There was no effect on the anti inflammatory action of prednisolone, but the anti-inflammatory action of indomethacin was enhanced. Administration of ranitidine reduced the frequency of aspirin- and indomethacin induced gastric erosions. The antinociceptive action of aspirin was reduced after ranitidine treatment.

Ranitidine, unlike cimetidine, does not inhibit the hepatic mixed function oxygenase system. Spectral interaction studies have shown that whilst cimetidine binds strongly to cytochrome P_{450}, ranitidine has only weak affinity for this enzyme. Cimetidine is known to impair the metabolism of pentobarbitone and warfarin. In doses of up to 166 mg/kg in the rat, ranitidine had no effect on the pentobarbitone sleeping time or the pharmacokinetics and pharmacodynamics of warfarin.

Metabolism, Distribution and Excretion

The metabolism of ranitidine hydrochloride has been studied in four species of laboratory animal (mouse, rat, rabbit and dog) using radio-labelled drug. The drug was rapidly absorbed after oral administration. In the mouse, rat and rabbit between 30% and 60% of the administered radioactivity was excreted in the urine, the remainder being recovered in the faeces.

In the mouse 47% was excreted in the urine within 24 hours. In the rat, N-demethylation of ranitidine was the major route of metabolism. 30% of the administered dose was excreted in the urine as unchanged drug, up to 14% as desmethylranitidine, 3-6% as the N-oxide and 4% as the S oxide. In rat bile the major radioactive components were ranitidine and an unidentified metabolite known as "Fast-Running Metabolite" (FRM) which is thought to be a charge transfer complex of ranitidine with bile pigments.

In the rabbit, sulphoxidation of ranitidine was the major route of metabolism, 18% of the administered dose being excreted in the urine as unmetabolised ranitidine, 8% as S-oxide, 2-4% as the N-oxide, and 2-4% as desmethylranitidine.

In the dog up to 70% of the administered dose was excreted in the first 24 hours. About 40% of the drug was excreted in the urine as unchanged ranitidine and up to 30% as the N-oxide, N-oxidation being the main route of metabolism of ranitidine in the dog. The N-oxide was also the major radioactive component present in dog bile together with small amounts of unchanged ranitidine and FRM.

In the rat, rabbit and dog, less than 10.1% of ranitidine in plasma is protein bound. Within one to seven days of administration of radio-labelled drug in the rat and dog over 99% of the radioactivity was cleared from the body. In common with many drugs, radioactivity persisted in the uveal tract of these two species, the half-life in the dog uveal tract being of the order of 6 months. Ranitidine and its S-oxide have greater affinity for melanin than the desmethyl metabolite; the N-oxide is bound only to a small extent.

The placental transfer of radioactive ranitidine and its metabolites has been studied in the pregnant rat and rabbit. Whole body autoradiography of rat and rabbit foetuses showed that small amounts of radioactivity were present in the

uveal tract of the foetal eye in both species, in the gall bladder and intestine of the rabbit foetus and in the bladder of the rat foetus. Radioactivity was also detected in the salivary and mammary glands of the maternal rat and at very low concentration, in the milk.

Human Pharmacokinetics

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range for up to 12 hours. There is a relationship between plasma concentrations of ranitidine and suppression of gastric acid production but wide interindividual variability exists.

Lower than prescription doses of ranitidine significantly reduce meal-stimulated intragastric acidity in human subjects. The effect is dose-related and acidity declines linearly with increasing doses of ranitidine.

Ranitidine is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring two to three hours after a 150 mg dose. The elimination half-life is 1.5 to 3 hours.

The pharmacokinetics of lower doses of ranitidine have also been studied. Peak plasma concentrations and AUC showed a linear relationship over the dose range 20-80 mg; T_{max}, $t_{1/2}$ and clearance were independent of dose.

Ranitidine is absorbed very rapidly after an intramuscular injection. Mean peak levels of 576 ng/mL occur within 15 minutes or less following a 50 mg intramuscular dose. Absorption from intramuscular sites is virtually complete, with a bioavailability of 90% to 100% compared with intravenous administration.

The principal route of excretion is the urine, with approximately 30% of the orally-administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 530 mL/min, indicating active tubular excretion, with a total clearance of 760 mL/min. The volume of distribution is 1.4 L/kg. Serum protein binding averages 15%.

Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant alterations in ranitidine half-life, distribution, clearance and bioavailability.

The gastric antisecretory activity of ranitidine metabolites has been examined. In man, both the principal metabolite in the urine, the N-oxide (4% of the dose) and the S-oxide (1%) possess weak H_2-receptor blocking activity but desmethylranitidine (1%) is only 4 times less potent than ranitidine in the rat and half as potent as ranitidine in the dog.

TOXICOLOGY

Toxicology, Impairment of Fertility, Carcinogenesis and Mutagenesis

Ranitidine hydrochloride has been subjected to exhaustive toxicological testing which has demonstrated the lack of any specific target organ or any special risk associated with its clinical use.

Acute Toxicity Studies

In mice and rats, the intravenous LD_{50} is of the order of 75 mg/kg, whereas orally, even doses of 1000 mg/kg are not lethal. In dogs, the oral minimum lethal dose is 450 mg/kg/day. High single doses of ranitidine (up to 80 mg/kg orally) show only minimal and reversible signs of toxicity, some of which are related to transitory histamine releases.

Long-Term Toxicity Studies

In the long-term toxicity and carcinogenicity studies, very high doses of ranitidine were given daily to mice (up to 2000 mg/kg/day) throughout their normal life-span, and to dogs (up to 450 mg/kg/day) for periods of up to one year.

These doses produced massive plasma ranitidine concentrations far in excess of those found in human patients receiving ranitidine at the recommended therapeutic dose. For example, in the dogs, peak plasma concentrations were in excess of 115 μg/mL and in mice basal plasma levels were in the range of 4-9 μg/mL. In man, after oral administration of 150 mg ranitidine, the mean peak

plasma concentration (C_{max}) was between 360 and 650 ng/mL. In the rat, doses as high as 2000 mg/kg/day were well tolerated, the only morphological change seen was the increased incidence of accumulations of foamy alveolar macrophages in the lungs. The accumulations of these cells is a natural phenomena in aging rats and chronic administration of a wide variety of drugs has been known to contribute to this process. Therefore, it is unlikely that the pharmacologic concentrations of ranitidine administered to these rats contributed to this natural process.

In the six-week and six-month oral studies in the dog (100 mg/kg/day) loose faeces were occasionally detected, while in the six-month study loose stools were accompanied on eight occasions by mucus-like material and sometimes by blood, mostly from one dog. Loose faeces, salivation and vomiting were observed in the 54-week dog study.

In isolated cases, dogs passed red-stained faeces which occasionally tested positive for occult blood. When the dose level was increased from 100 mg/kg/day to 225 - 450 mg/kg/day, no further red-stained faeces were seen, suggesting that any relationship to ranitidine is unlikely. Post mortem examination of the dogs revealed no ranitidine-induced changes in the alimentary tract.

One dog had marginally raised levels of plasma alanine aminotransferase and alkaline phosphatase during the six-week study. This same dog also showed

some necrotic foci in the liver. Small lesions of focal necrosis and fibrosis were also seen in one piece of liver from one female dog treated with 100 mg/kg for six months. No other differences were detected by light and electron microscopic examination of the treated and control livers. Since the focal lesions were seen in only one dog and were restricted to one piece of liver, it suggests that they were not caused by ranitidine.

Muscular tremors, an inability to stand, and rapid respiration were seen on occasion in dogs treated with 225 mg/kg/day in the 54-week study. The prevalence of these observations was increased when the dose was increased to a toxic level of 450 mg/kg/day. One dog died: no specific pathological changes or reason for the death was discovered.

Changes in the colour or granularity of the tapetum lucidum of the eye were detected in three dogs receiving the highest dose of ranitidine (450 mg/kg/day) during the 54-week study. In one dog this change was considered to be related to treatment. The change, a pallor of the tapetum, was reversible. No changes were seen with light or electron microscopic examination of the eye. The changes in the tapetum are of no clinical significance in humans since (i) humans do not have a tapetum lucidum and (ii) the changes were only seen at toxic pharmacological concentrations of ranitidine.

The mean serum glutamic pyruvic transaminase values for dogs treated at 450 mg/kg/day were significantly greater, albeit marginally, than the control values. These enzyme increases were not accompanied by any histological changes.

Studies in which ranitidine was administered parenterally were performed. No sign of specific local irritation attributable to ranitidine was detected. In the rat, no biochemical or histopathological changes were observed at intravenous dose levels as high as 20 mg/kg. Specifically, no significant changes were found in the veins or subcutis. Mild lesions in some muscle samples were observed: usually, the cells were basophilic and smaller than normal; and the nuclei were swollen, more numerous, and sometimes had migrated to the centre of the cell.

In the rabbit, slight infiltration of the pannicular muscle by mononuclear cells were noted. This minor subcutaneous reaction was uncommon and showed no group related distribution. There was no apparent difference in irritancy between ranitidine injection and placebo injection. In the rat, intravenous ranitidine at dose levels of 5.0 and 10.0 mg/kg daily for 15 days and 28 days produced no treatment related changes of biological importance in the haematopoietic system.

In Beagle dogs, intravenous ranitidine injection in doses up to 10 mg/kg/day for 28 and 42 days, produced no drug-related change in circulating erythrocytes or leukocytes and had no adverse effects on the haematopoietic system. No dose related changes were seen in electrocardiograms of Beagle dogs receiving up to

10 mg/kg ranitidine by intravenous injection. At dosage levels of up to 30 mg/kg, administered twice daily to Beagle dogs for 14 or 15 days, intravenous ranitidine injection produced no changes of biological significance in haematology, clinical chemistry or urinalysis.

No changes were observed in the eyes of dogs (specifically the tapetum lucidum) receiving ranitidine in doses up to 30 mg/kg twice daily for 15 days. At intravenous doses above 1.25 mg/kg, ranitidine injection produced immediate and transient reactions in the Beagle dog. The following reactions were typically produced by the administration of 1.25 mg/kg: bloodshot eyes, closing and watering of eyes, defaecation, diarrhoea, erythema, flatus, licking of lips, running nose, salivation, subdued behaviour, swallowing, tachycardia, and trembling. The range and severity of the effects was aggravated by increased dosage.

Reproduction Studies (Impairment of Fertility)

Reproduction studies were carried out in the rat and rabbit. Rats were exposed to ranitidine before and during mating, throughout pregnancy, lactation and during the weaning period. No effects on the reproductive process were seen and there was no evidence of an anti-androgenic effect.

A total of 2,297 foetuses from rats treated with ranitidine were examined. There was no evidence that ranitidine is a rat teratogen. Cleft palates occurred in

foetuses from both treatment groups, however, there were significantly more in the control rat population.

A total of 944 foetuses from rabbits treated with ranitidine were examined; no drug-related adverse events or abnormalities in the foetuses were observed.

Rabbits receiving a bolus intravenous injection of ranitidine (10 mg/kg) once daily on gestation days 7-16 exhibited a reduction in weight gain. Their foetuses weighed significantly less than foetuses of untreated controls. In addition, 12.4% of ranitidine exposed foetuses had cleft palates. Reanalysis of this and a companion study performed to assess reproducibility demonstrated a lack of data reproducibility. Therefore, the effects observed in the first trial are aberrant, and should not form the basis for maternal or foetal toxicity.

In the subsequent study, no evidence of maternal or foetal toxicity was observed in rabbits dosed with 100mg/kg ranitidine orally during days 2-29 of pregnancy. The peak plasma levels of ranitidine after a 100 mg/kg oral dose are similar to those obtained one minute after a 10 mg/kg dose administered intravenously (20-25 µg/mL). Therefore, no teratogenic effects of ranitidine have been demonstrated at doses of 10 mg/kg (IV) and 100 mg/kg (Tablets) in rabbits.

Carcinogenicity Studies

There is no evidence that ranitidine is a carcinogen. Long-term toxicity and carcinogenicity studies have involved the treatment of 600 mice and 636 rats at doses up to 2,000 mg/kg for two years and 129 weeks respectively and 42 dogs at doses up to 450 mg/kg/day for periods up to one year. These dose levels are far in excess of those to be used therapeutically in man. None of these animals had any intestinal metaplasia. There was no evidence of a tumorigenic effect of ranitidine in any other tissue.

Mutagenesis

Ranitidine is not mutagenic at doses as great as 30 mg/plate in the Ames Assay utilizing Salmonella typhimurium (TA 1538, TA 98, TA 100 and TA 1537) or in doses of 9 mg/plate utilizing Escherichia Coli (WP2 and WP2 uvrA) with or without activation.

Ranitidine at concentrations of 20-30 mg/plate had a weak direct mutagenic action in S.typhimurium TA 1535 and at 9 mg/plate in E.Coli WP67. Ranitidine was not mutagenic at a concentration of 2 mg/mL in E.Coli or S.typhimurium in the more sensitive Oral Solution microtitre fluctuation assay method. This weak direct mutagenic effect is of no clinical significance; the magnitudes of ranitidine concentration used in these assays are thousands of times greater than that attained therapeutically in human plasma.

The principal metabolites of ranitidine in man were not significantly mutagenic. This conclusion is supported by the following experiment. A test solution obtained by interacting ranitidine (10mM) and sodium nitrite (40mM) was mutagenic in S. Typhimurium (TA 1535) but not in S. Typhimurium (TA 1537) or in E. Coli (WP67 or WP2 uvrA). This positive result is attributable to the presence of a nitrosonitrolic acid derivative AH 23729, which was mutagenic. When the sodium nitrite concentration was reduced to 15mM or less, the solution was not mutagenic in any of the test microorganisms. The formation of AH23729 requires concentrations of nitrous acid far in excess of those encountered in any probable physiological conditions. The other nitrosation products were not mutagenic in any of the microorganisms tested. There is no reason, therefore, for supposing that ranitidine is likely to be mutagenic in animals or man as a consequence of nitrosation in the stomach.

There is no evidence from long-term toxicology, carcinogenicity and mutagenicity studies in animals to suggest that ranitidine is likely to have any deleterious effects in man when administered at therapeutic dose levels.

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