PRODUCT MONOGRAPH

[Pr]APO-RANITIDINE

Ranitidine Oral Solution USP
(ranitidine as ranitidine hydrochloride)

15 mg/mL

Histamine H_2- Receptor Antagonist

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Ranitidine Oral Solution USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Non-medicinal Ingredients
Oral	Solution 15mg/mL	None *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

APO-RANITIDINE (ranitidine hydrochloride) oral solution is indicated for the treatment of duodenal ulcer, benign gastric ulcer, reflux esophagitis, post-operative peptic ulcer, Zollinger-Ellison Syndrome, and other conditions where reduction of gastric secretion and acid output is desirable. These include the following:

- the treatment of nonsteroidal anti-inflammatory drug (NSAID) induced lesions, both ulcers and erosions, and their gastrointestinal (GI) symptoms and the prevention of their recurrence;
- the prophylaxis of GI hemorrhage from stress ulceration in seriously ill patients;
- the prophylaxis of recurrent hemorrhage from bleeding ulcers;
- the prevention of Acid Aspiration Syndrome from general anesthesia in patients considered to be at risk for this, including obstetrical patients in labour, and obese patients.

In addition, APO-RANITIDINE is indicated for the prophylaxis and maintenance treatment of duodenal or benign gastric ulcer in patients with a history of recurrent ulceration.

CONTRAINDICATIONS

APO-RANITIDINE (ranitidine hydrochloride) is contraindicated for patients known to have hypersensitivity to ranitidine or to any ingredient in the formulation. For a complete listing, see composition.

WARNINGS AND PRECAUTIONS

Gastric Ulcer

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, where gastric ulcer is suspected the possibility of malignancy should be excluded before therapy with ranitidine hydrochloride is instituted.

Concomitant NSAID Use

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with APO-RANITIDINE is recommended especially in the elderly and in those with a history of peptic ulcer. Baseline endoscopy and histological evaluation is necessary to rule out gastric carcinoma.

Use in Patients 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.

Renal

Ranitidine hydrochloride is excreted via the kidneys and, in the presence of severe renal impairment, plasma levels of ranitidine hydrochloride are increased and elimination prolonged. Accordingly, it is recommended in such patients, to decrease the dosage of ranitidine hydrochloride by one half. Accumulation of ranitidine hydrochloride with resulting elevated plasma concentrations will occur in patients with severe renal impairment (creatinine clearance less than 50 ml/min); a recommended daily dose of oral ranitidine in such patients should be 150 mg.

Special Populations

Pregnant Women: The safety of 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 have revealed no evidence of ranitidine hydrochloride induced impaired fertility or harm to the fetus. Ranitidine crosses the placenta. Nevertheless, if the administration of APO-RANITIDINE is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the fetus.

Nursing Women: Ranitidine hydrochloride is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated. Like other drugs, APO-RANITIDINE should only be used during nursing if considered essential.

Pediatrics (< 18 years of age): Experience with ranitidine hydrochloride products in children is limited. It has, however, been used successfully in children aged 8 to 18 years in oral doses up to 150 mg twice daily.

ADVERSE REACTIONS

The following adverse reactions have been reported as events in clinical trials or in the routine management of patients treated with ranitidine hydrochloride. A cause and effect relationship to ranitidine hydrochloride is not always 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, and hallucinations have been reported, predominantly in severely ill elderly patients. In addition, reversible involuntary movement disorders have been reported rarely.

Cardiovascular
Isolated reports of tachycardia, bradycardia, premature ventricular beats, AV block have been noted. Asystole has been reported in very few individuals with and without predisposing conditions following IV administration and has not been reported following oral administration of ranitidine hydrochloride (See **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

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

Renal
Very rare cases of acute interstitial nephritis have been reported.

Hepatic
In normal volunteers, transient and reversible SGPT and SGOT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving ranitidine 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. Therefore, it may be prudent to monitor SGOT and SGPT in patients receiving intravenous treatment for five days or longer and in those with pre-existing liver diseases. 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 and breast conditions (such as gynecomastia and galactorrhea).

Dermatologic
Rash, including cases suggestive of mild erythema multiforme. Rare cases of vasculitis and alopecia have been reported.

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 and reversible impotence has been reported rarely.

DRUG INTERACTIONS

Drug-Drug Interactions

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

Interactions occur by several mechanisms including:

1. Inhibition of cytochrome P450-linked mixed function oxygenase system:
   Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propranolol and theophylline.

   There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.

2. Competition for renal tubular secretion:
   Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other drugs eliminated by this route. High doses of ranitidine (e.g such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs.

3. Alteration of gastric pH:
   The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitnib).

   Sporadic cases 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 with theophylline and APO-RANITIDINE have not shown interaction.

If high doses (two grams) of sucralfate are coadministered with APO-RANITIDINE, the absorption of APO-RANITIDINE may be reduced. This effect is not seen if sucralfate is taken at least two hours after APO-RANITIDINE administration.

Special Populations

In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia. A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H_2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07 to 2.48).

Use in the Elderly

Since malignancy is more common in the elderly, particular consideration must be given to this before therapy with APO-RANITIDINE is instituted. Elderly patients receiving non-steroidal anti-inflammatory drugs concomitantly with APO-RANITIDINE should be closely supervised.

As with all medication in the elderly, when prescribing APO-RANITIDINE, consideration should be given to the patient's concurrent drug therapy. Sporadic cases of drug interaction 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 with theophylline and APO-RANITIDINE have not shown interaction. Elderly patients may be at increased risk for confusional states and depression.

DOSAGE AND ADMINISTRATION

Dosing Considerations

A 150 mg dose of ranitidine is equivalent to 10 mL (2 teaspoonfuls) of APO-RANITIDINE (ranitidine hydrochloride) Oral Solution, and 300 mg ranitidine is equivalent to 20 mL (4 teaspoonfuls) of APO-RANITIDINE Oral Solution.

Recommended Dose and Dosage Adjustment

Duodenal ulcer or benign gastric ulcer

300 mg once daily at bedtime or 150 mg twice daily taken in the morning and before retiring. It is not necessary to time the dose in relation to meals. In most cases of duodenal ulcer and benign gastric ulcer, healing will occur in four weeks. In the small number of patients whose ulcers may not have fully healed, these are likely to respond to a further four week course of therapy. In the treatment of duodenal ulcers, 300 mg twice daily for 4 weeks may be of benefit when more rapid healing is desired.

Maintenance therapy

Duodenal ulcers, benign gastric ulcers: Patients who have responded to short-term therapy, particularly those with a history of recurrent ulcer, may benefit from chronic maintenance therapy at a reduced oral dosage of 150 mg once daily at bedtime.

In the management of duodenal ulcers, smoking is associated with a higher rate of ulcer relapse (up to 9.2 times higher in one trial), and such patients should be advised to stop smoking. In those patients who fail to comply with such advice, 300 mg nightly provides additional therapeutic benefit over the 150 mg once daily dosage regimen.

Reflux Esophagitis

Acute treatment

300 mg once daily at bedtime, or alternatively 150 mg twice daily, taken in the morning and before retiring for up to eight weeks. In patients with moderate to severe esophagitis, the dosage of ranitidine may be increased to 150 mg four times daily for up to 12 weeks.

Long-term Management

For the long-term management of reflux esophagitis, the recommended adult oral dose is 150 mg twice daily.

Post-operative peptic ulcer

150 mg twice daily taken in the morning and before retiring.

Pathological hypersecretory conditions (Zollinger-Ellison Syndrome)

150 mg three times daily may be administered initially. In some patients, it may be necessary to administer APO-RANITIDINE 150 mg doses more frequently. Doses should be adjusted to individual patient needs. Doses up to six grams per day have been well tolerated.

Treatment of NSAID-induced lesions (both ulcers and erosions) and their gastrointestinal symptoms and prevention of their recurrence

In ulcers following non-steroidal anti-inflammatory drug therapy or associated with continued non-steroidal anti-inflammatory drugs, 150 mg twice daily for 8-12 weeks may be necessary. For the prevention of non-steroidal anti-inflammatory drug associated ulcer recurrence, 150 mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

Prophylaxis of acid aspiration syndrome (AAS)

150 mg the evening prior to anaesthesia induction is recommended, however, 150 mg two hours before anaesthesia induction is also effective. For the prevention of AAS in pre-partum patients who elect for anaesthesia, 150 mg every six hours may be employed, but if general anaesthesia is warranted, a non-particulate oral antacid (for example, sodium citrate) could supplement APO-RANITIDINE therapy. In an emergency situation, the use of alkalis, antacids, and meticulous anaesthetic technique is still necessary as APO-RANITIDINE does not affect the pH and volume of the existing gastric content.

Prophylaxis of haemorrhage from stress ulceration in seriously ill patients or prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration who are currently managed by intravenous ranitidine hydrochloride.

An oral dose of 150 mg twice daily may be substituted for the injection once oral feeding commences.

If necessary, APO-RANITIDINE oral solution may be administered by orogastric or nasogastric tube as an alternative.

Dosage for the Elderly
For all conditions listed above, the drug dosage for the elderly who are seriously ill should start at the lowest recommended dose and be adjusted as necessary with close supervision.

Patients over 50 years of age (see **ACTIONS AND CLINICAL PHARMACOLOGY, Patients over 50 years of age**).

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of 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. On a weight basis ranitidine is between 4 and 9 times more potent than cimetidine. 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 pancreozymin.

Pharmacodynamics
Ranitidine is rapidly absorbed after oral administration of 150 mg ranitidine, peak plasma concentrations (300 to 550 ng/mL) occurred after 1 to 3 hours. Two distinct peaks or a plateau in the absorption phase result from reabsorption of drug excreted into the intestine. 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% to 60 %. Serum protein binding of ranitidine in man is in the range of 10 to 19%. The elimination half-life is approximately 2 to 3 hours. The principal route of excretion is the urine (40% recovery of free and metabolized drug in 24 hours).

There is a significant linear correlation between the dose administered and the inhibitory effect upon gastric acid secretion for oral doses up to 300 mg. A plasma ranitidine concentration of 50 ng/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%. Estimates of the IC_{50}

range from 36 to 94 ng/mL. Following the administration of 150 mg ranitidine orally, plasma concentrations in excess of this lasted for more than 8 hours and after 12 hours, the plasma concentrations were sufficiently high to have a significant inhibitory effect upon gastric secretion. In patients with duodenal ulcer, 150 mg oral ranitidine every 12 hours significantly reduced mean 24-hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90%. Furthermore, 300 mg oral ranitidine at night is as effective in reducing 24-hour intragastric acidity as 150 mg ranitidine given orally twice daily.

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.

Absorption

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 2 to 3 hours.

Distribution

Serum protein binding averages 15%.

Metabolism

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.

Excretion

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 ranges from 96 to 142 L.

Special Populations and Conditions

Hepatic Insufficiency: 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.

Patients over 50 years of age

In patients over 50 years of age, half-life is prolonged (3 to 4 hours) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

STORAGE AND STABILITY

Store between 15°C and 30°C. Protect from light. Keep out of reach of children.

DOSAGE FORM, COMPOSITION AND PACKAGING

Packaging

APO-RANITIDINE (ranitidine hydrochloride) 15 mg/mL oral solution (300 mL) is supplied in an amber PET bottle (350 mL) with a white plastic polypropylene cap.

Composition

APO-RANITIDINE is a clear peppermint flavoured oral solution containing 168 mg ranitidine hydrochloride in 10 mL (150 mg ranitidine anhydrous freebase/10 mL oral solution). The inactive ingredients for this solution are: butylparaben, hypromellose, peppermint oil, potassium phosphate, propylparaben, purified water, saccharin sodium, sodium chloride, sodium phosphate dibasic, and sorbitol solution.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

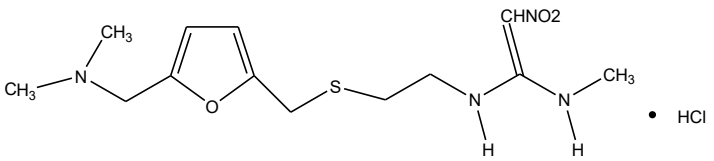
Proper Name: ranitidine hydrochloride

Chemical Names:

1) 1,1-Ethenediamine, *N*-[2-[[[5-(dimethylamino) methyl]-2-furanyl]-methyl] thio]ethyl]-*N*-methyl-2-nitro-, monohydrochloride
2) *N*-[2-[[[5-[(Dimethylamino) methyl]-2-furanyl]methyl]thio]-ethyl]-*N*-methyl-2-nitro-1,1-ethenediamine, hydrochloride
3) *N*-[2-[[[5-[(Dimethylamino) methyl]-furan-2-yl]methyl]-sulphanyl]ethyl]-*N'*-methyl-2-nitroethene-1,1-diamine, hydrochloride
4) 2-[[[5-(Dimethylamino)-methyl-2-furanyl]-methyl]thio]-ethylamino-2-methylamino-1-nitroethene

Molecular Formula and mass: $C_{13}H_{22}N_4O_3S \cdot HCl$
350.87 g/mol(as hydrochloride salt)

Structural Formula:



Physical Description: White to almost white, microcrystalline powder.

Solubility: Freely soluble in water and in methanol. Sparingly soluble in ethanol. Very slightly soluble in methylene chloride.

pH of 1% w/v Aqueous Solution: 4.5 to 6.0

pH Solubility Profile: Ranitidine hydrochloride is freely soluble (>1 gram/mL) over the physiological pH range from 1 to 7.5, including purified water

Polymorphism: Ranitidine HCl exists in 2 different polymorphic (crystal) forms: Form I (mp 134º - 140ºC) and Form II (mp 140º - 144ºC).

pKa: 1.89 (25ºC), 1.77 (37ºC)

Molar Absorptivity: 1.5 x 10^4 litre mol^{-1} cm^{-1} @ 315 nm

Melting Point: 140ºC to 144ºC

CLINICAL TRIALS

In 6 clinical trials examining the healing of duodenal ulcers in 1500 patients, a dose of 300 mg daily for 4 weeks was found to have an 83% healing rate; however, increasing the dose to 300 mg twice daily gave significantly better results (92% healed at 4 weeks; $p<0.001$).

Bioavailability comparison between Ranitidine hydrochloride Tablets and Ranitidine hydrochloride Oral Solution

A single dose, randomized, two-phase crossover bioavailability comparison between ranitidine hydrochloride tablets and ranitidine hydrochloride oral solution was performed. Eighteen male volunteers with a median age of 25 years (range 22 to 32 years) shown to be free from renal impairment, hepatic disease or hypersensitivity to H_2 receptor antagonists participated in the study. Subjects were administered, after a 72hour washout period, a single ranitidine dose consisting of either one 150 mg tablet or the equivalent dose of oral solution.

Aliquots of blood were drawn via an intravenous indwelling catheter at 0, 4, 8, 12, 16 and 20hours post-dose. Plasma ranitidine concentrations were determined by RIA techniques. The mean ± SEM serum ranitidine concentrations after either a 150 mg ranitidine hydrochloride dose administered as a tablet or oral solution is displayed below.

An overall summary of the pharmacokinetic parameters are shown below:

Pharmacokinetic Parameters for Eighteen Subjects Administered a Single Dose of either Ranitidine Hydrochloride Tablet or Oral Solution

	AUC (ng.hr/mL)	MRT (hr)	MAT (hr)	K_{el} (hr-1)	Half-life (hr)	C_{max} (ng/mL)	T_{max} (hr)
Syrup Formulation	2577	5.17	1.44	0.273	2.55	493	3.3 (Median)
Tablet Formulation	2615	5.15	1.46	0.276	2.51	575	3.0 (Median)
Fail to Reject Hypothesis of	YES	YES	YES	YES	YES	NO**	YES**

Pharmacokinetic Parameters for Eighteen Subjects Administered a Single Dose of either Ranitidine Hydrochloride Tablet or Oral Solution							
	AUC (ng.hr/ mL)	**MRT (hr)**	**MAT (hr)**	**K_{el} (hr-1)**	**Half-life (hr)**	**C_{max} (ng/mL)**	**T_{max} (hr)**
No Difference							
Satisfy 75/75 Rule	YES	--	--	--	--	YES	NO*
Statistical Power to Detect a 20% Difference	95%	>99%	<0%	>99%	>99%	--	--

* 38.9% (7/18) of the subjects satisfied the 75/75 rule; 83% (15/18) of the subjects had a T_{max} for the syrup that was at least 75% of the T_{max} for the tablet.

** Wilcoxon Matched-Pairs Signed-Rank Test, $\alpha = 0.05$

No significant differences were observed in the area under the curve (AUC), mean residence time (MRT), mean absorption time (MAT), elimination rate constant (K_{el}) or terminal elimination half-life ($t_{1/2}$). Some variation was observed in maximum concentration (C_{max}) between the two formulations. The time of maximum concentration (T_{max}) does not demonstrate a significant variability in the rate of absorption between the two formulations. The investigators concluded that since the extent of absorption for ranitidine from the oral solution and tablet formulations were identical and the C_{max} of the oral solution were within 13% of those for the tablet formulation, the oral solution and tablet formulations are judged to be bioequivalent.

DETAILED PHARMACOLOGY

Animal Pharmacology

Ranitidine is a potent competitive reversible, selective antagonist of histamine at H_2-receptors *in vitro* and *in vivo*. Thus, ranitidine antagonized 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 antagonized 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 anaesthetized 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 co administered with the following CNS modulating preparations; codeine, hexobarbitone, ethyl alcohol, chlordiazepoxide, chlorpromazine, imipramine, α-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 or 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 feces.

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. Thirty percent of the administered dose was excreted in the urine as unchanged drug, up to 14% as desmethylranitidine, 3 to 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 unmetabolized ranitidine, 8% as S-oxide, 2to 4% as the N-oxide, and 2to 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 fetuses showed that small amounts of radioactivity were present in the uveal tract of the fetal eye in both species, in the gall bladder and intestine of the rabbit fetus and in the bladder of the rat fetus. Radioacbtivity was also detected in the salivary and mammary glands of the maternal rat and at very low concentration, in the milk.

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 tong-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 mcg/mL and in mice basal plasma levels were in the range of 4to 9 mcg/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 accumulation of these cells is a natural phenomenon 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 tile 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 feces 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 feces, salivation and vomiting were observed in the 54-week dog study.

In isolated cases, dogs passed red-stained feces which occasionally tested positive for occult blood. When the dose level was increased from 100 mg/kg/day to 225 to 450 mg/kg/day, no further red-stained feces 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 hematology, 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, defecation, diarrhea, 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 fetuses from rats treated with ranitidine were examined. There was no evidence that ranitidine is a rat teratogen. Cleft palates occurred in fetuses from both treatment groups, however, there were significantly more in the control rat population.

A total of 944 fetuses from rabbits treated with ranitidine were examined; no drug-related adverse events or abnormalities in the fetuses 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 fetuses weighed significantly less than fetuses of

untreated controls. In addition, 12.4% of ranitidine-exposed fetuses 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 fetal toxicity.

In the subsequent study, no evidence of maternal or fetal toxicity was observed in rabbits dosed with 100 mg/kg ranitidine orally during days 2 to 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 (20to 25 mcg/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 hydrochloride 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 AH 23729 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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PART III: CONSUMER INFORMATION

Pr APO-RANITIDINE

Ranitidine Oral Solution USP

15 mg/mL

This leaflet is Part III of a three-part "Product Monograph" published when APO-RANITIDINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-RANITIDINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

APO-RANITIDINE is a brand name for the drug ranitidine hydrochloride. APO-RANITIDINE is used to treat stomach or intestinal ulcers and prevent their return. It can relieve discomfort from ulcer pain and the heartburn associated with acid reflux.

What it does:

APO-RANITIDINE belongs to a group of medicines called H_2-receptor site antagonists. It acts by blocking histamine receptors that are present on the cells in the stomach lining thereby reducing the amount of acid produced by these cells.

When it should not be used:

Do not take APO-RANITIDINE if you have previously had an allergic reaction to the medicine or any of the non-medicinal ingredients of the product. APO-RANITIDINE should not be used if you have a history of acute porphyria.

What the medicinal ingredient is:

Ranitidine Hydrochloride

What the non-medicinal ingredients are:

Butylparaben, hypromellose, peppermint oil, potassium phosphate, propylparaben, purified water, saccharin sodium, sodium chloride, sodium phosphate dibasic, sorbitol solution.

What dosage forms it comes in:

APO-RANITIDINE is available as an oral solution, 15 mg/mL (300 mL).

WARNINGS AND PRECAUTIONS

- This medicine can mask the symptoms of stomach cancer and therefore delay the diagnosis of this condition. For this reason, the possibility of stomach cancer should be excluded by your doctor before starting to use this medicine.
- If you have severe decreased renal function, the dosage of ranitidine should be reduced as advised by your doctor.
- Use in Pregnancy: This medicine is not recommended for use during pregnancy unless considered necessary by your doctor. The potential benefits must be weighed against possible hazards to you and your baby
- Use in Nursing Mothers: This medicine is secreted into breast milk. It should not be used during breast-feeding unless considered essential by your doctor.
- Use in Children (< 18 years of age): Experience with this medicine in children is limited. It has, however, been used successfully in children aged 8 to 18 years in oral doses up to 150 mg twice daily when used for short periods of time.
- Use in the Elderly (>65 years of age): If you are older than 65 years of age make sure that your doctor has ruled out the possibility of stomach cancer before starting this medicine. Also, make sure your doctor knows if you are taking non-steroidal anti-inflammatory drugs (NSAIDs, such as aspirin). Tell your doctor if you experience confusion and depression.
- This medicine should not be used if you have acute porphyria, a lifelong inherited blood disease characterized by sudden attacks of high blood pressure, mental disturbances and abdominal pain.

INTERACTIONS WITH THIS MEDICATION

APO-RANITIDINE interacts with other drugs, including:

- Non-steroidal anti-inflammatory
- Ketoconazole
- Hypoglycemic drugs
- Theophylline
- Sucralfate

You should check with your doctor or pharmacist before taking any 'over-the-counter' medicine or have concerns regarding drug interactions.

PROPER USE OF THIS MEDICATION

Usual dose:

Never take more than the prescribed dose. Discuss with your doctor or pharmacist for proper use of this medicine.

Elderly patients should start at the lowest recommended

dose and be adjusted as necessary.

Missed Dose:

If you miss a dose, take it as soon as you can. If it is almost time for your next dose, take only that dose. Do not take double or extra doses.

If you are still unsure, check with your doctor or pharmacist.

Overdose:

If you take more than the prescribed dose please consult your physician or Emergency room as soon as possible.

If you think you have taken too much APO-RANITIDINE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, APO-RANITIDINE can cause some side effects. These side effects are most likely to be minor and temporary.

Do not be alarmed by this list of possible side effects. You may not experience any of them. If any of these side effects are experienced, do not hesitate to report them to your doctor.

- Headache, sometimes severe; malaise; dizziness; somnolence; insomnia; vertigo; and reversible blurred vision. Isolated cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. In addition, reversible involuntary movement disorders have been reported rarely.
- Isolated reports of changes to heart rate (increase & decrease) and rhythm have been noted.
- Constipation, diarrhea, nausea/vomiting and abdominal discomfort/pain.
- Occasional reports of abnormal liver function and hepatitis with or without jaundice have been noted. Stop taking ranitidine immediately. These are usually reversible, but in exceedingly rare circumstances, death has occurred.
- Pain in the muscles and joints
- Change in results of liver function tests.
- Swelling of breasts or breast soreness in females and males.
- Rash, rare cases of inflammation near the skin or slight hair loss from the skin.
- Rare cases of allergic reactions (including chest pain, coughing, fever, rash, swelling, hives, low blood pressure) and small increases in serum creatinine have occasionally occurred after a single dose. Rare cases of acute pancreatitis and reversible impotence have been reported.

This is not a complete list of side effects. For any unexpected effects while taking APO-RANITIDINE, contact your doctor or pharmacist immediately

HOW TO STORE IT

Store between 15ºC and 30ºC. Protect from light. Keep all medicines out of the reach of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about APO-RANITIDINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products) or by calling 1-800-667-4708

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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