PRODUCT MONOGRAPH

APO-OMEPRAZOLE

Omeprazole Capsules

20 mg and 40 mg

H^+, K^+ -ATPase Inhibitor

Ctrl#092458

APOTEX INC.
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DATE OF PREPARATION:
December 3, 2001
DATE OF REVISION:
September 3, 2004

PRODUCT MONOGRAPH

APO-OMEPRAZOLE
Omeprazole Capsules
20 mg and 40 mg

THERAPEUTIC CLASSIFICATION

H^+, K^+ ATPase Inhibitor

ACTIONS AND CLINICAL PHARMACOLOGY

Omeprazole inhibits the gastric enzyme H^+, K^+ -ATPase (the proton pump) which catalyzes the exchange of H^+ and K^+. It is effective in the inhibition of both basal acid secretion and stimulated acid secretion. The inhibition is dose dependent. Daily oral doses of 20 mg omeprazole and higher showed a consistent and effective acid control.

Omeprazole is absorbed rapidly. After an initial oral dose, approximately 35% of the drug is absorbed from the gastrointestinal tract. Following one week of therapy, the percentage absorbed is 43. Neither food nor antacids have any effect on the bioavailability. Peak plasma levels occur within about 4 hours. The terminal plasma half–life is about 40 minutes.

The antisecretory effect of omeprazole is directly proportional to the AUC; it is not dependent on the plasma concentration at any given time. Omeprazole is 95% bound to plasma proteins.

Omeprazole undergoes first-pass metabolism by the cytochrome P450 2C19 system, mainly in the liver. Following I.V. and oral administration, 80% of the dose is recovered as urinary metabolites; the remaining 20% is excreted in the feces.

Comparative Bioavailability

Two comparative bioavailability studies were performed using healthy human volunteers – one under fasting conditions and one with food. The rate and extent of absorption of omeprazole following a single 40 mg (2 x 20 mg capsules) oral dose of APO-OMEPRAZOLE and LOSEC were measured and compared. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data (Fasting State)
Omeprazole (Dose: 2 x 20 mg) From Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Apo-Omeprazole	Losec→	
AUC_T (ng•hr/mL)	1194 1503 (77)	1161 1425 (73)	103.6
AUC_I (ng•hr/mL)	1215 1526 (77)	1190 1468 (75)	102.8
C_{max} (ng/mL)	682 795 (58)	671 764 (54)	102.5
T_{max} (hr)*	2.15 (36)	2.48 (52)	-
$t_{1/2}$ (hr)*	0.80 (40)	0.82 (45)	-

* Arithmetic means (CV%).

** Based on the least squares estimate of the geometric mean.

Losec→ is manufactured by Astra Pharma, and was purchased at a Canadian retail pharmacy.

Summary Table of the Comparative Bioavailability Data (With Food) Omeprazole (Dose: 2 x 20 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%) Apo-Omeprazole	Losec→□	Ratio of Geometric Means (%)**
AUC_T (ng•hr/mL)	1034 1526 (99)	952 1338 (96)	108.6
AUC_I (ng•hr/mL)	1059 1550 (99)	985 1370 (94)	107.6
C_{max} (ng/mL)	556 701 (66)	437 520 (62)	126.6
T_{max} (hr)*	4.88 (26)	5.15 (25)	-
$t_{1/2}$ (hr)*	0.75 (52)	0.79 (59)	-

* Arithmetic means (CV%).

** Based on the least squares estimate of the geometric mean.

□ Losec→ is manufactured by Astra Pharma, and was purchased at a Canadian retail pharmacy.

Two additional comparative bioavailability studies were performed using healthy human volunteers – one under fasting conditions and one with food. The rate and extent of absorption of omeprazole following a single 40 mg (2 x 20 mg capsules) oral dose of APO-OMEPRAZOLE and PRILOSEC were measured and compared. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data (Fasting State) Omeprazole (Dose: 2 x 20 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%) Apo-Omeprazole	Prilosec→□	Ratio of Geometric Means (%)**
AUC_T (ng•hr/mL)	1218 1664 (90)	1199 1706 (98)	101.6
AUC_I (ng•hr/mL)	1226 1681 (92)	1207 1730 (101)	101.6
C_{max} (ng/mL)	626 739 (54)	615 740 (63)	101.7
T_{max} (hr)*	2.33 (34)	1.89 (50)	-
$t_{1/2}$ (hr)*	1.03 (38)	1.08 (42)	-

* Arithmetic means (CV%).

** Based on the least squares estimate of the geometric mean.

□ Prilosec→ is manufactured by Merck & Co. Inc., and was purchased at a U.S. retail pharmacy.

Summary Table of the Comparative Bioavailability Data (With Food) Omeprazole (Dose: 2 x 20 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%) Apo-Omeprazole	Prilosec→□	Ratio of Geometric Means (%)**
AUC_T (ng•hr/mL)	734 959 (103)	729 969 (111)	101.0
AUC_I (ng•hr/mL)	743 982 (109)	757 1023 (115)	100.9
C_{max} (ng/mL)	353 420 (62)	327 399 (69)	109.0

T_{max} (hr)*	4.95 (17)	4.82 (18)	-
$t_{1/2}$ (hr)*	0.97 (43)	1.14 (41)	-

* Arithmetic means (CV%).

** Based on the least squares estimate of the geometric mean.

□ Prilosec→ is manufactured by Merck & Co. Inc., and was purchased at a U.S. retail pharmacy.

INDICATIONS AND CLINICAL USE

APO-OMEPRAZOLE (omeprazole) is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:

1. duodenal ulcer;
2. gastric ulcer;
3. reflux esophagitis;
4. symptomatic gastroesophageal reflux disease (GERD);
5. Zollinger-Ellison Syndrome (pathological hypersecretory conditions);
6. NSAID-associated gastric and duodenal ulcers.

CONTRAINDICATIONS

Hypersensitivity to omeprazole or any of the components of this medication (see

PHARMACEUTICAL INFORMATION).

WARNINGS

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with omeprazole is instituted, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Use in Pregnancy

The safety of omeprazole in pregnancy has not been established. APO-OMEPRAZOLE (omeprazole) should not be administered to pregnant women unless the expected benefits outweigh the potential risks.

Nursing Mothers

It is not known if omeprazole is secreted in human milk. APO-OMEPRAZOLE should not be given to nursing mothers unless its use is considered essential.

Use in Children

The safety and effectiveness of omeprazole in children has not yet been established.

PRECAUTIONS

Use in the Elderly

Elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination half-life (to 1.0 hour). The daily dose in elderly patients should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Hepatic Insufficiency

Patients with impaired liver function showed a 75% increase in bioavailability, reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours). 20 mg given once daily to these patients for 4 weeks was well tolerated, with no accumulation of omeprazole or its metabolites. The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION).

Patients with Renal Insufficiency

The disposition of intact omeprazole is unchanged in patients with impaired renal function, and no dose adjustment is needed in these patients (see DOSAGE AND ADMINISTRATION).

Carcinogenicity

The rat carcinogenicity study (24 months) revealed a gradual development from gastric ECL-cell hyperplasia to carcinoids at the end of their normal life span during administration with 14-140 mg/kg/day of omeprazole. No metastasis developed. No carcinoids developed during 18 months' high dose treatment of mice (14-140 mg/kg/day). Similarly, administration of omeprazole up to 28 mg/kg/day in dogs for 7 years did not cause any carcinoids.

The gastric carcinoids in rats were related to sustained hypergastrinemia secondary to acid inhibition and not to omeprazole per se (see TOXICOLOGY). Similar observations have been made after administration of histamine H_2-receptor blockers and also in partially fundectomized rats.

Short-term treatment and long-term treatment in a limited number of patients for up to 6 years have not resulted in any significant pathological changes in gastric oxyntic endocrine cells.

Drug Interactions

The absorption of some drugs might be altered due to decreased intragastric acidity. Thus, it can be predicted that the absorption of ketoconazole will decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

Omeprazole is metabolized in the liver. This occurs via the cytochrome P-450 system. The pharmacokinetics of the following drugs which are also metabolized through the cytochrome P-450 system have been evaluated during concomitant use of omeprazole in humans:

aminopyrine, antipyrine, diazepam, phenytoin, warfarin, theophylline, propranolol, metoprolol, lidocaine, quinidine, ethanol, piroxicam, diclofenac and naproxen.

Aminopyrine and Antipyrine: After 14 days' administration of 60 mg omeprazole once daily, the clearance of aminopyrine was reduced by 19%; the clearance of antipyrine was reduced by 14%. After 14 days' administration of 30 mg once daily, no significant changes in clearance were noted.

Diazepam: Following repeated dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54%. The corresponding decrease after omeprazole 20 mg was 26%.

Warfarin: Concomitant administration of omeprazole 20 mg in healthy subjects had no effect on plasma concentrations of the (S)-enantiomer of warfarin, but caused a slight, though statistically

significant increase (12%) in the less potent (R)-enantiomer concentrations. A small but statistically significant increase (11%) in the anticoagulant effect of warfarin was also seen. Concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin.

Phenytoin: Following three weeks' treatment with omeprazole 20 mg once daily, the steady state plasma levels of phenytoin in epileptic patients already receiving concomitant phenytoin treatment were not significantly affected. Urinary excretion of phenytoin and its main metabolite were also unchanged.

After single intravenous and oral doses of omeprazole 40 mg in young, healthy volunteers, the clearance of phenytoin was decreased by 15-20%, and half-life was prolonged by 20-30%. Following repeated dosing with omeprazole 40 mg once daily, the elimination half-life of

phenytoin was increased by 27%. Thus there appears to be a dose dependent inhibition of elimination of phenytoin by omeprazole.

Patients receiving phenytoin and warfarin should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Results from a range of interaction studies with omeprazole versus other drugs indicate that omeprazole, 20-40 mg given repeatedly, has no influence on any other clinically relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP 1A2 (caffeine, phenacetin, theophylline), CYP 2C9 (S-warfarin), CYP 2D6 (metoprolol, propranolol), CYP 2E1 (ethanol), and CYP 3A (cyclosporine, lidocaine, quinidine, estradiol).

Theophylline: No effects on oral or I.V. theophylline kinetics have been observed after repeated once daily doses of 40 mg omeprazole.

Propranolol and Metoprolol: No effects on propranolol kinetics were observed in a steady-state trial with 20 mg of omeprazole daily. Similarly, no effects on steady-state plasma levels of metoprolol were observed after concomitant treatment with 40 mg omeprazole daily.

Lidocaine: No interaction with a single intravenous dose of lidocaine or its active metabolite, MEGX, was found after one week's pre-treatment with omeprazole 40 mg once daily. There were no interactions between omeprazole and lidocaine or MEGX concerning pharmacokinetic variables.

Quinidine: After one week of omeprazole 40 mg once daily, no effect was observed on the kinetics or pharmacodynamics of quinidine.

Ethanol: There was no significant effect on the pharmacokinetics of ethanol after omeprazole 20 mg.

Piroxicam, Diclofenac and Naproxen: There was no significant effect on the steady state pharmacokinetics of piroxicam, diclofenac and naproxen following repeated dosing with omeprazole 20 mg in healthy volunteers.

No interaction with food and concomitantly administered antacids has been found.

ADVERSE REACTIONS

Omeprazole is well tolerated. Most adverse reactions have been mild and transient and have shown no consistent relationship with treatment. Adverse events have been recorded during controlled clinical investigations in 2764 patients exposed to omeprazole or reported from routine use. In a controlled clinical trial comparing omeprazole to placebo, the prevalence of adverse events with omeprazole 40 mg once daily was similar that with placebo. In short term comparative double-blind studies with histamine H_2-receptor antagonists, there was no significant difference in the prevalence of adverse events between omeprazole and the H_2-receptor antagonists. An extensive evaluation of laboratory variables has not revealed any significant changes during omeprazole treatment which are considered to be clinically important.

The following adverse events (at a rate of more than 1%) have been reported in individuals receiving omeprazole therapy in controlled clinical situations: diarrhea (2.8%); headache (2.6%); flatulence (2.3%); abdominal pain (1.7%); constipation (1.3%); and dizziness/vertigo (1.1%).

In addition, the following adverse events were reported in clinical trials or were reported from routine use:

Skin: Rarely, rash and/or pruritus. In isolated cases photosensitivity, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and alopecia.

Musculoskeletal: In isolated cases arthralgia, muscular weakness and myalgia.

Central and Peripheral Nervous System: Rarely dizziness, paresthesia, somnolence, insomnia and vertigo. In isolated cases reversible mental confusion, agitation, depression and hallucination occurring predominantly in severely ill patients.

Gastrointestinal: Nausea and vomiting. In isolated cases, stomatitis and gastrointestinal candidiasis.

Hepatic: In rare cases, increased liver enzyme levels. In isolated cases, encephalopathy in patients with pre–existing severe liver disease, hepatitis with or without jaundice and hepatic failure.

Endocrine: In isolated cases, gynecomastia.

Hematologic: In isolated cases, patients have developed leukopenia, thrombocytopenia, agranulocytosis and pancytopenia.

Other: Rarely, malaise. Hypersensitive reactions including urticaria (rarely) and, in isolated cases, angioedema, fever, bronchospasm, interstitial nephritis and anaphylactic shock. In isolated cases, increased sweating, peripheral edema, blurred vision, taste disturbances and hyponatremia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No information is available on the effects of higher doses in man, and specific recommendations for treatment cannot be given. Single oral doses of up to 400 mg omeprazole have not resulted in any severe symptoms, and no specific treatment has been needed. As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored.

The oral LD_{50} of omeprazole in male and female rats and mice was greater than 4000 mg/kg. In dogs, the only sign of acute toxicity was vomiting which occurred at doses of approximately 600 mg/kg (see TOXICOLOGY).

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dose of APO-OMEPRAZOLE is 20 mg given once daily. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional 2 weeks of treatment is recommended.

Refractory Patients: In patients with duodenal ulcer refractory to other treatment regimens, the recommended adult doses are 20 mg and 40 mg given once daily. Healing is usually achieved within 4 weeks in such patients.

Gastric Ulcer

Acute Therapy: The recommended adult dose is 20 mg given once daily. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: In patients with gastric ulcer refractory to other treatment regimens, the recommended adult dose is 40 mg omeprazole given once daily. Healing is usually achieved within 8 weeks.

Maintenance Therapy for Gastric Ulcer: The recommended omeprazole dose is 20 mg once daily, increased to 40 mg once daily, as necessary.

Reflux Esophagitis

Acute Therapy: The recommended adult dose is 20 mg given once daily. In most patients, healing occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

Refractory Patients: For patients with reflux esophagitis refractory to other treatment regimens, the recommended adult dose is 40 mg omeprazole given once daily. Healing is usually achieved within 8 weeks.

Symptomatic Gastroesophageal Reflux Disease

The recommended adult dose is 20 mg given once daily. Individual dose adjustment should be considered. Symptom relief should be rapid. If symptom control is not achieved after 4 weeks, further investigation is recommended.

NSAID-Associated Gastric and Duodenal Ulcers

Acute Therapy: In patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily. Symptom resolution is rapid and healing usually occurs within four weeks. For those patients not healed after this initial course of therapy, an additional four weeks of treatment is recommended.

Maintenance Therapy: For the prevention of relapse in patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily, for up to six months.

Zollinger-Ellison Syndrome

The dose of APO-OMEPRAZOLE used in the treatment of Zollinger-Ellison Syndrome will vary with the individual patient.

The recommended initial dose is 60 mg APO-OMEPRAZOLE, given once daily. More than 90% of the patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20 mg to 120 mg daily. With doses greater than 80 mg, the dose should be divided and given twice daily. Doses should be adjusted to the

individual patient's need and should continue as long as clinically indicated. Doses up to 120 mg three times daily have been administered.

Patients with Renal Insufficiency: No dose adjustment is required (see PRECAUTIONS).

Patients with Hepatic Insufficiency: No dose adjustment is required. The daily dose should not exceed 20 mg (see PRECAUTIONS).

Elderly Patients: No dose adjustment is required. The daily dose should not exceed 20 mg (see PRECAUTIONS).

The capsules should be swallowed whole with sufficient water.

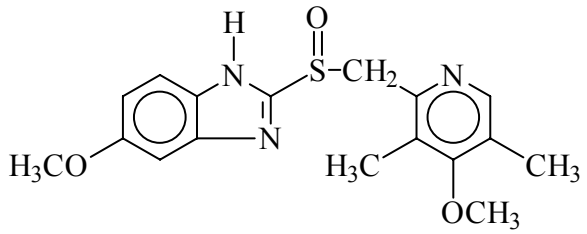
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: omeprazole

Chemical Name: 5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl}-1H-benzimidazole.

Structural Formula:



Molecular Formula: $C_{17}H_{19}N_3O_3S$

Molecular Weight: 345.4

Description: Omeprazole is a non-hygroscopic, crystalline substance which melts with decomposition at about 150˚C. The substance is slightly soluble in water. The pKa of the benzimidazole is 8.8 and that of the pyridinium ion, 4.0.

Composition

In addition to omeprazole, each capsule contains the non-medicinal ingredients mannitol, povidone, magnesium hydroxide, triethyl citrate and eudragit. The capsule shell contains the non-medicinal ingredients gelatin, red iron oxide and titanium dioxide.

Stability and Storage Recommendations

Store bottle tightly capped at room temperature 15 - 30˚C. Protect from moisture.

AVAILABILITY OF DOSAGE FORMS

APO-OMEPRAZOLE 20 mg and 40 mg capsules are two-piece hard gelatin capsules with an opaque pink body and an opaque reddish-brown cap, imprinted “APO 020” or “APO 40”. Available in bottles of 14, 28, 100 and 500.

INFORMATION FOR THE PATIENT

Read this leaflet carefully. It contains general points about APO-OMEPRAZOLE (omeprazole) and should add to more specific advice from your doctor or pharmacist.

WHAT IS APO-OMEPRAZOLE USED FOR AND HOW DOES IT WORK?

APO-OMEPRAZOLE is the brand name for a drug called omeprazole.

The most common uses of APO-OMEPRAZOLE are:

– for stomach ulcers or for duodenal ulcers,

– for ulcers caused by your medicine for pain and joint problems (NSAID-associated gastric and duodenal ulcers), and

– for the symptoms of gastroesophageal reflux disease such as: a burning sensation rising from the chest towards the neck (heartburn) and flow of bitter/sour juice into the mouth (regurgitation).

APO-OMEPRAZOLE may also be used in rare conditions like "Zollinger-Ellison syndrome", where the stomach produces large amounts of acid. APO-OMEPRAZOLE works by reducing the amount of acid made in your stomach. This helps in treating acid-related stomach problems.

Your doctor will have explained why you are being treated with APO-OMEPRAZOLE and will have told you what dose to take. Follow those directions carefully. They may differ from the information contained in this leaflet.

WHAT IS IN APO-OMEPRAZOLE?

Each APO-OMEPRAZOLE capsule contains omeprazole as the active ingredient. In addition, it contains the following non-medicinal ingredients (listed in alphabetical order): eudragit, gelatin, magnesium hydroxide, mannitol, povidone, red iron oxide, titanium dioxide and triethyl citrate.

Check with your doctor or pharmacist if you think you might be allergic to any of the "non-medicinal" substances which may be present in APO-OMEPRAZOLE.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING APO-OMEPRAZOLE?

Tell your doctor:

– about **all** health problems you have now or have had in the past,

– about other medicines you take, including ones you can buy without a prescription,

– if you are allergic to "non-medicinal" substances which may be present in APO-OMEPRAZOLE, and

– if you are pregnant, plan to become pregnant or are breastfeeding.

HOW DO I TAKE APO-OMEPRAZOLE PROPERLY?

Take all doses of APO-OMEPRAZOLE, as recommended by your doctor, even when you feel well. Daily doses are needed to help damaged areas heal. The recommended dose for treating acute disease is 20 to 40 mg once a day for 2 to 8 weeks. Your doctor may recommend that you continue taking APO-OMEPRAZOLE 20 to 40 mg to control symptoms of reflux disease, or APO-OMEPRAZOLE 20 mg to prevent ulcers from returning while you continue to take your medicine for pain and joint problems.

Take APO-OMEPRAZOLE until your doctor tells you to stop. Even if you start to feel better in a few days, your symptoms may return if APO-OMEPRAZOLE is stopped too soon. APO-OMEPRAZOLE needs to be taken for the full duration of treatment to help correct acid problems.

If you miss a dose of APO-OMEPRAZOLE and remember within 12 hours, take it as soon as possible. Then go back to your regular schedule. However, if more than 12 hours have passed when you remember, do not take the missed tablet. Just take your next dose on time.

APO-OMEPRAZOLE may be taken with food or on an empty stomach.

ARE THERE ANY SIDE EFFECTS?

Like any medication, APO-OMEPRAZOLE may cause side effects in some people. Side effects that do occur are usually mild and go away a short time after starting APO-OMEPRAZOLE. Tell your doctor if any of the following are severe or bother you for more than one or two days: nausea, stomach upset, diarrhea, constipation, headache or skin rash.

Other unwanted effects which cannot be predicted may occur in rare cases. If you experience any bothersome or unusual effects while using APO-OMEPRAZOLE, check with your doctor or pharmacist.

WHAT SHOULD I DO IN CASE OF OVERDOSE?

Call your doctor or pharmacist right away in case of an overdose. However, no severe symptoms have been seen in patients who have taken doses up to 400 mg.

WHERE SHOULD I KEEP APO-OMEPRAZOLE?

Remember to keep APO-OMEPRAZOLE well out of reach of children. APO-OMEPRAZOLE should be stored at room temperature (15 to 30°C), in tightly closed and moisture resistant containers. Do not keep APO-OMEPRAZOLE in the bathroom medicine cabinet or other warm, moist places. Keep all capsules in their container until it is time for a dose. If you do not, moisture from the air may damage the capsules.

Do not use Apo-Omeprazole after the expiry date marked on the pack.

IMPORTANT NOTE

This leaflet alerts you to some of the times you should call your doctor. Other situations which cannot be predicted may arise. Nothing in this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using APO-OMEPRAZOLE.

PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

Omeprazole differs from existing inhibitors of gastric acid secretion such as histamine H_2-receptor antagonists or anticholinergic agents in its ability to directly inhibit the gastric H^+, K^+-ATPase. This enzyme has been identified as the proton pump of the parietal cell.

Omeprazole had a long duration of action in all species studied. Repeated daily doses resulted in a progressive increase in the antisecretory effect during the first 3-5 days of administration. In dogs, a dose of 0.5 mmol/kg (given as enteric coated granules) inhibited histamine stimulated gastric acid secretion by about 20% when measured 24 hours after the first dose, and by 60-65% when measured 24 hours after dosing at steady state. Once steady-state conditions were reached (after 3-5 days), acid inhibition remained unchanged, as established in dogs treated for periods up to one year.

Acid secretion recovers after discontinuation of long-term treatment at the same rate as after a single dose of omeprazole, in parallel with the recovery of H^+, K^+-ATPase activity in the oxyntic mucosa. Whether this recovery reflects de novo synthesis of the H^+, K^+-ATPase molecules or the dissociation of the inhibitor from the enzyme has not yet been established.

Due to the potency and long duration of action of omeprazole, repeated administration of high doses in the rat resulted in a marked decrease of acid secretion and a secondary hypergastrinemia and hyperplasia of G-cells.

In rats, administration of omeprazole 14-140 mg/kg/day resulted in plasma gastrin levels of 1000-3000 pg/mL as compared to 150-200 pg/mL in controls. In dogs, high doses of omeprazole (28 mg/kg/day) produced marked hypergastrinemia (1000-2000 pg/mL after food intake), as compared to 100-300 pg/mL in controls. However, no hyperplasia of G-cells was evident in this species.

Secondary Pharmacological Effects

Mean arterial blood pressure and heart rate in the anesthetized dog were not affected by omeprazole under various challenges. Circulatory and respiratory functions in the dog were not affected by omeprazole, either at rest or during exercise. Omeprazole had no anticholinergic and no antihistamine (H_2-receptor) activity. In the rat, no effect on basal locomotor activity nor on exploratory activity was recorded, suggesting that omeprazole is devoid of sedative or neuroleptic effects.

Other Interactions

Omeprazole interacts with cytochrome P-450 in rat liver. Omeprazole prolonged hexobarbital sleeping time by 12%.

Pharmacokinetics

Absorption and Distribution: Omeprazole is degraded rapidly in acidic gastric juice (rat and dog studies). Absorption is rapid. Peak plasma levels were found within 20 minutes and 1 hour after intra-duodenal and oral administration respectively, in the dog. The drug has a low oral bioavailability, 5% in unstarved rats and 15-20% in starved male and female rats, if the drug is not protected by an enteric coating. The intra-duodenal bioavailability is approximately 70% and the oral bioavailability is approximately 15% in the dog. After absorption, omeprazole is rapidly distributed to extravascular sites and about 95% is bound to plasma proteins. The distribution of C^{14} labelled omeprazole in the mouse was investigated by autoradiography. Radioactivity was initially found in the blood and most organs. Sixteen hours after administration, the drug was confined predominantly to the stomach wall. At 48 hours, the radioactivity was eliminated. Penetration of omeprazole and/or its metabolites across the blood-brain and placental barriers was low.

Metabolism and Excretion: Omeprazole was extensively metabolized in all species studied. In rats and dogs, approximately 20-30% of the dose was excreted as urinary metabolites and the remainder by biliary excretion as metabolites in the feces. Elimination was virtually complete within 72 hours. Identifiable metabolites constituted about 50% (rats) and 70% (dogs) of the total metabolite excretion in 24 hours, and about 12% of the given dose in both species.

A study in lactating rats showed that omeprazole is excreted in breast milk. The concentration in the milk at 3-5 hours post dose was 100-200 times lower than the plasma concentration. It is not known if omeprazole is excreted in human milk.

Human Pharmacology

Pharmacodynamics

In both normal volunteers and hypersecretors, omeprazole inhibited basal nocturnal and daytime acid secretion as well as meal-, histamine-, and pentagastrin-stimulated secretion.

Table 2: Percentage inhibition of mean acid output after single oral doses of omeprazole

Stimulus	Type Of Subject	Omeprazole Dose (mg)		Time After Dose (hr)
		20	80	
Basal	HSu*	33%		1-4
Basal–Nocturnal	DU (rem)**	49%		15-24
Sham Feeding	HSu	23%		1.5-3.5
Betazol	HSu	38%		1-4
Pentagastrin	HSu	36%		1-4
Basal	ZES***		97%	2-3

* Healthy Subject ** Duodenal Ulcer in Remission *** Zollinger-Ellison Syndrome

Repeated oral dosing with 20 mg of omeprazole once daily provided rapid inhibition of gastric acid secretion, with the maximum effect achieved within the first four days of treatment. In duodenal ulcer patients, a mean decrease in 24-hour intragastric acidity of about 80% was then maintained. The mean decrease in peak acid output after pentragastrin stimulation was about 70% 24 hours after repeated dosing with omeprazole 20 mg. Omeprazole caused a transient

decrease in stimulated pepsin output which resolved within four hours of dosing. Omeprazole had no effect on intrinsic factor secretion.

Gastric emptying was unaffected by omeprazole. Increased concentrations of bacterial flora may occur in gastric juice during chronic therapy. These effects disappear within 3 days after discontinuation of treatment.

Other Pharmacodynamic Effects

The effect of omeprazole on various organ systems has been investigated. No clinically significant effects attributable to the drug could be found for the following parameters: *Endocrine:* plasma levels of insulin, C-peptide, glucagon, PTH, thyroid hormones or sex hormones, basal levels of cortisol; *Cardiovascular:* blood pressure, heart rate, electrocardiogram; *Renal:* renal handling of acid and electrolytes; *Hepatic:* liver enzymes. However, in some patients receiving omeprazole, elevated concentrations of alkaline phosphatase, S-ASAT and S-ALAT have been reported (see ADVERSE REACTIONS).

No clinically significant CNS effects have been recorded.

No clinically significant effects on other organ systems have been noted.

Omeprazole has no effect on acetylcholine or H_2-receptors.

Pharmacokinetics

Omeprazole is rapidly absorbed. After an initial oral dose of omeprazole, approximately 35% of the drug is absorbed from the gastrointestinal tract. Following one week of therapy, the percentage absorbed is 43. Neither food nor antacids have any effect on the bioavailability. After oral administration, peak plasma levels occur within about 4 hours. The terminal plasma half-life is approximately 40 minutes; the total plasma clearance is 0.6 L/min.

The antisecretory effect of omeprazole is directly proportional to the AUC, and thus it is not dependent on the plasma concentration at any given time. Omeprazole is 95% bound to plasma proteins.

Omeprazole undergoes first-pass metabolism and is completely metabolized by the cytochrome P-450 system (CYP), mainly in the liver. The major part of its metabolism is dependent upon the polymorphically expressed, specific isoform CYP 2C19 (S-mephenytoin hydroxylase). Following I.V. and oral administration, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces. Less than 0.1% of the dose administered is excreted in urine as unchanged drug.

Six urinary metabolites have been detected. The two main metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. Three metabolites have been identified in plasma, the sulphide and sulphone derivatives and hydroxyomeprazole. It is unlikely that these metabolites contribute to inhibition of acid secretion.

Elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination half-life (to 1.0 hour). The mean urinary excretion of

metabolites was 68% of the dose. These changes are consistent with reduction in presystemic and systemic elimination, typical in the elderly. The daily dose should, as a rule, not exceed 20 mg in this patient group (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

The pharmacokinetics of omeprazole in patients with impaired renal function was virtually the same as in healthy subjects. However, patients with impaired liver function showed a 75% increase in bioavailability, reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours). A dose of 20 mg given once daily to these patients for 4 weeks was well tolerated. Dosage for patients with liver cirrhosis and other liver dysfunction should, as a rule, not exceed 20 mg daily (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

TOXICOLOGY

Acute Toxicity

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse	M	p.o.[1*]	>4000
	F	p.o.[1*]	>4000
Mouse	M	p.o.[1]	1520
	F	p.o.[1]	1380
Mouse	M	I.V.	83
	F	I.V.	>100
Rat	M	p.o.[1*]	>4000
	F	p.o.[1*]	>4000
Rat	M	p.o.[1]	>5010
	F	p.o.[1]	3320
Rat	M	I.V.	>40
	F	I.V.	>40

[1] Suspension in Methocel®; not buffered.
* Non-micronized test compound.

The highest oral dose (4000 mg/kg) of non-micronized omeprazole did not cause death in any of the species tested. With micronized omeprazole suspended in Methocel®, the acute oral LD_{50} was approximately 1500 mg/kg in mice; in male rats, higher than the maximum dose (5000 mg/kg) and in female rats, approximately 3000 mg/kg. As much as 80% of the compound may not have been absorbed due to acid degradation in the stomach of these single doses. Death occurred within 2 days of ingestion and was preceded by reduced motor activity, reduced respiration frequency but increased respiration depth, reduced body temperature, and twitching, tremor or convulsions. The highest oral dose given to dogs (660 mg/kg) caused vomiting within 40-100 minutes of ingestion. The acute intravenous LD_{50} was 83 mg/kg in male mice and in

female mice >100 mg/kg. The corresponding figure in rats was >40 mg/kg. Death occurred within a few minutes of injection, preceded by cyanosis and convulsions.

Long-Term General Toxicity

The general, long-term toxicity of omeprazole was studied in mice, rats, and dogs after oral and intravenous administration. Mice received oral doses of 14-140 mg/kg for up to 18 months, rats 14-400 mg/kg for up to 24 months and dogs 1-140 mg/kg for up to 12 months. Intravenous omeprazole was given to rats in doses of 2-16 mg/kg for up to one month and dogs 1-9 mg/kg for up to one month.

In the dog, a slight to moderate atrophy of the chief cells and rugal hypertrophy were observed.

These changes were reversible after treatment cessation.

Following chronic intravenous administration of omeprazole to rats (~1.7-15.5 mg/kg/day) for one month and to dogs (~0.7-8.6 mg/kg/day) for one month, no treatment-related changes were observed.

In the rat, decreased plasma concentrations of triiodothyronine were observed in the two highest groups; TSH increased in the high dose males. Lower doses had no significant effect. General hypertrophy of the oxyntic mucosa was found; the size of some chief cells was decreased and some granularity was observed. Both the hypertrophy and chief cell changes were reversible.

Reproduction Studies

In studies with male and female rats given oral doses of up to 138 mg/kg/day (approximately 500 times the recommended human dose), fertility and reproductive performance were not affected.

In rabbits, increased embryo-lethality and fetal resorption were observed at maternotoxic doses of 69 and 138 mg/kg/day (250 and 500 times the human dose). No maternal or fetal toxicity was observed in pregnant rats treated at doses ranging from 13.8 to 138 mg/kg/day (50 to 500 times the human dose). In rats, a slight decrease in litter size at birth and slightly impaired postnatal viability and growth were observed in offspring resulting from parents treated with high doses of

138 mg/kg/day (500 times the human dose) of omeprazole. Similar effects were not seen at lower doses.

Mutagenicity

Omeprazole was tested in vivo (mouse micronucleus test, chromosome aberration in mice) and in vitro (Ames test, mouse lymphoma forward mutation assay) and showed no evidence of a mutagenic effect.

Carcinogenicity

An eighteen-month oral study was conducted in mice at doses of 14, 44 and 140 mg/kg/day. No evidence of carcinogenic potential was seen. A twenty-four month oral study was conducted in rats at doses of 14, 44, and 140 mg/kg/day. No increase in carcinomas was observed in any organ. However, there were dose- and time-dependent increases of tumour-like proliferations in the stomach. Histology showed a continuum from diffuse ECL-cell hyperplasia in the basal region of the gastric glands to less frequent micronoduli and occasional tumour-like proliferations, some extending into the sub-mucosa. The proliferations were classified as gastric carcinoids. The proliferation of ECL-cells and development of carcinoids were more frequent in female rats.

No metastases were identified in any of the animals. Carcinoids have not been observed after long-term administration of omeprazole to mice and dogs.

Gastric ECL-Cell Carcinoids

Extensive investigations have been carried out to explain the ECL-cell hyperplasia and the gastric carcinoid findings in rats. Gastrin produced by the G-cells in the antrum plays an important role in the feedback control of gastric acid secretion.

In one series of experiments, the antrum of rats was surgically excluded from the rest of the stomach. The removal of acid from the antrum in this way led to pronounced hypergastrinemia and, secondary to this, gastric ECL-cell proliferation. Antrectomy, which removes the source of

gastrin, led to a decrease in gastric ECL-cell density. These experiments indicated that gastrin has a direct trophic effect on gastric ECL-cells. In another series of experiments, high doses of omeprazole and a histamine H_2-receptor blocker caused hypergastrinemia and increased ECL-cell density. In antrectomized rats given a high dose of omeprazole, plasma gastrin levels remained normal, and consequently there was no increase in ECL-cell density. It has therefore been concluded that i) inhibition of gastric acid secretion by large doses of omeprazole or a histamine H_2-receptor blocker, evokes a natural feedback response leading to hypergastrinemia, ii) long-standing hypergastrinemia leads to gastric ECL-cell proliferation, and iii) there is no direct trophic effect of omeprazole on gastric ECL-cells.

An additional long-term (24 months) toxicity study in female rats (1.8-14 mg/kg/day) confirmed that the ECL-cell carcinoids were extreme end-life tumors and that there was a linear correlation between carcinoid incidence and dose of omeprazole (1.8-140 mg/kg/day). In rats given omeprazole 14 mg/kg/day for 12 months, no carcinoids were found and the ECL-cell hyperplasia recovered to normal during the next 12 months of no treatment.

No carcinoids have been found in mice, and in dogs following administration of 28 mg/kg/day for 7 years.

Investigation in man has demonstrated an initial moderate increase in gastrin levels during treatment with omeprazole, but no further increase occurred during long-term (up to 3 years)

treatment. No significant changes have been found in the endocrine cells of the oxyntic gastric mucosa during short- or long-term treatment with omeprazole in man, to date. Chronic treatment of patients with Zollinger-Ellison Syndrome with mean daily doses of omeprazole (60 mg/day) for up to 5 years has not influenced the pre-treatment hypergastrinemia, and no changes in the endocrine cells of the gastric mucosa have been found on repeat biopsies.

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