Losec advertisement.

[s.l.]: [s.n.], 1987

From the Astra/Merck Research Programs

New Losec®

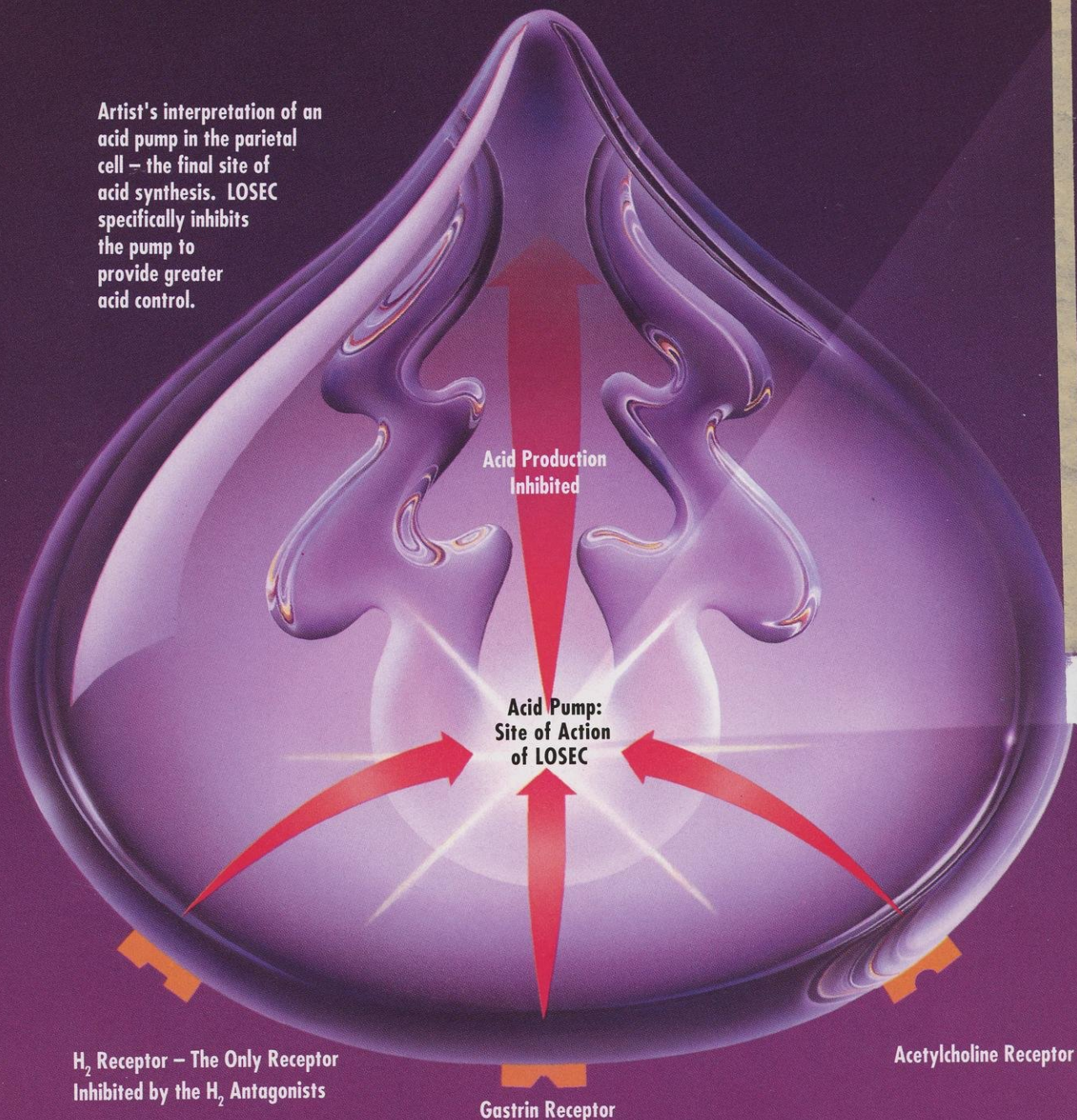
(OMEPRAZOLE|MSD)

A Completely Different Approach to Acid Control

LOSEC is a registered trademark of AB Astra.
Please see Brief Summary of Prescribing Information on the last page of this advertisement.

The Parietal Cell:
Site of gastric acid secretion

The First Therapy to Inhibit the Acid Pump Inside the Parietal Cell



LOSEC® (Omeprazole, MSD) should be used only for the conditions, dosages, and duration specified in the Prescribing Information. Before prescribing LOSEC, please review the Boxed WARNING contained in the Brief Summary of Prescribing Information on the last page of this advertisement.

Acts where other therapies cannot – providing greater acid control

LOSEC blocks H^+/K^+ ATPase – the "acid pump" – at the final site of acid production.

In contrast, H_2 antagonists inhibit the H_2 receptor – one of several pathways to acid production.

The unique inhibition of the acid pump achieved by LOSEC provides acid control regardless of the stimulus.

For severe erosive esophagitis or poorly responsive symptomatic GERD

New Losec®

(OMEPRAZOLE/MSD)

Acid Control Beyond H_2 Blockade

In clinical trials in patients with symptomatic esophagitis and endoscopically diagnosed erosive esophagitis

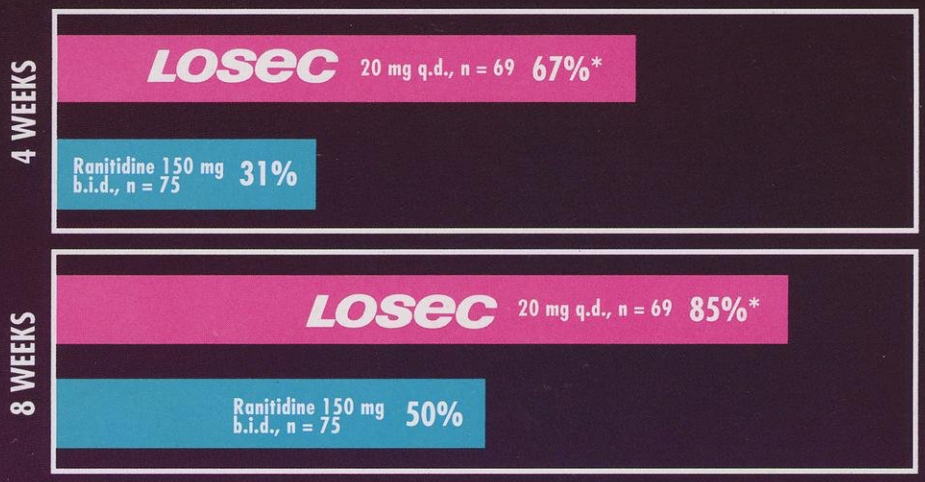
Healing in Significantly More Patients

LOSEC® (Omeprazole, MSD) SHOULD NOT BE USED FOR MAINTENANCE THERAPY (except in pathological hypersecretory conditions such as Zollinger - Ellison Syndrome). Please see Brief Summary of Prescribing Information on the last page of this advertisement.

Healing significantly superior to ranitidine*,[1]

LOSEC achieved 85% healing of esophageal erosions/ulcers at 8 weeks – as endoscopically demonstrated in a double-blind multicenter study.

Most of these patients healed at 4 weeks.



*Significantly different from ranitidine ($p \leq 0.0001$)

[1] Sandmark, S. et al.: Omeprazole or ranitidine in the treatment of reflux esophagitis, Scand. J. Gastroenterol. *23*:625-632, 1988.

LOSEC is indicated for the short-term treatment (4 to 8 weeks) of:

Symptomatic gastroesophageal reflux disease (GERD/esophagitis) poorly responsive to customary treatment, usually including an adequate course of H_2 antagonist therapy.

Severe erosive esophagitis (grade 2 or above) diagnosed by endoscopy.

For severe erosive esophagitis or poorly responsive symptomatic GERD

New Losec®

(OMEPRAZOLE/MSD)

Pain Relief and Healing Beyond H_2 Blockade

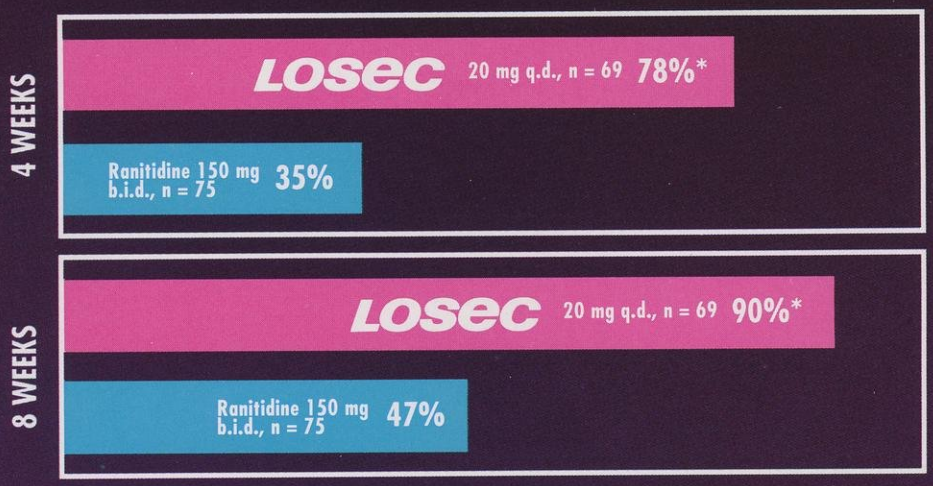
In clinical trials in patients with symptomatic esophagitis and endoscopically diagnosed erosive esophagitis

Complete Relief of Daytime and Nighttime Heartburn in More Patients

LOSEC® (Omeprazole, MSD) Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation. Please see Brief Summary of Prescribing Information on the last page of this advertisement.

Complete relief of heartburn in twice as many patients as ranitidine at 4 weeks*,[2]

90% of patients were completely relieved of heartburn with LOSEC at 8 weeks in a double-blind, multicenter study.



*Significantly different from ranitidine ($p \leq 0.01$)

[2] Data available from Merck Sharp & Dohme upon request

Clinically studied for over 7 years in more than 13,000 patients worldwide

Overall incidence and type of side effects were similar to ranitidine and placebo

Once-daily dosing: one 20-mg Delayed-Release Capsule before eating

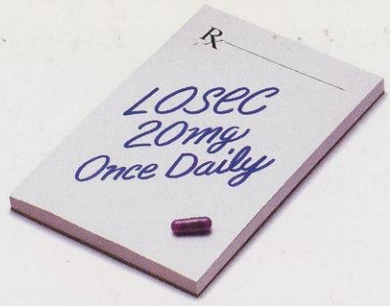
For severe erosive esophagitis or poorly responsive symptomatic GERD

New Losec®

(OMEPRAZOLE/MSD)

Pain Relief and Healing Beyond H_2 Blockade

New LOSEC® (OMEPRAZOLE|MSD)



CLINICAL PHARMACOLOGY

Mechanism of Action: Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2-histamine antagonistic properties but that suppress gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion, irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity: After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within 2 hours. Inhibition of secretion is about 50% of maximum at 24 hours, and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H^+/K^+ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after 4 days.

INDICATIONS AND USAGE

Gastroesophageal Reflux Disease (GERD):

Severe Erosive Esophagitis: LOSEC® (Omeprazole, MSD) Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of severe erosive esophagitis (grade 2 or above) which has been diagnosed by endoscopy.

Poorly Responsive Symptomatic GERD:

LOSEC Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of symptomatic gastroesophageal reflux disease (esophagitis) poorly responsive to customary medical treatment, usually including an adequate course of a histamine H_2-receptor antagonist.

The efficacy of LOSEC used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of severe or symptomatic GERD poorly responsive to customary medical treatment, additional 4-8 week courses of omeprazole may be considered. THE DRUG SHOULD NOT BE USED AS MAINTENANCE THERAPY (see Boxed WARNING).

Pathological Hypersecretory Conditions: LOSEC Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas, and systemic mastocytosis).

CONTRAINDICATIONS

LOSEC Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

WARNING

In long-term (2 year) studies in rats, omeprazole produced a dose-related increase in gastric carcinoid tumors (see PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairment of Fertility*). While available endoscopic evaluations and histologic examinations of biopsy specimens from human stomachs have not detected a risk from short-term exposure to LOSEC, further human data on the effect of sustained hypochlorhydria and hypergastrinemia are needed to rule out the possibility of an increased risk for the development of tumors in humans receiving long-term therapy with LOSEC. LOSEC should be prescribed only for the conditions, dosage, and duration described (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General: Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Information for Patients: LOSEC® (Omeprazole, MSD) Delayed-Release Capsules should be taken before eating. Patients should be cautioned that the LOSEC Delayed-Release Capsules should not be opened, chewed, or crushed and should be swallowed whole.

Drug Interactions: Omeprazole can prolong the elimination of diazepam, warfarin, and phenytoin, drugs that are metabolized by oxidation in the liver. Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with LOSEC. In clinical trials, antacids were used concomitantly with administration of LOSEC.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0, and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg/kg/day omeprazole (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% control). By the second year, the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay, and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose but with different (suboptimal) sampling times was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

Pregnancy: Pregnancy Category C: There are no adequate or well-controlled studies in pregnant women. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome, and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with LOSEC® (Omeprazole, MSD). Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably, or definitely related to the drug.

	Omeprazole (n=465)	Placebo (n=64)	Ranitidine (n=195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials are shown below, listed by body system. In many instances, the relationship to LOSEC was unclear. *Body as a Whole:* Fever, pain, fatigue, malaise, abdominal swelling. *Cardiovascular:* Chest pain or angina, tachycardia, bradycardia, palpitation, peripheral edema. *Digestive:* Elevated ALT (SGPT), elevated AST (SGOT), elevated γ-glutamyl transpeptidase, elevated alkaline phosphatase, elevated bilirubin (jaundice), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. *Metabolic/Nutritional:* Hypoglycemia, weight gain. *Musculoskeletal:* Muscle cramps, myalgia, joint pain, leg pain. *Nervous System/Psychiatric:* Dizziness, vertigo, insomnia, nervousness, apathy, somnolence, anxiety disorders, paresthesia, dream abnormalities, hemifacial dysesthesia. *Respiratory:* Epistaxis, pharyngeal pain. *Skin:* Rash, skin inflammation, urticaria, pruritus, alopecia, dry skin, hyperhidrosis. *Special Senses:* Tinnitus, taste perversion. *Urogenital:* Urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, glycosuria, hematuria, testicular pain. *Hematologic:* Agranulocytosis, pancytopenia, thrombocytopenia, neutropenia, anemia, leucocytosis.

The incidence of clinical adverse experiences in patients >65 years of age was similar to that in patients ≤65 years.

OVERDOSAGE

There is no experience to date with deliberate overdosage. Dosages of up to 360 mg/day have been well tolerated. No specific antidote is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

Severe Erosive Esophagitis or Poorly Responsive Gastroesophageal Reflux Disease (GERD): The recommended adult oral dose is 20 mg daily for 4 to 8 weeks (see INDICATIONS AND USAGE).

Pathological Hypersecretory Conditions: The dosage of LOSEC in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses.

No dosage adjustment is necessary for patients with renal impairment, hepatic dysfunction, or for the elderly.

HOW SUPPLIED

No. 3427– LOSEC Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst-colored capsules, coded MSD 727 on one side and LOSEC 20 on the other.

Storage: Store LOSEC Delayed-Release Capsules in a tight container protected from light and moisture. Store between 59° F and 86° F (15° C and 30° C).

For more detailed information, consult your MSD Representative or see Prescribing Information.

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
WEST POINT, PA 19486

Jointly manufactured by:

MSD MERCK SHARP & DOHME
Merck Sharp & Dohme
Division of Merck & Co., INC.
West Point, PA 19486
and
AB Astra Södertälje, Sweden

 J9LS03R(302)