SP 1

OTC Omeprazole Safety Assessment

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SP 2

OTC Omeprazole Has Minimal Risk

- Safety with prescription (Rx) use established
- OTC trial safety
- OTC risk potential managed by:
  - ***Dose***
  - ***Duration***
  - ***Instructions for seeking medical care***

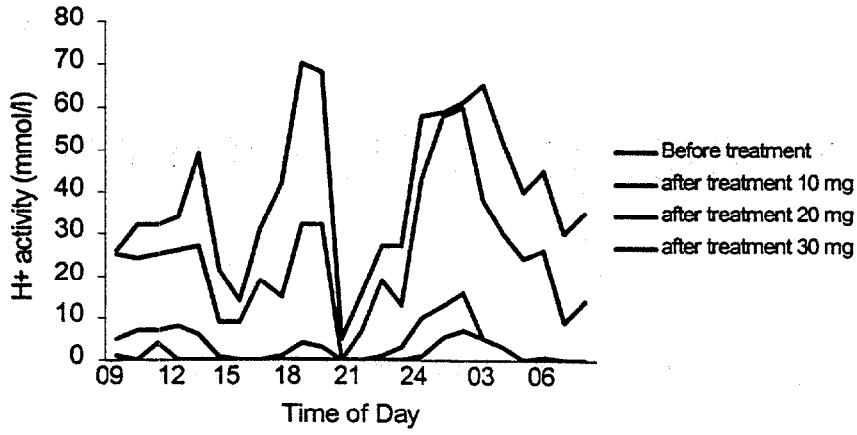
SP 3

Omeprazole Safety Assessment

1. *Potential effects due to acid suppression*
2. *Potential effects due to pharmacokinetics*
3. *General OTC safety considerations*
4. *Adverse event profile*

SP 4

24 Hour Gastric H^+ Activity



Adapted from Sharma B, Walt R, Pounder, R, et.al. Gut, 1984, 25, 957-964

Potential Effects: Acid Suppression SP 5

Absorption

- Achlorhydria is rare
- Effects on nutrient absorption
- No effects on nutrient depletion
- Reduced absorption of antifungals (labeled)
- Decreased potential for effects with OTC use

Potential Effects: Acid Suppression SP 6

Rebound Acid Hypersecretion

- Acid secretion normalizes 3–5 days after stopping omeprazole
- Hypersecretion after 40 mg / day x 8 weeks
- Inconsistent findings in shorter term studies
- Reversible effect
- OTC trials: symptoms no worse than placebo after cessation of omeprazole treatment
- Decreased potential for effects with OTC use

Potential Effects: Acid Suppression SP 7

Neoplastic Potential: Animal Studies

- Rats treated daily with high doses over their lifetime showed a dose related increase in carcinoid tumors
- Carcinoids in rats caused by disruption of gastric homeostatic mechanisms

Potential Effects: Acid Suppression SP 8

Neoplastic Potential: Humans

- Previously, Rx product had boxed warning based on findings of carcinoid tumors in rats
- Boxed warning removed from Rx label in 1995 based on long-term data in humans
- Findings in rat carcinogenicity studies have not been demonstrated to be relevant in humans

Potential Effects: Acid Suppression SP 9

Neoplastic Potential: Humans

- Increases in gastrin stabilize at 2 wks; normalizes < 2 weeks after stopping
- Rarely, gastrin > 4X ULN (8 – 15X in rats)
- ECL hyperplasia
- No ECL dysplasia, neoplasia or carcinoids
- GI epithelial neoplasia or malignancy not attributed to omeprazole

Potential Effects: Acid Suppression SP 10

Conclusions: OTC Omeprazole Safety

Minimal risks due to acid suppression

- Nutrient depletion not expected
- Potential effect on absorption of antifungals (labeled) probably decreased
- Rebound hypersecretion not likely
- GI neoplasia or malignancy not attributed to omeprazole

Potential Effects: Pharmacokinetics SP 11

Drug-Drug Metabolic Interactions

Cytochrome P450 enzymes

- CYP2C19
  - Diazepam (Phenytoin, R-Warfarin, Tolbutamide)
- CYP3A4 – minor pathway for omeprazole
- CYP1A2
- CYP2C9
- CYP2D6
- CYP2E1

Potential Effects: Pharmacokinetics SP 12

"Slow Metabolizers"

- 15–20% Asians lack CYP2C19
- $t_{1/2}$ longer than in "rapid metabolizers" (2.1 vs 0.7 hours)
- Area under the plasma concentration-time curve ~ 5-fold higher than "rapid metabolizers"
- No drug accumulation because elimination $t_{1/2}$ is short relative to dosing interval
- Labeled Rx dose in Japan is same as in US

Potential Effects: Pharmacokinetics SP 13

Hepatic or Renal Impairment

Hepatic impairment:

- $t_{1/2}$ longer than in "rapid metabolizers" (2.8 vs 0.7 hours)
- Area under plasma concentration-time curve ~ 7-fold higher than "rapid metabolizers"
- No drug accumulation

Renal impairment:

- Elimination of metabolites of omeprazole is less than in healthy subjects

Potential Effects: Pharmacokinetics SP 14

Conclusions: OTC Omeprazole Safety

- Minimal risks due to pharmacokinetic profile
- No clinically significant effects expected for:
  - Metabolic drug-drug interactions at CYP2C19
  - "Slow metabolizers"
  - Hepatically impaired
  - Renally impaired
- Dose adjustment not necessary
- Decreased potential for effects with OTC use

SP 15

General OTC Safety Considerations

- Pediatric and geriatric use
- Use during pregnancy
- Misuse potential
  - Overdose
  - Abuse
  - Chronic use

General OTC Safety Considerations

SP 16

Pediatric and Geriatric Use

- No safety issues in 0–16 year olds in Rx clinical trials or post-marketing
- Proposed label indicates use is for adults age 18 years and older
- Hepatic, renal function reduced in elderly, but no difference in AE profile

General OTC Safety Considerations SP 17

Use During Pregnancy

- No clinical trials in pregnant women
- Post-marketing reports and epidemiologic studies evaluating exposures to omeprazole during pregnancy were submitted to FDA in supplemental NDA for Rx omeprazole
- No increased risk of adverse pregnancy outcome demonstrated

General OTC Safety Considerations SP 18

Misuse Potential: Overdose

- OD up to 900 mg with no serious outcome
  - 2 deaths associated with multiple drugs
- Transient symptoms:
  - confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth
- AAPCC: reports in children < 6 yrs classified as "unintentional" most common
- Label instructions

General OTC Safety Considerations SP 19

Misuse Potential: Drug Abuse

- No evidence for omeprazole abuse
- No evidence for omeprazole to potentiate effects of drugs of abuse
- No evidence for omeprazole to potentiate effects of ethanol
  - No effect on hepatic CYP2E1 isoenzyme
  - No effect on gastric alcohol dehydrogenase

General OTC Safety Considerations SP 20

Misuse Potential: Chronic Use

- Not likely with alarm symptoms (labeled)
  - Dysphagia (trouble swallowing food)
  - Unexplained weight loss
  - GI bleeding (including anemia)
  - Wheezing chronic cough
  - Persistent symptoms
- Possible with responders who do not seek medical advice (despite label warning)

General OTC Safety Considerations SP 21

Chronic Use Potential in Responders

- Possible non-neoplastic upper GI condition
  - Reflux, dyspepsia
  - Erosions, ulcers
- Possible upper GI malignancies
- Possible upper GI conditions with risk of malignancy

General OTC Safety Considerations SP 22

Chronic Use Potential in Responders

Possible upper GI malignancy (esophagus, stomach)

- Different symptoms (e.g., dysphagia, nausea, vomiting, early satiety)
- Often present at first presentation for medical care
- Unusual in endoscoped populations

Chronic Use Potential in Responders

Possible upper GI conditions with risk of malignancy

- Barrett's esophagus (GERD complication)
  - Common, but rare progression to malignancy
  - Difficult to effectively manage risk in population with spectrum of heartburn to malignancy

Conclusions: OTC Omeprazole Safety

Minimal risks with OTC use

- No safety issues in children and elders
- Overdose: non-fatal, transient effects
- No abuse potential
- Chronic use in responders is possible (despite label warnings)
- OTC dose less effective than Rx doses for heartburn control in GERD patients

SP 25

Adverse Event Profile of Omeprazole

Rx clinical trials (n = 5,757 patients)

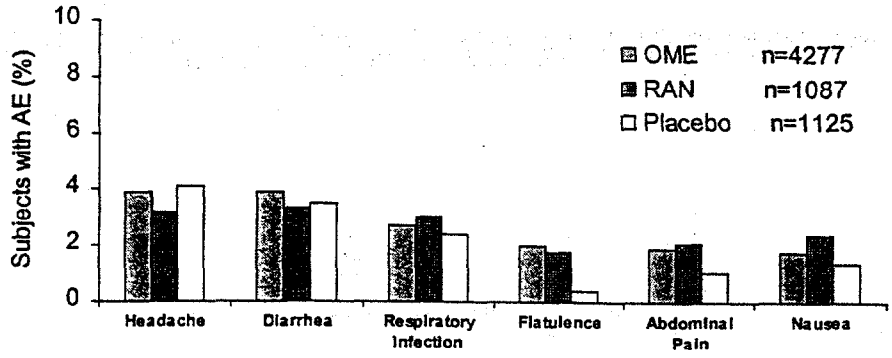
OTC clinical trials (n = 8,670 subjects)

Post-Marketing
(380 million prescriptions)

SP 26

Adverse Event Profile

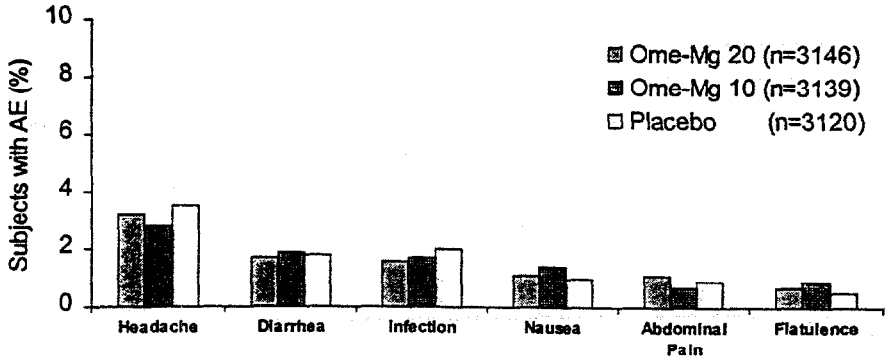
Most Common Adverse Events:
Controlled Rx Trials in Reflux Disease up to 12 Weeks



SP 27

Adverse Event Profile

Most Common Adverse Events:
Controlled OTC Trials up to 2 Weeks



SP 28

Adverse Event Profile

Serious Adverse Events Worldwide Post-Marketing

Period	*90–91*	*92–93*	*94–95*	*96–97*	*98–99*
Rx (millions)	23	52	74	102	135
Number of SAEs	455	733	1141	1112	1556
Incidence / Million Rx	19.8	14.1	15.4	10.9	11.5

Adverse Event Profile in Rx Post-Marketing SP 29

Serious Adverse Events: First 5 Years

Product	*Reported SAEs per million Rx*
Omeprazole	16
Ranitidine	20
Nizatidine	33
Famotidine	47

Adverse Event Profile in Rx Post-Marketing SP 30

Most Frequent Serious Adverse Events

Reported Term	*Incidence per Million* 1990–1994	1995–1999
Thrombocytopenia	0.4	0.4
Interaction	0.3	0.2
Fever	0.3	0.1
Hepatitis	0.2	0.2
Interstitial Nephritis	0.2	0.2
Leukopenia	0.2	0.2
Pancytopenia	0.2	0.2
Agranulocytosis	0.1	0.2
Confusion	0.1	0.2
Hyponatremia	0.1	0.2

SP 31

Conclusions: OTC Omeprazole Safety

Minimal risks based on safety assessment

- AE profile similar to ranitidine or placebo in Rx and OTC clinical trials
- Excellent post-marketing safety profile
- AE profile not dose-dependent
- Serious AEs strictly attributable to omeprazole are reported rarely
- Increased risks with long term use not documented
- Wide margin of safety expected in OTC population

SP 32

Conclusions: OTC Omeprazole Safety

Recommendations based on safety assessment:

- ***Dose:*** 10 mg (Rx: 20–40 mg)
- ***Duration:*** up to 10 days (Rx: ≥ 4 weeks)
- ***Instructions for seeking medical care***