

Rabeprazole and Its Salts

Rabeprazole is a benzimidazole proton pump inhibiting drug used to treat “acid reflux disease” and other conditions, such as ulcers of the stomach and duodenum, Zollinger-Ellison Syndrome, and *Helicobacter pylori* infection. This drug, which may be administered as a salt (e.g., rabeprazole sodium), blocks gastric acid secretion in the stomach.

Rabeprazole and its salts passed the animal data screen, underwent a preliminary toxicological evaluation, and are being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Two-year gavage studies in rats
 - Male and female Sprague-Dawley rats: FDA (1999a, pp. 109-117); FDA (1999b, p. 13)
 - *Increased incidence of rare gastric stomach neuroendocrine cell (carcinoid) tumors (by pairwise comparison and trend) in females*
 - Male and female F344 rats: FDA (1999a, pp. 88-94)
 - *Increased incidences of adrenal medulla pheochromocytoma, testicular interstitial cell tumors, and monocytic leukemia (each by pairwise comparison) in males*
 - *Increased incidence of pituitary tumors (by pairwise comparison) in females*
- Long-term studies gavage in mice
 - 88-week study in male CD-1 mice: FDA (1999a, pp. 84-87); FDA (1999b, p. 13)
 - *Increased incidence of pulmonary adenoma (by pairwise comparison with vehicle controls, but not with cage controls)*
 - Two-year study in female CD-1 mice: FDA (1999a, pp.84-87); FDA (1999b, p. 13)
 - *No treatment-related tumor findings*

Other relevant data

- Genotoxicity: FDA (1999a, pp. 132-155); FDA (1999b, p. 13)
 - Reverse mutations in *S. typhimurium* (positive and negative) and *E. coli* (positive and negative)

- Forward mutations in Chinese hamster ovary cells and mouse lymphoma L5178Y/TK^{+/-} cells (*positive*)
 - Chromosome aberrations in Chinese hamster lung cells (*negative*)
 - *In vivo* mouse micronuclei (*negative*)
 - Unscheduled DNA synthesis in rat hepatocytes *in vitro* and *in vivo* (*negative*)
- Genotoxicity of five rabeprazole metabolites: FDA (1999a, pp. 139-144); FDA (1999b, p. 13)
 - Demethylated metabolite and carboxylic acid metabolite
 - Mutations in *S. typhimurium* (*positive*)
 - Three other metabolites
 - Mutations in *S. typhimurium* (*negative*)
- Mechanistic considerations regarding neuroendocrine tumors of the stomach: Poynter and Selway (1991); Powers *et al.* (1995)
- Structure activity considerations
 - Similarity with other proton pump inhibitors, including pantoprazole and omeprazole, which also induce tumors in animals.
 - Omeprazole, pantoprazole and rabeprazole all induce neuroendocrine cell tumors in the gastric fundus in rats.

References¹

Food and Drug Administration (FDA, 1999a). Aciphex /Rabeprazole Sodium: Pharmacology reviews. Submitted by Eisai Inc. New Drug Application (NDA) # **020-973**. Center for Drug Evaluation and Research, Department of Health and Human Services.

Food and Drug Administration (FDA, 1999b). Aciphex (Rabeprazole Sodium) Delayed Release Tablets. New Drug Application (NDA) # **020-973**. Annotated package insert. Submitted by Eisai Inc. Center for Drug Evaluation and Research. Department of Health and Human Services.

Powers RE, Lawton GP, Modlin IM (1995). Genotoxicity, carcinogenicity and acid-suppressing medications. *Pharmac Ther* **65**:303-317.

Poynter D, Selway SAM (1991). Neuroendocrine cell hyperplasia and neuroendocrine carcinoma of the rodent fundic stomach. *Mutat Res* **248**:303-319.

¹ Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.