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<sup>+</sup>/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)


- 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.

References<sup>1</sup>


<sup>1</sup> 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.