Pantoprazole and Its Salts

Pantoprazole is a benzimidazole proton pump-inhibiting drug used to treat "acid reflux disease." This drug, which may be administered as a salt (e.g. pantoprazole sodium), blocks gastric acid secretion in the stomach.

Pantoprazole 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 studies

- Two-year gavage studies in rats
  - Male and female Sprague-Dawley (SD) rats: FDA (2000b, pp. 181-183, 186-193); FDA (2000a, pp. 24-26)
    - *Increased incidences of forestomach squamous cell tumors (trend), and rare gastric stomach neuroendocrine cell tumors, hepatocellular tumors, and thyroid follicular cell tumors (each by pairwise comparison and trend), and additional rare stomach tumors (chief cell adenocarcinoma, adenomatous polyps) in females*
    - *Increased incidence of forestomach squamous cell tumors, rare gastric stomach neuroendocrine cell tumors, hepatocellular tumors, and thyroid follicular cell tumors (each by pairwise comparison and trend), and additional rare gastrointestinal tumors (adenocarcinoma of duodenum, adenomatous polyps of stomach fundus) in males*
  - Male and female F344 rats: FDA (2000a, pp. 24-26); FDA (2000b, pp. 1-3 of part 5, pp. 196-197)
    - *Increased incidence of rare gastric stomach neuroendocrine cell tumors (by pairwise comparison and trend) in females*
    - *Increased incidence of rare gastric stomach neuroendocrine cell tumors (by pairwise comparison and trend) in males*

- 12-month oral dosing plus 9-month recovery period studies in rats
  - Male and female SD rats: FDA (2001, p. 22)
    - *Rare malignant gastric stomach neuroendocrine cell tumor in one out of 11 treated female rats*

- Two-year gavage studies in mice
  - Male and female B6C3F$_1$ mice: FDA (2000b, pp. 172, 173, 178,

179)
    - *Increased incidence of hepatocellular tumors (by pairwise comparison and trend) in females*

- Transgenic mouse studies
  - 26-week gavage studies in male and female transgenic p53(+/-) mice: PDR (2005)
    - *No treatment-related tumor findings*

- Tumor promotion studies in rats
  - Male and female SD rats received N-methyl-N-nitroso–guanidine in drinking water for three months (tumor initiation), followed by promotion with pantoprazole (oral gavage for 52 weeks): FDA (2000b, pp. 204-210)
    - *Apparent promoting activity in females, based on increased incidence of glandular stomach adenocarcinoma (antral region)*
  - Male and female SD rats received four weekly intravenous injections of N-nitroso-N-methylurea (tumor intiation), followed by two weeks with no treatment, and then promotion with pantoprazole (oral gavage for 52 weeks): FDA (2000b, pp. 210-218)
    - *Inconclusive findings*

Other relevant data

- Genotoxicity
  - *In vitro* genotoxicity tests: FDA (2001, p. 31); FDA (2000b, pp. 231-247); PDR (2005)
    - Positive responses in the following tests:
      - Chinese hamster ovary cell *HGPRT* forward mutations
      - human lymphocyte chromosomal aberrations (CA)
    - Negative responses in the following tests:
      - *Salmonella typhimurium* and *Escherichia coli* reverse mutation*s*
      - AS52/GPT mammalian cell forward mutations
      - Mouse lymphoma L5178Y cell *Tk* mutations
      - Rat hepatocyte unscheduled DNA synthesis
      - Malignant transformation of mouse C3H fibroblasts and Syrian hamster embryo cells
  - *In vivo* genotoxicity tests: FDA (2001, p. 31); FDA (2000b, pp. 231-253)
    - Rat liver DNA covalent binding and DNA adduct formation (*positive*)
    - Mouse bone marrow micronucleus (MN)(*positive and negative*)
    - Rat bone marrow CA (*negative*)

- Genotoxicity of the thiol metabolite of pantoprazole: FDA (2000b, pp. 255-260, p. 338)
    - *In vivo* mouse bone marrow MN test (*positive and negative)*
    - *Salmonella typhimurium* reverse mutations*(negative)*
    - Malignant transformation of mouse C3H fibroblasts and Syrian hamster embryo cells (*negative*)

- Mechanistic considerations regarding neuroendocrine tumors of the stomach: Poynter and Selway (1991); Powers *et al*. (1995)

- Structure activity considerations: FDA (2001, pp. 27-29)
    - Similarity with other benzimidazole proton pump inhibitors, including omeprazole and rabeprozole, which also induce tumors in animals
    - Pantoprazole, omeprazole and rabeprozole all induce neuroendocrine cell tumors in the gastric fundus in rats

References[1]

Food and Drug Administration (FDA, 2000a). June 25, 1999. Memorandum in Pharmacology Reviews: PROTONIX™ -- Pantoprazole Sodium Tablets – Rat carcinogenicity studies – Consultation from contracted pathologists – labeling changes . New Drug Application (NDA) #20,987. Department of Health and Human Services, FDA Center for Drug Evaluation and Research. (link: www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20987_Protonix.cfm).

Food and Drug Administration (FDA, 2000b). Protonix (Pantoprazole Sodium) Delayed-Release Tablets: Pharmacology Reviews. New Drug Application (NDA) #20,987. Department of Health and Human Services, Public Health Service. FDA Center for Drug Evaluation and Research. (Web link: www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20987_Protonix.cfm).

Food and Drug Administration (FDA, 2001). April 30, 1999. Pharmacology Reviews: Review and Evaluation of Pharmacology and Toxicology Data. New Drug Application (NDA) #20,988. Department of Health and Human Services, Public Health Service. FDA Center for Drug Evaluation and Research.

Physicians' Drug Reference (PDR, 2005). Pantoprazole. From 2005 Thomson PDR® Electronic Library. Pages 3389-3391. Published by Physicians' Desk Reference 59th edition.

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. *Mut 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.