Omeprazole and Its Salts

Omeprazole is a proton pump-inhibiting drug available either as a prescription medication (e.g., Prilosec®), or over-the-counter to treat "acid reflux disease." It is a benzimidazole compound. This drug, which may be administered as a salt (e.g., omeprazole magnesium), blocks gastric acid secretion in the stomach. There is widespread exposure to people who take this drug.

Omeprazole 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

- Case reports
  - *Esophageal cancer*: Cary *et al*. (1993)
  - *Gastric carcinoid tumor*: Dawson and Manson (2000); Daniels (2001)

Animal carcinogenicity studies

- Long-term studies in rats
  - Two-year gavage studies in male and female Sprague-Dawley rats: Havu (1986)
    - *Increased incidence of rare gastric stomach neuroendocrine cell tumors in rats of both sexes*
  - Two-year studies in male and female rats (strain not specified): FDA (2005, under "Carcinogenesis, Mutagenesis, Impairment of Fertility")
    - *Increased incidence of rare gastric stomach neuroendocrine tumors in rats of both sexes*
  - Female rats (one-year treatment period + one year observation): FDA (2005)
    - *No treatment-related tumor findings*
  - One-year studies in male and female Sprague Dawley rats: FDA (2005)
    - *Brain astrocytomas found in some male rats*

- Long-term studies in mice
  - 78-week studies in male and female CD-1 mice: Havu (1986)
    - *No treatment related tumor findings*

- Transgenic mouse studies
  - 26-week transgenic p53(+/-) mouse study: FDA (2005)
    - *No treatment-related tumor findings*

Other relevant data

- Genotoxicity
    - Binding to rat DNA *in vivo*: Phillips *et al.* (1992)
    - Reviews: Powers *et al*. (1995, pp. 311-312), FDA (2005, under "Carcinogenesis, Mutagenesis, Impairment of Fertility")

- Mechanistic considerations regarding neuroendocrine tumors of the stomach: Diaz *et al*. (1990); Poynter and Selway (1991); Ryberg *et al*. (1989); Powers *et al*. (1995, pp. 312-313)

- Structure activity considerations
    - Similarity with other benzimidazole proton pump inhibitors, including pantoprazole and rabeprozole, which also induce tumors in animals.
    - Omeprazole, pantoprazole and rabeprozole all induce rare gastric stomach neuroendocrine cell tumors in the gastric fundus in rats.

Review

- FDA (2005)

References[1]

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Dawson R, Manson JM (2000). Omeprazole in oesophageal reflux disease. *Lancet* **356**:1770-1771.

Diaz D, Fabre I, Daujat M, Saint Aubert B, Bories P, Michel H, Maurel P. (1990). Omeprazole is an aryl hydrocarbon-like inducer of human hepatic cytochrome P450. *Gastroenterology* **99**:737-747.

Food and Drug Administration (FDA, 2005). Label for Prilosec (omeprazole) delayed-release capsules. New Drug Application (NDA) 19-810. Revised July 2005.

[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.

Havu N (1986). Enterochromaffin-like carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. *Digestion* **35**(Suppl 1):42-55.

Phillips D, Hewer A, Osborne MR (1992). Interaction of omeprazole with DNA in rat tissues. *Mutagenesis* **7**(4):277-283.

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. *Mutation Res* **248**:303-319.

Ryberg B, Bishop AE, Bloom SR, Carlsson E, Hakanson R, Larsson H, Mattsson H, Polak JM, Sundler F (1989). Omeprazole and rantidine, antisecretagogues with different modes of action, are equally effective in causing hyperplasia of enterochromaffin-like cells in rat stomach. *Regulatory Peptides* **25**:235-246.