Clomiphene and Its Salts

Clomiphene and its salts are widely prescribed as pharmaceutical agents to treat infertility and induce ovulation in women, and to treat oligospermia (low sperm count) in men. Clomiphene is a selective estrogen receptor modulator.

Clomiphene and its salts passed the human 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

- Cohort Studies
    - *Increased incidence of breast cancer associated with clomiphene*
    - *Increased risk of uterine cancer, malignant melanoma, and cancer at any site associated with clomiphene*
    - *Increased risk of borderline ovarian tumors (a subset of epithelial ovarian tumors) associated with clomiphene treatment for ovulatory dysfunction*
    - *Increased risk of uterine cancer associated with clomiphene*
    - *Increased risk of thyroid cancer associated with clomiphene*
    - *Increased risk of uterine cancer associated with clomiphene*

- Case-cohort study
  - Ovarian cancer cases in a cohort of women evaluated for infertility in Seattle, 1974-1985: Rossing et al. (1994)
    - *Increased risk of ovarian cancer associated with clomiphene*
• Case-control study
    ▪ No increased risk of ovarian cancer associated with clomiphene

• Meta-analyses of case-control studies of ovarian cancer
  o Invasive epithelial ovarian cancer: Whittemore et al. (1992)
    ▪ Increased risk associated with use of fertility drugs
  o Epithelial ovarian tumors of low malignant potential: Harris et al. (1992)
    ▪ Increased risk associated with use of fertility drugs

• Case Reports
  o Ovarian cancer in users of fertility drugs: Spirtas et al. (1993)
  o Ovarian cancer in user of clomiphene: IARC (1979, p. 558)
  o Breast cancer in users of clomiphene: IARC (1979, p. 558)
  o Testicular cancer in users of clomiphene: IARC (1979, p. 558); IARC (1987)
  o Hepatoblastoma in female infant exposed to clomiphene in utero: IARC (1987)
  o Liver adenoma in user of clomiphene: IARC (1987)

Animal carcinogenicity data

• Neonatal rat subcutaneous injection study
  o Female Sprague-Dawley rats (single s.c. injection on day 1 of life, observed for 100 days): Clark and McCormack (1977)
    ▪ Occurrence of hilus-cell tumors of ovary and tumors of uterus

Other relevant data

• Genotoxicity
  o Rat in vivo bone marrow micronuclei assay (positive): Duran et al. (2006)
  o Review: IARC (1987)
    ▪ Mouse in vivo bone marrow micronuclei and chromosomal aberration assays (negative)
  o Review: Van Gompel et al. (2005, p. 451, 453)
    ▪ Salmonella reverse mutation assay (positive)
    ▪ In vitro chromosome aberration or micronucleus assays (positive and negative)
    ▪ GreenScreen (yeast) assay for genotoxicity (positive)
• Endocrine system effects
  o Estrogenic and anti-estrogenic activity: IARC (1979)

• Structure activity considerations
  o Structurally similar to another selective estrogen receptor modulator, tamoxifen, which is a Proposition 65 and IARC Group 1 carcinogen.

Reviews

• IARC (1979; 1987)

References


---

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.


