

## 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
  - Historical prospective cohort study of women treated for infertility in Sweden, 1961-1976: Orgéas *et al.* (2009)
    - *Increased incidence of breast cancer associated with clomiphene*
  - Population-based historical cohort study of women in the Jerusalem Perinatal Study who gave birth in 1974-1976: Calderon-Margalit *et al.* (2009)
    - *Increased risk of uterine cancer, malignant melanoma, and cancer at any site associated with clomiphene*
  - Historical cohort study of women assessed and treated for infertility and infertility-associated disorders in Sweden, 1961-1975: Sanner *et al.* (2009)
    - *Increased risk of borderline ovarian tumors (a subset of epithelial ovarian tumors) associated with clomiphene treatment for ovulatory dysfunction*
  - Historical cohort study of women evaluated for infertility treatment in London, 1963-1999: dos Santos Silva *et al.* (2009)
    - *Increased risk of uterine cancer associated with clomiphene*
  - Historical cohort study of women with infertility problems referred to Danish fertility clinics, 1963-1998: Hannibal *et al.* (2008)
    - *Increased risk of thyroid cancer associated with clomiphene*
  - Retrospective cohort study of U.S. women evaluated for infertility, 1965–1988: Althuis *et al.* (2005)
    - *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
  - Population-based study of ovarian cancer in U.S. women: Rossing *et al.* (2004)
    - *No increased risk of ovarian cancer associated with clomiphene*
- Meta-analyses of case-control studies of ovarian cancer
  - Invasive epithelial ovarian cancer: Whittemore *et al.* (1992)
    - *Increased risk associated with use of fertility drugs*
  - Epithelial ovarian tumors of low malignant potential: Harris *et al.* (1992)
    - *Increased risk associated with use of fertility drugs*
- Case Reports
  - Ovarian cancer in users of fertility drugs: Spirtas *et al.* (1993)
  - Ovarian cancer in user of clomiphene: IARC (1979, p. 558)
  - Breast cancer in users of clomiphene: IARC (1979, p. 558)
  - Testicular cancer in users of clomiphene: IARC (1979, p. 558); IARC (1987)
  - Hepatoblastoma in female infant exposed to clomiphene *in utero*: IARC (1987)
  - Liver adenoma in user of clomiphene: IARC (1987)

### **Animal carcinogenicity data**

- Neonatal rat subcutaneous injection study
  - 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
  - Rat *in vivo* bone marrow micronuclei assay (*positive*): Duran *et al.* (2006)
  - Review: IARC (1987)
    - Mouse *in vivo* bone marrow micronuclei and chromosomal aberration assays (*negative*)
  - 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
  - Estrogenic and anti-estrogenic activity: IARC (1979)
- Structure activity considerations
  - Structurally similar to another selective estrogen receptor modulator, tamoxifen, which is a Proposition 65 and IARC Group 1 carcinogen.

## Reviews

- IARC (1979; 1987)

## References<sup>1</sup>

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<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.

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