



WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

## Volume 66 Some Pharmaceutical Drugs

### Summary of Data Reported and Evaluation

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#### **Benzodiazepines and related compounds and phenytoin**

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# DIAZEPAM (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 37)

**CAS No.:** 439-14-5

**Chem. Abstr. Name:** 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Diazepam is the most widely used of the benzodiazepine pharmaceuticals. Produced since the 1960s, it is prescribed for the treatment of anxiety and as a sedative, muscle relaxant, and anticonvulsant.

### 5.2 Human carcinogenicity data

Studies investigating unspecified hypnotics or tranquilizers as well as diazepam specifically have been included in this monograph because of the dominance of this benzodiazepine among those prescribed. The risk for a variety of cancers, especially of the breast, associated with diazepam use has been investigated in two cohort studies and in six distinct and three related case-control studies.

In none of the two cohort or five case-control studies on benzodiazepine or diazepam use in relation to breast cancer was a positive association found. One case-control study of ovarian cancer reported an increased risk for diazepam use, that was not confirmed by another study. This latter study reported no association between diazepam use and the risk of several other types of cancer.

### 5.3 Animal carcinogenicity data

Diazepam was tested for carcinogenicity in one experiment in mice, in one experiment in rats and in one experiment in hamsters by oral administration in the diet and also in one limited study in gerbils. An increase in the incidence of hepatocellular tumours occurred in male mice. No significant increase in the incidence of tumours was observed in rats, hamsters or gerbils.

In one study in mice, oral administration of diazepam enhanced the occurrence of hepatocellular tumours induced by *N*-nitrosodiethylamine. In two studies in rats initiated with 2-acetylaminofluorene or 3'-methyl-4-(dimethylamino)azobenzene, there was no promoting effect of diazepam. In gerbils initiated with *N*-nitrosodiethylamine, simultaneous administration of diazepam decreased the incidence of cholangiocarcinomas.

### 5.4 Other relevant data

Diazepam is absorbed rapidly and extensively in humans. A 30-fold range of peak plasma concentrations is obtained when the same dose is given to different subjects. Diazepam is metabolized initially to *N*-desmethyldiazepam (nordiazepam) and temazepam, both of which may be converted to oxazepam. Diazepam clearance shows marked inter-subject variability. The mean elimination half-life is about 32 h.

There is wide inter-species variability in diazepam metabolism. While formation of *N*-desmethyldiazepam and temazepam occurs to some extent in all species studied, hydroxylation in the 5-phenyl ring is the major pathway in rats.

Diazepam has low acute and chronic toxicity for humans at therapeutic concentrations. The main adverse effects of chronic administration are psychological and physical dependence and withdrawal phenomena. Specific organ toxicity of diazepam to humans has not been observed.

The acute toxicity of diazepam to experimental animals can be considered as low. In subchronic toxicity assays in dogs, high doses of diazepam induced mild toxic effects in the blood, liver and gonads, while in rats, slight chemical-related histopathological changes were observed in the kidneys and thyroid gland. The effects of diazepam on the immune system have been investigated mainly in in-vitro experiments with conflicting results: both stimulatory and inhibitory effects have been demonstrated. There are no data on immunosuppressing or immunomodulating effects in humans.

In several cultured cell systems, diazepam inhibits cell proliferation.

No consistent association between orofacial clefts and diazepam has been identified in humans. No increase in the prevalence at birth of congenital abnormalities has been found associated with attempted maternal suicide using high doses of diazepam, in some instances during the first trimester. While excesses of anomalies associated with regular psychotherapeutic benzodiazepine use have been observed, the types of developmental defects involved have not been consistent between studies.

High doses of diazepam induce cleft palate in mice, but not in rats. In hamsters, exencephaly and limb defects are seen, as well as cleft palate.

In general, diazepam did not induce gene or chromosomal mutations in bacteria, yeast or cultured mammalian cells. In cultured mammalian cells, it induced micronuclei and aneuploidy, and inhibited gap-junctional intercellular communication. There are contradictory results on the induction of gene mutation in bacteria by the urinary metabolites of treated mice.

In general, diazepam did not induce micronuclei, chromosomal aberrations, aneuploidy, c-mitoses or polyploidy in bone marrow of mice *in vivo*. In rats *in vivo*, neither chromosomal aberrations in bone marrow, nor DNA strand breaks or alkali-labile sites in liver were found. In mouse spermatocytes, but not in oocytes, diazepam induced aneuploidy.

#### *Mechanistic considerations*

Diazepam does not cause gene mutations or chromosomal aberrations. One of its metabolites, oxazepam, increased the incidence of liver tumours (benign and malignant) (see Monograph on oxazepam). However, it is not clear that levels of oxazepam sufficient to induce hepatic effects are achieved in mice treated with diazepam.

## **5.5 Evaluation**

There is *evidence suggesting lack of carcinogenicity* of diazepam to the breast and inadequate evidence for carcinogenicity at other sites in humans.

There is *inadequate evidence* in experimental animals for the carcinogenicity of diazepam.

### **Overall evaluation**

Diazepam is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

## Synonyms

- Aliseum
- Alupram
- Amiprol
- An-Ding
- Anksiyolin
- Ansiolin
- Ansiolisina
- Antenex
- Apaurin
- Apozepam
- Armonil
- Assival
- Atensine
- Atilen
- Avex
- Bensedin
- Betapam
- Bialzepam
- Calmocitene
- Calmpose
- Canazepam
- Cercine
- Cereglart
- Condition
- Deprestop
- Diacepam
- Diaceplex
- Dialag
- Dialar
- Diapam
- Diatran
- Diaz
- Diazem
- Diazemuls
- Diazepam-Lipuro
- Diazidem
- Dienpax
- Dipam
- Dizac
- Dizam
- Domalium
- Doval
- Drenian
- Ducene
- Duksen
- Duxen
- E-Pam
- Eridan
- Erital
- Eurosan
- Euphorin
- Evacalm
- Faustan
- Gewacalm

- Hexalid
- Horizon
- Kiatrium
- LA 111
- Lamra
- Lembrol
- Levium
- Liberetas
- Lizan
- Lorinon
- Mandrozep
- Methyldiazepinone
- Metil Gobanal
- Méval
- Morosan
- Néo-Calme
- Neosorex
- Nervium
- Neurolytril
- Noan
- Notense
- Novazam
- Novodipam
- Paceum
- Pacipam
- Pacitran
- Pax
- Paxate
- Paxel
- Pro-Pam
- Psychopax
- Q-Pam
- Quétilnil
- Quievita
- Relaminal
- Relanium
- Relivan
- Remedium
- Renborin
- Rival
- Ro 5-2807
- Saromet
- Scriptopam
- Sedapam
- Sedipam
- Seduxen
- Serenak
- Serenamin
- Serenzin
- Servizepam
- Setonil
- Sibazon
- Sibazone
- Sico Relax
- Solis
- Somasedan
- Sonacon
- Stesolid
- Stesolin

- Stress-Pam
- Tensium
- Tensopam
- Tiromne
- Tranimul
- Tranqase
- Tranquirit
- Tranquo-Puren
- Tranquo-Tablinen
- Umbrium
- Unisedil
- Valaxona
- ValCaps
- Valclair
- Valeo
- Valibrin
- Valiquid
- Valitran
- Valium
- Valrelease
- Vatran
- Vival
- Vivol
- Wy 3467
- Zepam
- Zetran

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# DOXEFAZEPAM (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 97)

**CAS No.:** 40762-15-0

**Chem. Abstr. Name:** 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-3-hydroxy-1-(2-hydroxyethyl)-2H-1,4-benzodiazepin-2-one

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Doxefazepam is a benzodiazepine hypnotic that was used in the past to a limited extent in the short-term management of insomnia.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

Doxefazepam was tested for carcinogenicity in one experiment in rats by oral administration in the diet. A slight dose-related increase in the incidence of hepatocellular adenomas was observed.

### 5.4 Other relevant data

Doxefazepam disposition has received little study. In humans, the drug was eliminated in urine mainly as a conjugate, and two oxidative metabolites were identified. The elimination half-life was 3-4 h. No satisfactory metabolism studies in animals were available. Data on human toxicity were not available. In rats treated with 60 mg/kg bw per day for 26 weeks, increased liver weights were reported without other clinical, haematological or histopathological signs of toxicity. In a single study, doxefazepam was not teratogenic in rats or rabbits. The few data available on genetic effects were negative.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of doxefazepam.

There is *limited evidence* in experimental animals for the carcinogenicity of doxefazepam.

### Overall evaluation

Doxefazepam is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

### Synonyms

- *N*-1-Hydroxyethyl-3-hydroxyflurazepam
- Doxans
- SAS 643

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# ESTAZOLAM (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 105)

**CAS No.:** 29975-16-4

**Chem. Abstr. Name:** 8-Chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Estazolam is a triazolobenzodiazepine used since the 1970s for short-term management of insomnia.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

Estazolam was tested for carcinogenicity in one experiment in mice and one experiment in rats by oral administration in the diet. No increase in the incidence of tumours was found.

### 5.4 Other relevant data

Estazolam is rapidly and almost completely absorbed in humans. It is extensively metabolized to at least 11 metabolites and excreted mainly in the urine. The elimination half-life is 14-19 h. Metabolism is extensive in various animal species. Rabbits and dogs excrete the metabolites principally in urine, while in mice, rats and guinea-pigs the excretion is mainly in faeces. Some metabolites are species-specific. There were no data available on reproductive effects of estazolam. The data available on genetic effects were negative.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of estazolam.

There is *evidence suggesting a lack of carcinogenicity* in experimental animals for estazolam.

### Overall evaluation

Estazolam is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

### Synonyms

- A 47631
- Abbott 47631

- Bay k 4200
- Cannoc
- D 40TA
- Deprinocte
- Domnamid
- Esilgan
- Eurodin
- Hypnomat
- Julodin
- Kainever
- Nemurel
- Noctal
- Nuctalon
- ProSom
- Sedarest
- Somnatrol
- Tasedan
- U 33737

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# OXAZEPAM (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 115)

**CAS No.:** 604-75-1

**Chem. Abstr. Name:** 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Oxazepam is a benzodiazepine used extensively since the 1960s for the treatment of anxiety and insomnia and in the control of symptoms of alcohol withdrawal. It is a metabolite of diazepam, prazepam and temazepam, among the benzodiazepines considered in this volume.

### 5.2 Human carcinogenicity data

In one case-control study evaluating benzodiazepine use, subjects using oxazepam were included, but were too few to analyse as a separate category.

### 5.3 Animal carcinogenicity data

Oxazepam was tested for carcinogenicity in three experiments in two strains of mice by oral administration in the diet. Significant increases in the incidence of benign and malignant liver tumours were found in two of the studies. The incidence of an uncommon malignant liver tumour, hepatoblastoma, was also increased in one strain of mice. In the third study, an increased incidence of liver adenomas was found. In one of the studies, a small increase in the incidence of thyroid gland adenomas was observed in females of one strain of mice.

Oxazepam promoted liver tumour development in one two-stage model in mice and in one of three studies in rats.

### 5.4 Other relevant data

Oxazepam is rapidly and completely absorbed in humans and is largely eliminated in urine conjugated with glucuronic acid. The half-life averages 5-6 h.

Oxazepam is also extensively metabolized in animals. In some species (miniature swine), conjugation predominates, while in others (rats) oxidative metabolism is the major route.

Oxazepam has low acute and chronic toxicity for humans at therapeutic concentrations. The main adverse effects of chronic administration are psychological and physical dependence and withdrawal phenomena; specific organ toxicity of oxazepam to humans has not been observed.

The acute toxicity of oxazepam to experimental animals is also low. Short-term, high-dose administration of oxazepam to mice and rats resulted in increased liver weights. A transient increase in cell proliferation was observed in oxazepam-treated mice.

Perinatal death and neurodevelopmental retardation have been reported in the offspring of women who were

exposed to oxazepam during pregnancy (see the monograph on diazepam for further discussion relating to cleft palate). However, confounding factors could not be controlled adequately in these studies.

Malformations have been observed following high doses of oxazepam in mice, but not at moderate doses in this species or in rats or rabbits.

Oxazepam is inactive in most genetic toxicity assays, although it has been shown to cause micronuclei and neuploidy *in vitro* and to inhibit gap-junctional intercellular communication in human hepatoma cells *in vitro*. No data were available on humans.

#### *Mechanistic considerations*

There is no evidence that oxazepam interacts with DNA. Evidence of mutagenic activity is limited to aneuploidy in cell culture systems.

The induction of hepatocellular proliferation and hepatic cytochromes P450 by oxazepam was observed in mice at doses that were carcinogenic following long-term exposure. These adaptive effects are typical of several non-genotoxic compounds with promoting activity that are carcinogenic in mouse liver. Oxazepam has demonstrated promoting activity. Furthermore, the formation of hepatocellular tumours and hepatoblastomas by oxazepam does not involve the H-ras codon 61 pathway. Similarities have been observed between the hepatic effects of oxazepam and those of phenobarbital, which also promotes development of hepatocellular tumours in mice. Taken together, these data support the conclusion that liver tumours are produced in mice by a promoting mechanism.

The implications of these findings with respect to potential cancer risk of oxazepam exposure in humans are unclear. Specifically, information on the relevant effects of oxazepam in human groups or systems is not available. In general, the sensitivity of human liver to tumour formation, even if induction of cytochromes P450 and hepatocellular proliferation at levels comparable to those in mice were to occur, has not been established.

Levels of thyroid-stimulating hormone were increased in mice fed oxazepam at doses that induced adenomas and hyperplasia following long-term exposure. Sustained thyroid stimulation has been implicated as a mechanism of thyroid tumorigenesis in rodents.

## **5.5 Evaluation**

There is *inadequate evidence* in humans for the carcinogenicity of oxazepam.

There is *sufficient evidence* in experimental animals for the carcinogenicity of oxazepam.

### **Overall evaluation**

Oxazepam is *possibly carcinogenic to humans (Group 2B)*.

In making the overall evaluation, the Working Group took into account that:

- (i) uncertainty exists regarding the formation of mouse liver tumours by oxazepam as a relevant end-point for evaluation of carcinogenic risks to humans.
- (ii) appropriate mechanistic information in humans is lacking.

For definition of the italicized terms, see [Preamble Evaluation](#)

**Previous evaluation:** Suppl. 7 (1987) (p. 69)

## Synonyms

- Abboxapam
- Adumbran
- Alepam
- Alopam
- Antoderin
- Anxiolit
- Anxiolit retard
- Aplakil
- Aslapax
- Astress
- Azutranquil
- Benzotran
- Bonare
- Buxopax
- CB 8092
- Constantonin
- *N*-Desmethylemazepam
- Drimuel
- Droxacepam
- Durazepam
- Enidrel
- Hilong
- Iranil
- Isodin
- Lederpam
- Limbial
- Murelax
- Nesontil
- Neurofren
- Noctazepam
- Nortemazepam
- Novoxapam
- Nozepam
- Oxa
- Oxabenz
- Oxahexal
- Oxa-10 L.U.T.
- Oxanid
- Oxa-Puren
- Oxepam
- Oxpam
- Praxiten
- Propax
- Psicopax
- Psiquiwas
- Purata
- Quen
- Quilibrex
- Ro 5-6789
- Rondar
- Sedokin
- Serax
- Serenal
- Serenid
- Serepax
- Seresta
- Serpax

- Sigacalm
- Sobile
- Sobril
- Tarchomin
- Tazepam
- Uskan
- Vaben
- Wy 3498
- Zapex
- Zaxopam

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# PRAZEPAM (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 143)

**CAS No.:** 2955-38-6

**Chem. Abstr. Name:** 7-Chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Prazepam is a benzodiazepine used since the late 1970s for treatment of anxiety.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

Prazepam was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration in the diet. No significant increase in the incidence of tumours was found.

### 5.4 Other relevant data

Prazepam is rapidly and extensively absorbed in humans, but its plasma concentrations are low and of short duration as a consequence of its rapid conversion to *N*-desmethyldiazepam and, to a lesser extent, 3-hydroxyprazepam. The elimination half-life is about 1 h.

Prazepam is extensively metabolized in rats, and the primary metabolite *N*-desmethyldiazepam is further converted to at least eight derivatives. Oxazepam is the major metabolite in dogs and monkeys. There is no evidence to suggest that prazepam causes any organ toxicity other than effects associated with its pharmacological action on the central nervous system in humans or experimental animals.

There are no data on the teratogenicity of prazepam in humans. In one study, prazepam increased the incidence of short tail and hydrops fetalis (subcutaneous oedema) in rats. In a single study in the rabbit, it was not teratogenic.

The two available studies on genetic effects were negative.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of prazepam.

There is *inadequate evidence* in experimental animals for the carcinogenicity of prazepam.

### Overall evaluation

Prazepam is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

## Synonyms

- Centrax
- Demetrin
- Equipaz
- K 373
- Lysanxia
- Mono Demetrin
- Prazene
- Reapam
- Sedapran
- Settima
- Trepidam
- Verstran
- W-4020

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# RIPAZEPAM (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 157)

**CAS No.:** 26308-28-1

**Chem. Abstr. Name:** 1-Ethyl-4,6-dihydro-3-methyl-8-phenylpyrazolo[4,3-e][1,4]diazepin-5(1*H*)-one

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Ripazepam is a pyrazolodiazepine with anxiolytic properties which has never been marketed for human use.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

Ripazepam was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration in the diet. An increased incidence of benign liver tumours was found in male mice. No increase in the incidence of tumours was found in female mice or in rats of either sex.

### 5.4 Other relevant data

No data were available to the Working Group on the metabolism, toxicity, reproductive or genetic and related effects of ripazepam.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of ripazepam. There is *limited evidence* in experimental animals for the carcinogenicity of ripazepam.

### Overall evaluation

Ripazepam is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

### Synonym

- Pyrazapon

# TEMAZEPAM (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 161)

**CAS No:** 846-50-4

**Chem. Abstr. Name:** 7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Temazepam is a benzodiazepine prescribed widely since the 1970s for short-term management of insomnia. Temazepam is a minor metabolite of diazepam.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

Temazepam was tested for carcinogenicity in one experiment in mice and in one experiment in rats by oral administration in the diet. A slight increase in the incidence of liver adenomas was found in female mice.

### 5.4 Other relevant data

Temazepam is absorbed rapidly and completely in humans from appropriate oral formulations. It is eliminated mainly in urine as the glucuronide conjugate; oxazepam is a minor metabolite. The mean elimination half-life is about 10 h.

Conjugation and *N*-demethylation to oxazepam are the major metabolic pathways recognized in mice and dogs.

Chronic administration of pharmacological doses does not induce organ toxicity. Repeated-dose toxicity studies lasting up to six months did not reveal specific organ toxicity in dogs, rats or mice.

No data were available on teratogenic effects of temazepam.

Few data on genetic effects of temazepam were available. It did not produce DNA strand breaks in the livers of rats.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of temazepam.

There is *inadequate evidence* in experimental animals for the carcinogenicity of temazepam.

## Overall evaluation

Temazepam is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

## Synonyms

- Crisonar
- ER 115
- Euhypnos
- Euipnos
- Gelthix
- 3-Hydroxydiazepam
- K 3917
- Levaxene
- Levaxol
- Mabertin
- Methyloxazepam
- *N*-Methyloxazepam
- Neodorm SP
- Norkotral Tema
- Normison
- Oxydiazepam
- Perdorm
- Planum
- Pronervon
- Razepam
- Redupax Planpak
- Remestan
- Reposium
- Restoril
- Ro 5-5345
- Signopam
- Signopharm
- Temaz
- Temaze
- Temazep
- Temazin
- Tenox
- Tenso
- Texapam
- Veroqual
- Wy 3917
- Z-Pam

# PHENYTOIN (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 175)

**CAS No.:** 57-41-0

**Chem. Abstr. Name:** 5,5-Diphenyl-2,4-imidazolidinedione

**CAS No:** 630-93-3

**Chem. Abstr. Name:** 5,5-Diphenyl-2,4-imidazolidinedione, monosodium salt

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Phenytoin, often administered as its sodium salt, has been widely used since the 1930s as an anticonvulsant in the treatment of epilepsy and, to a lesser extent and more recently, in the treatment of certain cardiac arrhythmias.

### 5.2 Human carcinogenicity data

Many case reports have suggested that there may be a relationship between lymphomas and anticonvulsants, especially phenytoin. In a cohort study in Denmark of epileptic patients exposed to anticonvulsants, including phenytoin, there was an increase in overall cancer risk, attributable to an excess of brain and lung cancer. Nevertheless, brain tumours probably caused the seizure disorder; an evaluation of brain tumour risk over time showed that these tumours were unlikely to be drug-related.

Nested case-control studies based on the Danish cohort investigated in detail the influence of several treatments with anticonvulsants on the risk of cancers of the lung, bladder and liver and non-Hodgkin lymphoma. Anticonvulsant treatment with phenytoin was not associated with lung, bladder or liver cancer. There was an elevated risk for non-Hodgkin lymphoma associated with phenytoin use, but this was not significant.

Two case-control studies investigated the relationship between multiple myeloma and the use of phenytoin, among many other factors. One found no association between phenytoin use and a risk for multiple myeloma. The other study found a nonsignificantly elevated risk associated with the use of phenytoin. The power of both studies to assess an effect of phenytoin was low.

### 5.3 Animal carcinogenicity data

Phenytoin was tested for carcinogenicity by oral administration in three experiments in mice and in two experiments in rats. It was also tested by perinatal/adult exposure in one study in mice and rats and by intraperitoneal administration in one study in mice.

In one experiment in three strains of female mice, oral administration of the sodium salt of phenytoin was reported to increase the incidence of lymphomas. Oral administration to female mice in another study decreased the incidence of mammary gland adenocarcinomas, leukaemias and polyps of the endometrium; in a further study, the incidence of hepatocellular tumours was reduced in males. Oral administration to rats did not increase the incidence of tumours in two studies.

In the experiment using combinations of adult and perinatal exposure, adult exposure resulted in a dose-dependent increase in the incidence of hepatocellular tumours in female mice. Perinatal treatment followed by adult exposure increased the incidence of hepatocellular tumours in both male and female mice and slightly in male rats. Following intraperitoneal injection of phenytoin into mice, leukaemias and lymphomas were observed.

In one experiment in mice, phenytoin increased the incidence of hepatocellular tumours induced by *N*-nitrosodiethylamine. In a mouse lung adenoma assay, phenytoin decreased the multiplicity of lung adenomas induced by urethane.

#### 5.4 Other relevant data

Phenytoin is well absorbed in humans. It is eliminated mainly as the glucuronide of the major metabolite, 5-(4'-hydroxyphenyl)-5-phenylhydantoin, which typically accounts for 67-88% of the dose in urine. Several other metabolites are known. The elimination kinetics are non-linear, but an apparent mean half-life of 22 h is a useful guide.

5-(4'-Hydroxyphenyl)-5-phenylhydantoin is the main metabolite in all animal species except dogs (5-(3'-hydroxyphenyl)-5-phenylhydantoin) and cats (the *N*-glucuronide).

Acute phenytoin intoxication in humans presents usually with cerebellar-vestibular effects such as nystagmus, ataxia, diplopia, vertigo and dysarthria. Chronic administration of phenytoin at therapeutic doses may rarely induce various adverse health effects such as symptoms associated with impairment of the nervous system described above. Gingival overgrowth, sometimes together with increased thickness of the craniofacial bones as well as folic acid deficiency and development of megaloblastic anaemia, are well established adverse effects of the drug. Phenytoin has also been associated with various forms of cutaneous hypersensitivity reactions, sometimes accompanied by lymphadenopathy and benign lymphoid hyperplasia. In rare cases, the histological architecture of the lymph nodes is lost (pseudolymphoma). Phenytoin may also induce a variety of endocrine effects such as reduction of thyroxine concentrations, hypocalcaemia, osteomalacia and hyperglycaemia.

The nervous system appears to be the major target of acute and chronic phenytoin toxicity in experimental animals. In addition, repeated administration of phenytoin induces increased liver and kidney weights, centrilobular hepatic hypertrophy and diverse immunosuppressive effects. Phenytoin may reduce thyroxine concentrations and increase bone thickness in rodents, but gingival hyperplasia has been observed only in cats and monkeys and not in rodents. Phenytoin is an inducer of certain hepatic cytochrome P450 activities in humans and mice. There is evidence for the teratogenicity of phenytoin in humans ingesting 100-800mg per day during the first trimester of gestation. Phenytoin is teratogenic in mice and rats. Animal and a few human studies suggest that neurobehavioural deficits occur at doses which produce no dysmorphic effect.

Phenytoin induced mutations in *Salmonella typhimurium* in the presence of a metabolic activation system in one study. No mutagenic effect was observed in *Drosophila* or in mammalian cells *in vitro* in the absence of an exogenous metabolic system. Aneuploidy was induced in one study in primary mouse embryonic fibroblasts *in vitro*. Cell transformation was induced in Syrian hamster embryo. A single study showed increased clone sizes of murine macrophages in a host-mediated assay. Phenytoin inhibited gap-junctional intercellular communication. In human lymphocytes *in vitro*, sister chromatid exchanges were induced in one study and chromosomal aberrations were induced in two of five studies. Aneuploidy was observed in human amnion cells but not in lymphocytes. Phenytoin induced micronuclei in three of five studies in rodents *in vivo*. Aneuploidy, in one of two studies, aberrant sperm morphology and dominant lethal mutations were induced, but not sister chromatid exchange or chromosomal aberrations.

In general, studies of human lymphocytes *in vivo* showed no induction of micronuclei, chromosomal aberrations or aneuploidy but an increase of polyploidy was found in one study and of sister chromatid exchange frequencies in three of seven studies. Neither chromosomal aberrations nor aneuploidy were induced in human bone marrow.

The metabolite 5-(4'-hydroxyphenyl)-5-phenylhydantoin was mutagenic in *Salmonella typhimurium* in the presence of a metabolic activation system; it did not induce micronuclei in mouse bone marrow *in vivo*.

### *Mechanistic considerations*

Evidence is available to support the conclusion that phenytoin induces liver tumours in mice by a promoting mechanism. The increase in liver weight, centrilobular hypertrophy and pattern of cytochrome P450 induction are similar to those observed with other non-genotoxic mouse liver tumour promoters such as phenobarbital. In addition, the inhibition of cell-cell communication by phenytoin *in vitro* supports the role of promotion in mouse carcinogenesis.

The metabolic activation of phenytoin to a reactive intermediate has been proposed to account for the teratogenicity and possible genotoxicity of phenytoin. One possible intermediate is an arene oxide, that is hypothesized to result in binding to cellular macromolecules. However, this possibility has not been evaluated definitively, and studies of potential DNA damage in mouse liver or hepatocytes have not been reported. The mechanism of induction of aneuploidy by phenytoin *in vitro* is unclear, as is its relationship to carcinogenicity in mouse liver.

## 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of phenytoin.

There is *sufficient evidence* in experimental animals for the carcinogenicity of phenytoin.

### Overall evaluation

Phenytoin is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

**Previous evaluation:** Suppl. 7 (1987) (p. 319)

### Synonyms for Phenytoin

- Aleviatin
- Denyl
- Difhydan
- Dihycon
- Di-Hydan
- Dihydantoin
- Dilabid
- Di-Lan
- Dilantin
- Dilantin-125
- Dilantin Infatabs
- Dilantin-30 Pediatric
- Dintoina
- Diphantoin
- Diphedan
- Diphenylhydantoin
- DPH
- Diphentyn
- Ekko

- Enkefal
- Epanutin
- Epdantoin Simple
- Epelin
- Epiland
- Epinat
- Eptoin
- Fenantoin
- Hidantal
- Hydantin
- Hydantol
- Lehydan
- Lepitoin
- Novophenytoin
- Phenhydan
- Phenhydantin
- Sodanton
- Tacosal
- Zentropil

### **Synonyms for Phenytoin Sodium**

- Soluble phenytoin
- Alepsin
- Aleviatin
- Aleviatin sodium
- Antisacer
- Citrullamon
- Danten
- Dantoin
- Denyl
- Difenin
- Difetoin
- Difhydan
- Dilantin
- Di-Len
- Dintoina
- Diphantoine
- Di-Phen
- Diphenin
- Diphenine
- Diphenylan
- Diphenylhydantoin sodium
- 5,5-Diphenylhydantoin sodium
- Ditoin
- Enkefal
- Epanutin
- Epdantoin Simple
- Epelin
- Epilan D
- Epilantin
- Epsolin
- Eptoin
- Hidantal
- Hydantin
- Hydantoinal
- Idantoin
- Minetoin

- Muldis
- Neosidantoina
- Novodiphenyl
- Om-Hydantoïne;
- Phenhydantoin
- Pyorédol
- SDPH
- Sodium diphenylhydantoin
- Sodium 5,5-diphenylhydantoin
- Sodium diphenylhydantoinate
- Sodium 5,5-diphenyl-2,4-imidazolidinedione
- Sodium phenytoin
- Solantyl
- Tacosal
- Thilophenyt
- Zentropil

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Last Updated 05/22/97

# DROLOXIFENE

## (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 241)

**CAS No.:** 82413-20-5

**Chem. Abstr. Name:** (*E*)-3-(1-(4(2-(Dimethylamino)ethoxy)phenyl)-2-phenyl-1-butenyl)phenol

**CAS No.:** 97752-20-0

**Chem. Abstr. Name:** (*E*)-3-(1-(4(2-(Dimethylamino)ethoxy)phenyl)-2-phenyl-1-butenyl)phenol, 2-hydroxy-1,2,3-propanetricarboxylate(1:1)

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Droloxifene is a phenolic analogue of tamoxifen which is undergoing clinical trials for the treatment of metastatic breast cancer, but is not yet registered in any country.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

Droloxifene was tested for carcinogenicity by oral administration in one study in rats. No increase in the incidence of tumours was reported. Droloxifene was studied in two experiments in rats for its modulation of chemically induced mammary tumours. In one study with 7,12-dimethylbenz[*a*]anthracene, inhibition of mammary tumours was observed, while in another study with *N*-methyl-*N*-nitrosourea, there was no effect or a slight increase in the incidence of mammary tumours.

### 5.4 Other relevant data

Droloxifene is well absorbed in humans after oral doses. It undergoes both oxidative metabolism and direct glucuronidation, and the elimination half-life is about 24 h. Metabolites were identified in rats and mice that were not found in humans. Toxic effects were infrequent in a phase II trial in postmenopausal women with metastatic breast cancer. Short- (four weeks) and longer- (six months) term toxicity studies in rats at doses of up to 200 mg/kg bw showed biochemical changes but little toxicity. Droloxifene did not induce cell transformation *in vitro* or form DNA adducts in rat liver *in vivo*.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of droloxifene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of droloxifene.

### Overall evaluation

Droloxifene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

### **Synonyms for Droloxifene**

- (*E*)-1-(4'-(2-Dimethylaminoethoxy)phenyl)-1-(3-hydroxyphenyl)-2-phenylbut-1-ene
- *trans*-1-(4-β-Dimethylaminoethoxyphenyl)-1-(3-hydroxyphenyl)-2-phenylbut-1-ene
- 3-Hydroxytamoxifen

### **Synonyms for Droloxifene citrate**

- (*E*)-1-(4'-(2-Dimethylaminoethoxy)phenyl)-1-(3-hydroxyphenyl)-2-phenylbut-1-ene citrate
- *trans*-1-(4-β-Dimethylaminoethoxyphenyl)-1-(3-hydroxyphenyl)-2-phenylbut-1-ene citrate
- *E*-Droloxifene
- FK 435
- 3-Hydroxytamoxifen citrate
- K 060
- K 060E
- K 21.060E

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Last updated 05/22/97

# TAMOXIFEN

## (Group 1)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 66 (1996) (p. 253)

**CAS No.:** 10540-29-1

**Chem. Abstr. Name:** (Z)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine

**CAS No.:** 54965-24-1

**Chem. Abstr. Name:** (Z)-2-[4-(1,2-Diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Tamoxifen has been available since the early 1970s for the first-line treatment of metastatic breast cancer in postmenopausal women. Since the 1980s, it has become the therapy of choice for this condition. Tamoxifen has also become the adjuvant therapy of choice for treatment of postmenopausal, node-positive women with positive oestrogen-receptor or progesterone-receptor levels and, since the early 1990s, for the treatment of postmenopausal, node-negative women with positive oestrogen-receptor or progesterone-receptor levels. It is also widely used in treating postmenopausal receptor-negative women and premenopausal women with node-negative, receptor-positive disease. When used as adjuvant therapy, tamoxifen reduces the annual rates of both death from and recurrence of breast cancer by about 25%. Tamoxifen is commonly given at doses of 20 mg daily for periods of two to five years in the adjuvant setting, although doses of up to 40 mg daily have been used in the past. Several clinical trials are in progress to study the efficacy of tamoxifen in preventing breast cancer in healthy women believed to be at high risk of developing the disease.

Tamoxifen has been widely adopted as the first-line therapy of choice for hormone-responsive male breast cancer and is frequently used as adjuvant therapy for oestrogen receptor- or progesterone receptor-positive male breast cancer.

Tamoxifen is registered for use in nearly 100 countries and cumulative use since 1973 is estimated at 7 million patient-years.

### 5.2 Human carcinogenicity data

The potential effect of tamoxifen in increasing the risk of endometrial cancer has been reported in one adequate cohort study, four adequate case-control studies and 14 randomized controlled trials.

In the cohort study, based on follow-up of registered cases of breast cancer in the population-based Surveillance, Epidemiology and End Results (SEER) database in the United States, the only available data on therapy were those reported at the time of initial registration. Both groups of women with reported tamoxifen use and those with no such reported use had elevated rates of endometrial cancer compared with the rates expected from the SEER database as a whole. The risk was significantly greater for women with reported tamoxifen use. The similar stage distribution in the two groups suggests a lack of serious detection bias in this study. The absence of hysterectomies could not be confirmed in this study.

The case-control studies were based on the identification of a series of women with breast cancer who had subsequently been diagnosed with endometrial cancer, with tamoxifen exposure assessed in comparison with breast cancer patients who had not developed endometrial cancer. In two of these, case and control selection

was based on the records of population-based cancer registries, and two used the same source as well as hospital-based cancer registries. For the Swedish study, although an increased risk of endometrial cancer for tamoxifen use was found, the only information on treatment was that recorded in the cancer registry. Further, the absence of hysterectomy in the control series could not be confirmed. For the remaining three case-control studies, more detailed data on treatment and on hysterectomies were obtained from medical records. In the studies in France and the Netherlands, a nonsignificant elevation of risk for endometrial cancer with use of tamoxifen was found, with a significant increase in risk with increasing duration of therapy in one. In the United States study, which reported on shorter duration of use, the point estimate of risk was less than unity.

Although several potential confounders were not systematically addressed in most studies, the Working Group considered that these were unlikely to have had a major effect on the reported relative risks.

In most of the randomized trials, small numbers of endometrial cancers were reported, and for many the data were not reported in a way that corrected for the greater survival time in most trials of the tamoxifen-treated patients compared to the control series. In two of the largest trials, however, there was a strong and statistically significant association between risk for endometrial cancer and use of tamoxifen. Although there may have been a tendency for publication bias and there is some possibility of a detection bias as a result of investigations in women with side-effects from tamoxifen, the magnitude of the risk found in the two large trials is unlikely to be explained by such biases. Further, for the trials that reported deaths in women with endometrial cancer, to date there have been eight deaths in women allocated to tamoxifen treatment groups and one in those not allocated to tamoxifen.

One case series reported significantly more high-grade endometrial tumours in tamoxifen-treated cancer patients than in patients without prior tamoxifen use. However, in at least six other studies, this difference was not found.

The SEER-based cohort study found a significantly reduced risk for contralateral breast cancers in the tamoxifen-treated women, compared with women with no reported tamoxifen use. The case-control study from the United States also reported a significant reduction of risk for contralateral cancers of the breast following tamoxifen use.

Although for some small trials there seemed to be little difference in the numbers of contralateral breast cancers in tamoxifen-treated women compared with controls, for the large trials, there was a substantially and significantly reduced risk for contralateral breast cancer in tamoxifen-treated women compared with controls. Further, in an overview analysis of nearly all trials published in 1992 with data available to 1990, there was a significant reduction of 39% in contralateral breast cancers in the tamoxifen-treated groups.

For all other cancer sites, no significant excess of any cancer has been found in either the cohort study or the trials. Although an excess of gastrointestinal cancer was reported following a combined analysis of three Scandinavian trials, this has not yet been confirmed by other studies.

### **5.3 Animal carcinogenicity data**

Tamoxifen was tested for carcinogenicity by oral administration in one study in mice and in eight studies in rats, only one of which was a formal two-year study. In mice, the incidences of benign ovarian and testicular tumours were increased. In rats, tamoxifen induced preneoplastic liver lesions and benign or malignant liver tumours. In one study, the incidence of some tumours in hormone-dependent tissues was decreased, including in the mammary gland, although reduced weight gain may have been a contributing factor. In two studies in which tamoxifen was tested by subcutaneous implantation in intact or ovariectomized female mice, it inhibited mammary tumour development in both.

In mice, tamoxifen was reported to inhibit 3-methylcholanthrene-induced cervical cancer and virus-induced leukaemia. In several studies in both male and female rats, tamoxifen enhanced the hepatocarcinogenicity of previously administered *N*-nitrosodiethylamine. In one study in rats, tamoxifen enhanced the development of *N*-nitrosodiethylamine-induced kidney tumours. In a number of studies in rats, tamoxifen inhibited 7,12-

dimethylbenz[a]anthracene-induced mammary tumour development. In two studies in hamsters, tamoxifen inhibited hormonal carcinogenesis induced by 17 $\beta$ -oestradiol in the kidney and zeranol in the liver.

#### 5.4 Other relevant data

Orally administered tamoxifen is well absorbed and maximum plasma levels are reached in about 5 h. Steady-state concentrations of tamoxifen in humans are reached in 3-4 weeks and those of the primary metabolite, *N*-desmethyltamoxifen, in about eight weeks. Tissue concentrations tend to be higher than plasma concentrations. Metabolism involves phenyl hydroxylation, alkyl hydroxylation, demethylation and *N*-oxide formation. Metabolism results in more products in man and rats than in mice. Much higher oral doses of tamoxifen are required for rats or mice to achieve plasma concentrations similar to human levels.

Tamoxifen is an antioestrogen with complex pharmacology encompassing variable species-, tissue-, cell-, gene-, age- and duration of administration-specific effects from oestrogen-like agonist actions to complete blockade of oestrogen action. This complexity is consistent with the various, and sometimes paradoxical, effects that have been associated with tamoxifen administration in animals and humans.

The most frequent side-effects of tamoxifen administration are hot flushes and vaginal discharge. Tamoxifen has effects on the human uterus, inducing atrophy, hyperplasia and, less frequently, polyps. Randomized placebo-controlled trials revealed a slight increase of thromboembolic events, but also a protective effect regarding myocardial diseases, according to hospital admission rates and deaths. Tamoxifen administration has been shown to decrease blood total cholesterol and low-density lipoprotein-cholesterol concentrations in a number of studies. Several preliminary trials have suggested mildly positive effects of tamoxifen in preserving bone mineral density in postmenopausal women, but much longer follow-up is required to confirm its potentially beneficial effect.

The acute toxicity of tamoxifen in experimental animals is low. In repeated-dose studies in rats, tamoxifen induced hypertrophy, but not cell proliferation, in the endometrial epithelium; endometrial hyperplasia was, however, reported in mice. Furthermore squamous metaplasia and atrophy of the uterine epithelium was observed in chronic studies in rats. Induction of cytochromes P450 and preneoplastic lesions have been detected in the livers of rats.

Ocular toxicity, including lipidosis of the retina and cornea and increased incidence of cataract, was reported in studies in rats of chronic exposure to tamoxifen.

In the presence of human, mouse, rat and hamster microsomes, tamoxifen binds covalently to protein. Tamoxifen has oestrogenic effects on human fetal genital tracts grown in athymic mice. In rats, doses above 2 mg/kg body weight produce irregular ossification of ribs in the fetus, which is thought to be secondary to reduction of the size of the uterus of the dam. No effects on the fetus have been reported in rabbits, marmosets or cynomolgus monkeys.

There is no direct evidence that tamoxifen is active in tests for gene mutation. Evidence for the genotoxic potential of tamoxifen is supported by data obtained on DNA adduct formation in rodent liver cells *in vitro* and *in vivo*, and in rodent and human liver microsomal systems; on unscheduled DNA synthesis in rat hepatocytes *in vitro*; and on the induction of clastogenic events both *in vitro*, in genetically-engineered human cells, and *in vivo* in rat liver.

There is evidence from <sup>32</sup>P-postlabelling studies that three metabolites, ( $\alpha$ -hydroxytamoxifen, 4-hydroxytamoxifen and (*Z*)-1,2-diphenyl-1-(4-hydroxyphenyl)but-1-ene (metabolite E) can be further metabolized to products that react with DNA. The major DNA adduct formed in rodent liver cells has been identified as (*E*)-( $\alpha$ -(*N*<sup>2</sup>-deoxyguanosinyl) tamoxifen. Human hepatocytes do not form detectable DNA adducts when treated *in vitro* with tamoxifen; they form 300-fold lower levels of adducts than rat and mouse hepatocytes when treated with  $\alpha$ -hydroxytamoxifen.

Preliminary studies indicate that tamoxifen does not give rise to detectable levels of DNA adducts in human

liver *in vivo* or in human endometrium *in vitro* and *in vivo*.

### *Mechanistic considerations*

Tamoxifen increases liver tumour incidence in rats, which may involve both DNA damage leading to increased numbers of initiated cells and oestrogen receptor-mediated clonal expansion of those initiated cells.

The available evidence suggests that tamoxifen is carcinogenic in rat liver by a genotoxic mechanism. Preliminary information from studies of human tissues suggests that humans are less susceptible to the genotoxicity of tamoxifen. Tamoxifen also possesses tumour-promoting activity in the rat liver.

Several studies have shown that the liver contains significant quantities of oestrogen receptor in hepatocytes, Kupffer cells and endothelial cells.

Tamoxifen acts as an oestrogen agonist and/or antagonist by binding directly to the oestrogen receptor. In some tissues, such as breast, tamoxifen exhibits antioestrogenic properties by binding to the oestrogen receptor with high affinity. The tamoxifen-oestrogen receptor complex is incapable of binding to DNA-responsive elements. Thus, oestrogen receptor binding does not result in normal transcriptional activity. In other tissues, such as bone and liver, tamoxifen acts as a partial agonist, possibly because cells from those tissues contain a different array of DNA binding sites, thereby leading to typical oestrogen-mediated changes in gene expression and subsequent biological effects on growth and differentiation. Therefore, tissue-specific effects of tamoxifen-oestrogen receptor on gene expression may be involved in the ability of tamoxifen to increase or decrease tumour risk.

## **5.5 Evaluation**

There is *sufficient evidence* in humans for the carcinogenicity of tamoxifen in increasing the risk for endometrial cancer and there is conclusive evidence that tamoxifen reduces the risk for contralateral breast cancer in women with a previous diagnosis of breast cancer.

There is *inadequate evidence* in humans for the carcinogenicity of tamoxifen in other organs.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tamoxifen.

### **Overall evaluation**

Tamoxifen is *carcinogenic to humans (Group 1)* and there is *conclusive evidence* that tamoxifen reduces the risk of contralateral breast cancer.

(Dr Cuzick dissociated himself from the evaluation process because he considered that the range of evaluation statements available within the framework of the Monographs was not suitable for this agent.)

For definition of the italicized terms, see [Preamble Evaluation](#)

### **Synonyms for Tamoxifen**

- 1-*para*- $\beta$ -Dimethylaminoethoxyphenyl-*trans*-1,2-diphenylbut-1-ene
- (*Z*)-2-[4-(1,2-Diphenylbut-1-enyl)phenoxy]ethyl dimethylamine

### **Synonyms for Tamoxifen citrate**

- Apo-Tamox

- Citofen
- Dignotamoxi
- Duratamoxifen 5
- Emblon
- ICI-46474
- Jenoxifen
- Kessar
- Ledertam
- Noltam
- Nolvadex
- Nourytam
- Novofen
- Oestrifen
- Oncotam
- Retaxim
- Tafoxen
- Tam
- Tamaxin
- Tamifen
- Tamofen
- Tamone
- Tamoplex
- Tamoxasta
- Tamox-Gry
- Z-Tamoxifen citrate
- Tamoxigenat
- Tamox-Puren
- Taxfeno
- Terimon
- Valodex
- Zemide
- Zitazonium

# TOREMIFENE

## (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL:** 66, (1996) (p. 367)

**CAS No:** 89778-26-7

**Chem. Abstr. Name:** (Z)-2-[4-(4-Chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine

**CAS No:** 89778-27-8

**Chem. Abstr. Name:** (Z)-2-[4-(4-Chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Toremifene, a chlorinated analogue of tamoxifen, was first marketed in 1990 and by 1995 was registered in five countries. It is currently undergoing further clinical trials for the treatment of metastatic breast cancer as well as trials for use as adjuvant therapy.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

Toremifene was tested for carcinogenicity in one study by oral administration to male and female rats and in four studies of limited duration in female rats. No increase in tumour incidence was observed in these studies. In the one study of long duration, toremifene decreased the incidence of tumours in some hormone-dependent tissues, notably mammary gland.

In one study in female rats, toremifene increased the incidence of kidney tumours and the proportion of malignant liver tumours induced by *N*-nitrosodiethylamine.

In four other experiments in rats, toremifene inhibited the development of 7,12-dimethylbenz[*a*]anthracene- or *N*-methyl-*N*-nitrosourea-induced mammary tumours.

### 5.4 Other relevant data

Toremifene is well absorbed in humans. The major metabolites result from *N*-demethylation, hydroxylation and deamination, and are excreted predominantly in faeces. The elimination half-life is about six days. The metabolism is qualitatively similar, but quantitatively different, in rats.

In a single study, no teratogenic effect of toremifene was found in rats.

Toremifene induced micronucleus formation in one study that used genetically engineered cell lines. Low levels of DNA adducts were detected in rat liver in one of three studies. Low levels of DNA adduct formation have also been reported in human lymphocytes *in vitro*.

## 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of toremifene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of toremifene.

### Overall evaluation

Toremifene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

### Synonyms for Toremifene

- (Z)-4-Chloro-1,2-diphenyl-1-[4-(2-(N,N-dimethylamino)ethoxy)phenyl]-1-butene
- Z-Toremifene
- Toremifene base

### Synonyms for Toremifene citrate

- (Z)-4-Chloro-1,2-diphenyl-1-[4-[2-(N,N-dimethylamino)ethoxy]phenyl]-1-butene citrate (1:1)
- Fareston
- FC 1157a
- NK 622

# CLOFIBRATE

## (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

**VOL:** 66 (1996) (p. 391)

**CAS No.:** 637-07-0

**Chem. Abstr. Name:** 2-(4-Chlorophenoxy)-2-methylpropanoic acid, ethyl ester

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Clofibrate was introduced in the 1960s to reduce plasma concentrations of triglycerides and cholesterol in patients at high risk of coronary heart disease. Since the late 1970s, its use has decreased considerably.

### 5.2 Human carcinogenicity data

In 1978, a randomized trial of the World Health Organization, conducted to determine whether clofibrate treatment would lower the incidence of ischaemic heart disease in men, raised concern over a nonsignificant excess of deaths from cancer in treated subjects.

Subsequently the association between clofibrate and cancer risk was examined in three randomized trials and a small case-control study. A further four-year follow-up of the WHO trial showed no difference in the age-standardized death rates from malignant neoplasms. In two other trials, there was also no difference in cancer deaths between clofibrate-treated patients and a placebo-treated group. A meta-analysis of results from six trials also found no excess cancer mortality due to use of clofibrate as a cholesterol-lowering drug. The case-control study, that had several methodological limitations, showed a nonsignificant excess of soft-tissue sarcoma.

### 5.3 Animal carcinogenicity data

Clofibrate was tested for carcinogenicity by oral administration in the diet in two experiments in mice and in three experiments in rats, and in one experiment in marmosets by gastric instillation. No increase in incidence of tumours was reported in mice or marmosets. In rats, clofibrate produced hepatocellular carcinomas. Clofibrate was tested in several experiments by combined administration with other chemicals. It enhanced the hepatocarcinogenicity of *N*-nitrosamines in rats and hamsters. It did not enhance the carcinogenicity of 2-acetylaminofluorene in rat liver.

### 5.4 Other relevant data

Clofibrate exerts similar pharmacological responses in humans and rodents. Absorption and metabolism of clofibrate are similar in humans and rats. Elimination of clofibric acid, the free acid form of the drug as it appears in the circulation, is more rapid in rats, possibly due to lower binding to plasma proteins. Clofibrate-induced peroxisome proliferation and cell proliferation have been demonstrated in feeding studies in rats. Peroxisome proliferation has not been found in studies of clofibrate in human livers or hepatocytes. There are a number of case reports of reversible impotence in men treated with clofibrate. No noteworthy effect on the fetus has been observed in studies in rats or rabbits. Clofibrate is inactive in most tests for genetic activity, although it induced cell transformation in one study.

*Mechanistic considerations*

The weight of evidence indicates that clofibrate does not act as a direct DNA-damaging agent and that its mechanism of tumour induction is indirect. Two biological responses have been proposed to account for liver carcinogenesis by peroxisome proliferators in rodents. These are (i) induction of peroxisome proliferation and (ii) increased hepatocellular proliferation. Upon exposure to clofibrate, proliferation of both peroxisomes and cells occurs in rat liver and of peroxisomes in cultured rat hepatocytes, whereas peroxisome proliferation does not occur in human liver or cultured hepatocytes. These observations suggest that the mechanism of liver carcinogenesis in clofibrate-treated rats would not be operative in humans.

## 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of clofibrate.

There is *limited evidence* in experimental animals for the carcinogenicity of clofibrate.

### Overall evaluation

Clofibrate is *not classifiable as to its carcinogenicity in humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Previous evaluation:** Suppl. 7 (1987) (p. 171)

### Synonyms

- Amotril
- Anparton
- Apolan
- Arterioflexin
- Artes
- Artevil
- Ateculon
- Ateriosan
- Aterosol
- Atheromide
- Atheroprone
- Atrofort
- Atrolen
- Atromid
- Atromid-S
- Atromidin
- Atrovis
- AY 61123
- Azionyl
- Bioscleran
- Cartagyl
- *para*-Chlorophenoxyisobutyric acid ethyl ester
- 2-(*para*-Chlorophenoxy)-2-methylpropionic acid ethyl ester
- Citiflus
- Claripex
- Claripex CPIB
- Cloberat
- Clobrat
- Clobren SF
- Clof

- Clofibril
- Clofibrat
- Clofinit
- Clofipront
- Clofirem
- CPIB
- Deliva
- ECPIB
- EPIB
- Estaprol
- Ethyl *para*-chlorophenoxyisobutyrate
- Ethyl 2-(*para*-chlorophenoxy)isobutyrate
- Ethyl 2-(4-chlorophenoxy)isobutyrate
- Ethyl  $\alpha$ -(*para*-chlorophenoxy)isobutyrate
- Ethyl  $\alpha$ -(4-chlorophenoxy)isobutyrate
- Ethyl  $\alpha$ -(*para*-chlorophenoxy)- $\alpha$ -methylpropionate
- Ethyl  $\alpha$ -(4-chlorophenoxy)- $\alpha$ -methylpropionate
- Ethyl 2-(4-chlorophenoxy)-2-methylpropionate
- Ethyl clofibrate
- Geromid
- Healthstyle
- Hyclorate
- ICI 28257
- Ipolipid
- Klofiran
- Levatrom
- Lipavil
- Lipavlon
- Lipilim
- Lipomid
- Liponorm
- Liporan
- Liprinal
- Lobetrin
- Lostat
- MG 46
- Miscleron
- Misclerone
- Neo-Atromid
- NSC 79389
- Normet
- Normolipol
- Novofibrate
- Recolip
- Regelan
- Sclerovasal
- Serotinex
- Sklerolip
- Skleromexe
- Sklero-Tablinen
- Ticlobran
- Xyduril
- Yoclo

# GEMFIBROZIL (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

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**CAS No.:** 25812-30-0

**Chem. Abstr. Name:** 5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoic acid

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Gemfibrozil has been used since the early 1980s to lower serum triglycerides and raise high-density lipoprotein-cholesterol in patients at high risk for coronary heart disease.

### 5.2 Human carcinogenicity data

In a Finnish trial that aimed to reduce cholesterol concentration with gemfibrozil, no difference was found in cancer incidence or mortality between the treated and control groups.

### 5.3 Animal carcinogenicity data

Gemfibrozil was tested for carcinogenicity by oral administration in the diet in one experiment in mice and one experiment in rats. There was a slight, not dose-related increase in the incidence of hepatocellular carcinomas in male mice and the incidence of lung adenomas was decreased. In male rats, increases were observed in the incidence of hepatocellular tumours, interstitial-cell tumours of the testis and adrenal pheochromocytomas; the latter was not dose-related.

### 5.4 Other relevant data

Gemfibrozil exerts similar pharmacological responses in humans and laboratory rodents. It is readily absorbed, metabolized and eliminated in human subjects. Data are not available to characterize adequately its pharmacokinetic behaviour in animals, although maximal serum levels of gemfibrozil in rats are similar to those in humans receiving therapeutic doses of gemfibrozil. Gemfibrozil-induced peroxisome proliferation has been demonstrated in rats. An indirect measure of cell proliferation, liver weight, is also increased in rats. Peroxisome proliferation has not been observed in studies of human livers with gemfibrozil. There are a number of case reports of reversible impotence in men treated with gemfibrozil. No noteworthy effects on the fetus have been observed in studies in rats or rabbits. Neither gemfibrozil nor its metabolites were mutagenic in bacteria in a single study.

#### *Mechanistic considerations*

The data on gemfibrozil are too limited to allow mechanistic assessment. In particular, genotoxicity has not been excluded. Upon exposure to gemfibrozil, proliferation of peroxisomes occurs in rat liver, whereas proliferation of peroxisomes does not occur in human liver. These observations suggest that the mechanism of liver carcinogenesis in gemfibrozil-treated rats would not be operative in humans.

### 5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of gemfibrozil.

There is *limited evidence* in experimental animals for the carcinogenicity of gemfibrozil.

### **Overall evaluation**

Gemfibrozil is *not classifiable as to its carcinogenicity in humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

### **Synonyms**

- Bolutol
- CI-719
- Decrelip
- Elmogan
- Fibrocit
- GEM
- Gemlipid
- Genlip
- Gevilon
- Hipolixan
- Ipolipid
- Lipozid
- Lipur
- Lopid
- Micolip
- Trialmin