TEMAZEPAM

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

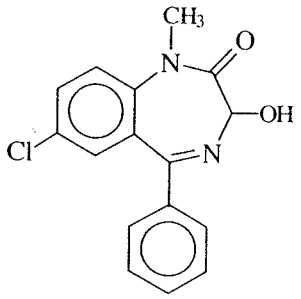
Chem. Abstr. Serv. Reg. No.: 846-50-4

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

IUPAC Systematic Name: 7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one

Synonyms: 3-Hydroxydiazepam; methyloxazepam; *N*-methyloxazepam; oxydiazepam

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{16}H_{13}ClN_2O_2$ Relative molecular mass: 300.75

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White crystals (Gennaro, 1995)

(*b*) *Melting-point*: 119–121 °C (Budavari, 1995)

(*c*) *Spectroscopy data*: Infrared spectroscopy data have been reported (British Pharmacopoeial Commission, 1993)

(*d*) *Solubility*: Very slightly soluble in water (< 1 in 10 000); sparingly soluble in ethanol (Dollery *et al.*, 1991; Gennaro, 1995); freely soluble in chloroform (British Pharmacopeial Commission, 1993)

(*e*) *Dissociation constant*: pK_a, 1.6 (Gennaro, 1995)

1.1.4 *Technical products and impurities*

There are two enantiomeric forms of the temazepam structure (asymmetric at C_3), but temazepam in pharmaceutical preparations is invariably the racemic mixture (British Pharmacopoeial Commission, 1993).

Temazepam is available as 7.5-, 10-, 15-, 20- and 30-mg capsules, 10- and 20-mg tablets and an oral solution containing 10 mg/5 mL. Preparations also may contain benzyl alcohol, butylparaben, carboxymethylcellulose sodium, crospovidone (a cross-linked homopolymer of polyvinylpyrrolidone), edetate calcium disodium, gelatin, glycerol, lactose, magnesium stearate, mannitol, methylparaben, polyethylene glycol 400, propylparaben, silicon dioxide, sodium lauryl sulfate, sodium ethyl *para*-oxybenzoate, sodium propionate, sodium propyl *para*-oxybenzoate, sorbitol, synthetic red ferric oxide, titanium oxide, FD&C Blue 1 (Brilliant Blue FCF) or FD&C Red 3 (Erythrosine). Various capsule formulations of temazepam have been available (liquid, gel or powder formulations in hard or soft capsules), and differences in peak blood levels and half-life of temazepam among the various formulations have been noted (see Section 4.1 of this monograph) (Thomas, 1991; Farmindustria, 1993; Hingorani & Ainsworth, 1993; Reynolds, 1993; British Medical Association/Royal Pharmaceutical Society of Great Britain, 1994; Medical Economics, 1996)

A potential impurity limited by the requirements of the European Pharmacopoeia is 5-chloro-2-methylaminobenzophenone (Council of Europe, 1994). Another is the product of oxidation of the hydroxyl group of temazepam, the 2,3-dione (Fatmi & Hickson, 1988).

Trade names and designations of the chemical and its pharmaceutical preparations include: Crisonar; ER 115; Euhypnos; Euipnos; Gelthix; K 3917; Levanxene; Levanxol; Mabertin; Neodorm SP; Norkotral Tema; Normison; 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.

1.1.5 *Analysis*

Several international pharmacopoeias specify potentiometric titration with perchloric acid or liquid chromatography as assays for purity of temazepam, and thin-layer and liquid chromatography for determining impurities and decomposition products, particularly 5-chloro-2-methylaminobenzophenone. The assay for temazepam in capsules applies liquid chromatography using a standard (British Pharmacopoeial Commission, 1993; Council of Europe, 1994; United States Pharmacopeial Convention, 1994). Other methods of analysis in pharmaceutical preparations include: fluorimetry (Walash *et al.*, 1994), polarography (Chan & Fogg, 1981), spectrophotometry (El-Brashy *et al.*, 1993), mass spectrometry (McCarley & Brodbelt, 1993) and high-performance liquid chromatography (Gordon *et al.*, 1986; Fatmi & Hickson, 1988).

Temazepam can be analysed in biological fluids and tissues by fluorimetry (Walash *et al.*, 1994), adsorptive stripping voltammetry (Zapardiel *et al.*, 1988), electron-capture gas chromatography (Divoll & Greenblatt, 1981; Löscher, 1982; Riva *et al.*, 1982),

capillary gas chromatography (Beischlag & Inaba, 1992), gas chromatography–mass spectrometry (Maurer & Pfleger, 1987) and high-performance liquid chromatography (Ho *et al.*, 1983; Komiskey *et al.*, 1985; Patterson, 1986; Lau *et al.*, 1987; Fernández *et al.*, 1991; Kunsman *et al.*, 1991; Chopineau *et al.*, 1994).

1.2 Production and use

1.2.1 *Production*

Temazepam is prepared by acylating 2-(methylamino)-5-chlorobenzhydrol with chloroacetyl chloride. Heating the product with sodium iodide yields the iodoacetamido compound. Treatment of the iodoacetamido compound with hydroxylamine effects dehydration and dehydrohalogenation to form the benzodiazepine derivative, which rearranges to temazepam, with esterification when treated with acetic anhydride. Saponification liberates temazepam (Gennaro, 1995).

1.2.2 *Use*

Temazepam was first introduced in Europe in 1970 and in the United States of America in 1981 (Sternbach & Horst, 1982). During 1992–94, temazepam accounted for 40–45% of the United States pharmaceutical market for hypnotics (Sandoz Pharmaceuticals Corp., 1996).

Temazepam is a benzodiazepine hypnotic used in the short-term management of insomnia (see the monograph on diazepam, pp. 39–41, for a brief overview of the pharmacology of therapeutic action for this class of drugs). The usual oral dose for adults is 15 mg taken before retiring at night, although 7.5 mg may be sufficient for some patients and others may need 30 mg, or exceptionally up to 60 mg. Temazepam should be given at reduced dosages to elderly or debilitated patients: one half of the usual adult dose, or less, may be sufficient. For premedication before surgical or investigative procedures, the usual dose is 20–40 mg (Reynolds, 1993; Medical Economics, 1996).

Clinical uses of temazepam and other benzodiazepines have been reviewed (Hollister *et al.*, 1993).

Comparative data on sales of temazepam in several countries are presented in Table 1. Overall, sales worldwide increased by approximately 7% from 1990 to 1995, and United States prescriptions increased by about 6% (see Table 2 in the monograph on diazepam, p. 43).

1.3 Occurrence

Temazepam is not known to occur as a natural product. It is a minor metabolite of diazepam in humans.

1.4 Regulations and guidelines

Temazepam is listed in the British, European, French and United States pharmacopoeias (Reynolds, 1993; British Pharmacopoeial Commission, 1993; Council of Europe, 1994; United States Pharmacopeial Convention, 1994; Vidal, 1995).

Table 1. Sales of temazepam in various countries[a] (no. of standard units[b], in thousands)

Country	1990	1995	Country	1990	1995
Africa			Europe		
South Africa	4 226	4 574	Belgium	2 480	1 577
North America			France	13 370	7 532
Canada	16 365	40 238	Germany	30 901	36 695
USA	177 054	200 677	Greece	2 394	2 111
South America			Italy	0	10 912
Venezuela	879	885	Netherlands	46 055	52 843
Asia			Portugal	4 426	4 378
Republic of Korea	15	16	Spain	2	0
Australia	80 984	79 864	Switzerland	2 312	2 109
			United Kingdom	324 041	311 519

[a] Data provided by IMS

[b] Standard dosage units, uncorrected for temazepam content

2. Studies of Cancer in Humans

No data were available to the Working Group (see the monograph on diazepam, pp. 44–54, for a discussion of benzodiazepines).

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 100 male and 100 female Charles River CD-1 mice, five weeks of age, were given 0 (control), 10, 80 or 160 mg/kg bw temazepam (99% pure) per day in the diet for up to 78 weeks. The temazepam/diet mixtures were prepared freshly each week and offered *ad libitum*. Mice that died during the first 35 days were replaced. Body-weight gains tended to be slightly less than those of controls for both male and female treated mice throughout the study [exact details not given]. Food consumption was similar in control and treated mice. Mortality was increased in male mice receiving either

80 mg/kg bw (56% survival) or 160 mg/kg bw (47% survival) while the low-dose and control mice had survival greater than 80%. Among females, the mortality was generally similar in all groups (greater than 75% survival), with the mid- and high-dose groups tending to have slightly increased mortality. All surviving animals were killed at 78 weeks. Complete histological examinations were performed on 99–100 males per group and 100 females per group. Hepatic hyperplastic lesions occurred in 2% of control, 3% of low-dose, 3% of mid-dose and 10% of high-dose males, and in 0% of control, 0% of low-dose, 1% of mid-dose and 8% of high-dose female mice. No significant increase in the incidence of benign hepatocellular adenomas was observed for male or female mice. The incidence of hepatocellular adenomas was: males — control, 8/100; low-dose, 4/99; mid-dose, 2/100; and high-dose, 10/100; females — control, 0/100; low-dose, 1/100; mid-dose, 1/100; and high-dose, 4/100 ($p = 0.056$, Fisher exact test) [$p = 0.014$, trend test] (Robison *et al.*, 1984). [The Working Group noted that the study was terminated at 78 weeks.]

3.1.2 *Rat*

Groups of 90 male and 90 female Charles River weanling CD rats were given 0 (control), 10, 40 or 160 mg/kg bw temazepam (99% pure) per day in the diet for up to 104 weeks. The temazepam/diet mixtures were prepared freshly each week and offered *ad libitum*. Ten males and 10 females from each group were killed at weeks 27 and 53. In rats exposed to 160 mg/kg bw, body weights were less than those of controls for both males (except at weeks 13 and 26) and females. Food consumption was similar in control and treated rats. All treated males and low-dose females had higher mortality than the controls. The survival was satisfactory, with at least 24 animals remaining in each group. Complete histopathological examination, including visually apparent lesions, was performed. No significant increase in the incidence of tumours was observed in male or female rats. The incidence of hepatocellular carcinomas was: males — control, 10/90; low-dose, 9/90; mid-dose, 6/90; and high-dose, 10/90; females — control, 13/90; low-dose, 4/90; mid-dose, 10/90; and high-dose, 8/90. No liver adenoma was reported (Robison *et al.*, 1984).

3.2 Carcinogenicity of metabolites

See the monograph on oxazepam in this volume (pp. 119–123).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Information on the absorption of temazepam is somewhat confused by the issue of differing formulations. Studies in the United States when the drug was first marketed in a

hard gelatin capsule (1981) indicated relatively slow absorption, with maximal plasma concentrations attained about 2.5 h after dosing. This contrasted with data relating to the soft gelatin capsule, which became available earlier in Europe and gave peak plasma levels within 1.5 h. For example, after a 10-mg dose, Jochemsen *et al.* (1983) found peak plasma concentrations of 227 ± 92 ng/mL at 1.2 ± 0.9 h in Dutch subjects and Klem *et al.* (1986) found peak plasma concentrations of 306 ± 32 ng/mL at median 0.75 h in British geriatric patients given soft gelatin capsules. Fuccella *et al.* (1977) administered 20 mg temazepam in hard and soft capsules to male volunteers, and measured peak plasma concentrations of 668 ± 121 ng/mL and 892 ± 101 ng/mL at 1.44 ± 0.21 h and 0.83 ± 0.25 h, respectively. More recent data from the United States show that reformulation there achieved a product comparable with that marketed in Europe, and more appropriate for use as a hypnotic. In this study, the peak plasma concentration was 873 ± 43 ng/mL at 1.36 ± 0.15 h following a single 30-mg dose (Locniskar & Greenblatt, 1990). Controversy has also arisen in relation to the elimination half-life, but this study seems to confirm a mean value of 10 h. A sex difference was reported in another study (Divoll *et al.*, 1981) in which, irrespective of age, the elimination half-life of temazepam was about 12 h in men and about 17 h in women. No such sex difference was seen in the much smaller study of Klem *et al.* (1986).

Schwarz (1979) reported that 80% of a 0.41-mg/kg bw dose was recovered in urine, while another 12% was recovered in faeces. The percentages of the dose excreted in urine were temazepam (1.5%), conjugated temazepam (72.5%), oxazepam (1.0%) and conjugated oxazepam (5.8%). Temazepam can cross the human placenta (Heel *et al.*, 1981). Locniskar and Greenblatt (1990) found that direct conjugation of temazepam with glucuronic acid was a major pathway of metabolic clearance, and 39 ± 3% of the oral dose was eliminated in urine as the glucuronide; only 0.2% of the dose was recovered as temazepam. Oxazepam glucuronide accounted for a further 4.7% of the dose. Approximately 50% of the dose was not accounted for, possibly because of non-renal elimination or formation of unrecognized metabolites (see Figure 1).

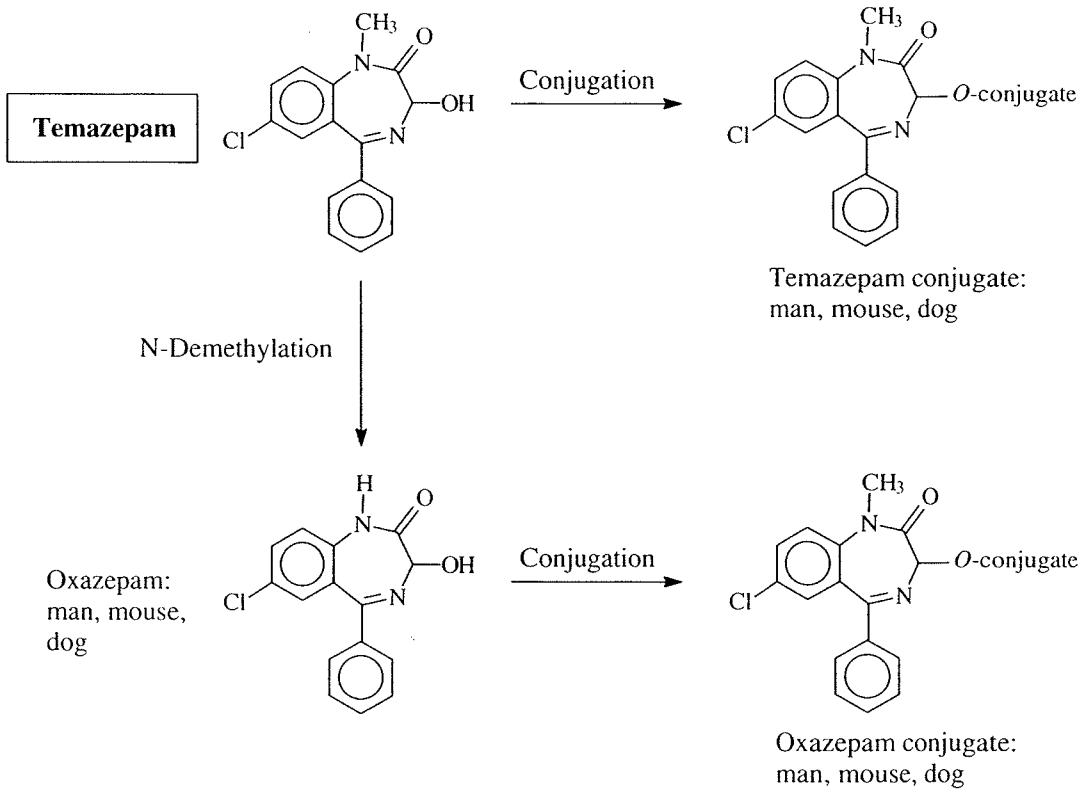
4.1.2 *Experimental systems*

The disposition of temazepam has been studied in various animal species including mice, rats and dogs (Schwarz, 1979) (see Figure 1). Conjugation and N-demethylation were the major metabolic pathways in mice and dogs. In rats, excretion of temazepam was primarily in the faeces (78%), resulting from biliary excretion of metabolites (59%) rather than from incomplete absorption; only 15% was excreted in urine. Male Wistar rats excreted 85–90% of an intravenous dose of [^{14}C]temazepam in the bile within 8 h (Tse *et al.*, 1983a) and about 85% of this material was reabsorbed to be re-excreted predominantly in the bile (Tse *et al.*, 1983b). Mice and dogs excreted 37% in the urine and about 55% in the faeces. Temazepam can cross the placenta in rats and rabbits (Schwarz, 1979).

Expressed as percentages of the dose, the major urinary metabolites in mice were oxazepam conjugate(s) (23%), while in dogs approximately equal quantities of temazepam and oxazepam conjugates were excreted (15% and 16%, respectively). In rats, the

major proportion in urine was unidentified metabolites (only about 1% of the dose was identified) (Schwarz, 1979). In metabolic studies using rat liver microsomes, it has been shown that CYP3A enzymes are involved in the C_3-hydroxylation of diazepam to yield temazepam, but not in the N-dealkylation of temazepam and diazepam (Reilly *et al.*, 1990).

Figure 1. Postulated metabolic pathways of temazepam



From Schwarz (1979)
Conjugate is glucuronide or sulfate

4.2 Toxic effects

4.2.1 *Humans*

(*a*) *Acute toxicity*

In a recent report on 573 lethal intoxications due to self-poisoning with temazepam alone or in combination in the United Kingdom during the 1980s, temazepam was found to be associated with a higher death rate per million prescriptions than any other benzodiazepine hypnotic drug except flurazepam (Serfaty & Masterton, 1993). In another study, temazepam was detected in post-mortem blood samples of 15 overdose deaths. In all cases, ethanol and additional drugs were identified, such as paracetamol, dextropropoxyphene, chlorpromazine and trifluoperazine. In 12 cases, the blood concentrations were well above the highest concentration found after therapeutic doses (750 µg/L) (Forrest *et al.*, 1986). Disulfiram has been reported to precipitate temazepam

toxicity by increasing central nervous system depression (Hardman *et al.*, 1994). There are also several reports of deaths from pulmonary microembolisms after intravenous injection of temazepam from tablets by drug abusers. However, these are clearly not due to the compound itself but to other tablet constituents such as crospovidone (a plastic-like carrier material) which may cause pulmonary foreign-body reaction (Hingorani & Ainsworth, 1993).

(*b*) *Chronic toxicity*

In a post-marketing surveillance report, covering a period of three to five years, of 24 000 patients treated with 10–60 mg temazepam, approximately 10% of the patients experienced adverse effects. Gastrointestinal complaints, sleep disturbances, vertigo, headaches, weakness, lack of concentration, loss of equilibrium and falling were frequently reported. Severe adverse effects such as hypotension, blood dyscrasias and jaundice were reported only in single cases (reviewed by Dollery *et al.*, 1991).

4.2.2 *Experimental systems*

Toxicological tests lasting six months at doses up to 120 mg/kg bw per day in beagle dogs and rats did not show significant organ toxicity (Dollery *et al.*, 1991). In the study of Robison *et al.* (1984) described in Section 3.1.1, the increased mortality observed in the groups of male mice given 80 or 160 mg/kg bw per day was associated with an increased bite wound rate resulting from an apparently drug-related increase in fighting behaviour. There was no significant effect on food consumption, or organ or haematological toxicity in either rats or mice.

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

Dusci *et al.* (1990) described the excretion of temazepam in plasma and breast milk from a lactating mother taking high-dose diazepam and oxazepam. The infant showed no overt physical or mental symptoms of benzodiazepine intoxication.

Kargas *et al.* (1985) reported a stillbirth at term of a female infant (3.82 kg) less than 8 h after maternal ingestion of therapeutic doses of diphenhydramine (50 mg) (Benadryl, an H1-receptor antagonist) and temazepam (30 mg); the authors suggested that a synergistic interaction of the drugs was the most likely cause of death (see Section 4.3.2).

4.3.2 *Experimental systems*

Kargas *et al.* (1985) treated 13 healthy pregnant New Zealand white rabbits on days 29 and 30 (parturition) of gestation with both diphenhydramine (15 mg/kg bw orally) and temazepam (10 mg/kg bw orally). Eighty-one per cent of the fetuses were stillborn or died shortly after birth, exhibiting marked irritability and seizures. In contrast, administration of diphenhydramine alone (up to 50 mg/kg bw) or temazepam alone (up to 80 mg/kg bw) did not increase mortality significantly.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 2 for references and Appendices 1 and 2)

No mitotic spindle abnormality was observed by electron microscopy in the marine flagellate, *Dunaliella bioculata*. No increase in DNA strand breaks and/or alkali-labile sites was observed in the liver of rats given a single or multiple daily doses of temazepam.

Table 2. Genetic and related effects of temazepam

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
*, Mitotic abnormalities, protozoa	–	NT	30	Miernik *et al.* (1986)
DVA, DNA strand breaks, rat liver *in vivo*	–		300 po × 1	Carlo *et al.* (1989)
DVA, DNA strand breaks, rat liver *in vivo*	–		60 po × 15	Carlo *et al.* (1989)

*Not shown on profile

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day

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[1]

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).*

6. References

Beischlag, T.V. & Inaba, T. (1992) Determination of nonderivatized *para*-hydroxylated metabolites of diazepam in biological fluids with a GC megabore column system. *J. analyt. Toxicol.*, **16**, 236–239

British Medical Association/Royal Pharmaceutical Society of Great Britain (1994) *British National Formulary Number 27 (March 1994)*, London, p. 139

British Pharmacopoeial Commission (1993) *British Pharmacopoeia* 1993, Vols. I and II, London, Her Majesty' Stationery Office, pp. 652–653, 1121–1122

Budavari, S., ed. (1995) *The Merck Index*, 12th Ed., Rahway, NJ, Merck & Co.

[1]For definition of the italicized terms, see Preamble, pp. 22–25.

Carlo, P., Finollo, R., Ledda, A. & Brambella, G. (1989) Absence of liver DNA fragmentation in rats treated with high oral doses of 32 benzodiazepine drugs. *Fundam. appl. Toxicol.*, **12**, 34–41

Chan, H.K. & Fogg, A.G. (1981) Polarographic determination of temazepam in soft gelatin capsule formulations. *Analyst*, **106**, 768–775

Chopineau, J., Rivault, F., Sautou, V. & Sommier, M.F. (1994) Determination of temazepam and its active metabolite, oxazepam in plasma, urine and dialysate using solid-phase extraction followed by high-performance liquid chromatography. *J. liq. Chromatogr.*, **17**, 373–383

Council of Europe (1994) *European Pharmacopoeia*, 2nd Ed., Part II, 18th fasc., Sainte-Ruffine, France, Maisonneuve S.A., pp. 954-1–954-3

Divoll, M. & Greenblatt, D.J. (1981) Plasma concentrations of temazepam, a 3-hydroxybenzodiazepine, determined by electron-capture gas-liquid chromatography. *J. Chromatogr. biomed. Appl.*, **222**, 125–128

Divoll, M., Greenblatt, D.J., Harmatz, J.S. & Shader, R.I. (1981) Effect of age and gender on disposition of temazepam. *J. pharm. Sci.*, **70**, 1104–1107

Dollery, C., Boobis, A.R., Burley, D., Davies, D.M., Davies, D.S., Harrison, P.I., Orme, M.E., Park, B.K. & Goldberg, L.I. (1991) *Therapeutic Drugs: Temazepam*, Edinburgh, Churchill Livingstone, pp. T4–T8

Dusci, L.J., Good, S.M., Hall, R.W. & Ilett, K.F. (1990) Excretion of diazepam and its metabolites in human milk during withdrawal from combination high dose diazepam and oxazepam. *Br. J. clin. Pharmacol.*, **29**, 123–126

El-Brashy, A., Aly, F.A. & Belal, F. (1993) Determination of 1,4-benzodiazepines in drug dosage forms by difference spectrophotometry. *Mikrochim. Acta*, **110**, 55–60

Farmindustria (1993) *Repertorio Farmaceutico Italiano* (Italian Pharmaceutical Directory), 7th Ed., Milan, Associazione Nazionale dell'Industria Farmaceutica, CEDOF S.P.A., pp. A-552–A-553

Fatmi, A.A. & Hickson, E.A. (1988) Determination of temazepam and related compounds in capsules by high-performance liquid chromatography. *J. pharm. Sci.*, **77**, 87–89

Fernández, P., Hermida, I., Bermejo, A.M., López-Rivadulla, M., Cruz, A. & Concheiro, L. (1991) Simultaneous determination of diazepam and its metabolites in plasma by high-performance liquid chromatography. *J. liq. Chromatogr.*, **14**, 2587–2599

Forrest, A.R.W., Marsh, I., Bradshaw, C. & Braich, S.K. (1986) Fatal temazepam overdoses (Letter to the Editor). *Lancet*, **i**, 226

Fuccella, L.M., Bolcioni, G., Tamassia, V., Ferrario, L. & Tognoni, G. (1977) Human pharmacokinetics and bioavailability of temazepam administered in soft gelatin capsules. *Eur. J. clin. Pharmacol.*, **12**, 383–386

Gennaro, A.R., ed. (1995) *Remington: The Science and Practice of Pharmacy*, 19th Ed., Vol. II, Easton, PA, Mack Publishing Co., pp. 1160–1161

Gordon, S.M., Freeston, L.K. & Collins, A.J. (1986) Determination of temazepam and its major degradation products in soft gelatin capsules by isocratic reversed-phase high-performance liquid chromatography. *J. Chromatogr.*, **368**, 180–183

Hardman, M., Biniwale, A. & Clarke, C.E. (1994) Temazepam toxicity precipitated by disulfiram (Letter to the Editor). *Lancet*, **344**, 1231–1232

Heel, R.C., Brogden. R.N., Speight, T.M. & Avery, G.S. (1981) Temazepam: a review of its pharmacological properties and therapeutic efficacy as an hypnotic. *Drugs*, **21**, 321–340

Hingorani, A.D. & Ainsworth, R.W. (1993) Pulmonary microembolisation and temazepam (Letter to the Editor). *Br. med. J.*, **307**, 623–624

Ho, P.C., Triggs, E.J., Heazlewood, V. & Bourne, D.W.A. (1983) Determination of nitrazepam and temazepam in plasma by high-performance liquid chromatography. *Ther. Drug Monit.*, **5**, 303–307

Hollister, L.E., Müller-Oerlinghausen, B., Rickels, K. & Shader, R.I. (1993) Clinical uses of benzodiazepines. *J. clin. Psychopharmacol.*, **13** (Suppl. 1)

Jochemsen, R., van Boxtel, C.J., Hermans, J. & Breimer, D.D. (1983) Kinetics of five benzodiazepine hypnotics in healthy subjects. *Clin. Pharmacol. Ther.*, **34**, 42–47

Kargas, G.A., Kargas, S.A., Bruyere, H.J., Jr, Gilbert, E.F. & Opitz, J.M. (1985) Perinatal mortality due to interaction of diphenhydramine and temazepam (Letter to the Editor). *New Engl. J. Med.*, **313**, 1417–1418

Klem, K., Murray, G.R. & Laake, K. (1986) Pharmacokinetics of temazepam in geriatric patients. *Eur. J. clin. Pharmacol.*, **30**, 745–747

Komiskey, H.L., Rahman, A., Weisenburger, W.P., Hayton, W.L., Zobrist, R.H. & Silvius, W. (1985) Extraction, separation and detections of ^{14}C-diazepam and ^{14}C-metabolites from brain tissue of mature and old rats. *J. analyt. Toxicol.*, **9**, 131–133

Kunsman, G.W., Manno, J.E., Przekop, M.A., Manno, B.R., Llorens, K.A. & Kunsman, C.M. (1991) Determination of temazepam and temazepam glucuronide by reversed-phase high-performance liquid chromatography. *J. Chromatogr. biomed. Appl.*, **568**, 427–436

Lau, C.E., Dolan, S. & Tang, M. (1987) Microsample determination of diazepam and its three metabolites in serum by reversed-phase high-performance liquid chromatography. *J. Chromatogr. biomed. Appl.*, **416**, 212–218

Locniskar, A. & Greenblatt, D.J. (1990) Oxidative versus conjugative biotransformation of temazepam. *Biopharm. Drug Dispos.*, **11**, 499–506

Löscher, W. (1982) Rapid gas-chromatographic measurement of diazepam and its metabolites desmethyldiazepam, oxazepam and 3-hydroxydiazepam (temazepam) in small samples of plasma. *Ther. Drug Monit.*, **4**, 315–318

Maurer, H. & Pfleger, K. (1987) Identification and differentiation of benzodiazepines and their metabolites in urine by computerized gas chromatography-mass spectrometry. *J. Chromatogr.*, **422**, 85–101

McCarley, T.D. & Brodbelt, J. (1993) Structurally diagnostic ion-molecule reactions and collisionally activated dissociation of 1,4-benzodiazepines in a quadrupole ion trap mass spectrometer. *Analyt. Chem.*, **65**, 2380–2388

Medical Economics (1996) *PDR®: Physicians' Desk* Reference, 50th Ed., Montvale, NJ, Medical Economics Data Production Co., pp. 2284–2286

Miernik, A., Santa-Maria, A. & Marano, F. (1986) The antimitotic activities of some benzodiazepines. *Experientia*, **42**, 956–958

Patterson, S.E. (1986) Determination of temazepam in plasma and urine by high-performance liquid chromatography using disposable solid-phase extraction columns. *J. pharm. biomed. Analysis*, **4**, 271–274

Reilly, P.E.B., Thompson, D.A., Mason, S.R. & Hooper, W.D. (1990) Cytochrome P450IIIA enzymes in rat liver microsomes: involvement in C_3-hydroxylation of diazepam and nordazepam but not N-dealkylation of diazepam and temazepam. *Mol. Pharmacol.*, **37**, 767–774

Reynolds, J.E.F., ed. (1993) *Martindale: The Extra Pharmacopoeia*, 30th Ed., London, The Pharmaceutical Press, pp. 616–617

Riva, R., Albani, F. & Baruzzi, A. (1982) Determination of camazepam and its metabolite, temazepam, in man by gas-liquid chromatography with electron-capture detection. *Farm. Ed. Prat.*, **37**, 15–19

Robison, R.L., Van Ryzin, R.J., Stoll, R.E., Jensen, R.D. & Bagdon, R.E. (1984) Chronic toxicity/carcinogenicity study of temazepam in mice and rats. *Fundam. appl. Toxicol.*, **4**, 394–405

Sandoz Pharmaceuticals Corp. (1996) *Temazepam*, East Hanover, NJ, United States

Schwarz, H.J. (1979) Pharmacokinetics and metabolism of temazepam in man and several animal species. *Br. J. clin. Pharmacol.*, **8** (Suppl. 1), 23S–29S

Serfaty, M. & Masterton, G. (1993) Fatal poisonings attributed to benzodiazepines in Britain during the 1980s. *Br. J. Psychiatr.*, **163**, 386–393

Sternbach, L.H. & Horst, W.D. (1982) Psychopharmacological agents. In: Grayson, M. & Eckroth, D., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 19, New York, John Wiley & Sons, pp. 342–379

Thomas, J., ed. (1991) *Prescription Products Guide 1991*, 20th Ed., Victoria, Australian Pharmaceutical Publishing Co., pp. 757–758, 1228–1229, 1605–1606

Tse, F.L.S., Ballard, F. & Jaffe, J.M. (1983a) Biliary excretion of [^{14}C]temazepam and its metabolites in the rat. *J. pharm. Sci.*, **72**, 311–312

Tse, F.L.S., Ballard, F., Jaffe, J.M. & Schwarz, H.J. (1983b) Enterohepatic circulation of radioactivity following an oral dose of [^{14}C]temazepam in the rat. *J. Pharm. Pharmacol.*, **35**, 225–228

United States Pharmacopeial Convention (1994) *The 1995 US Pharmacopeia*, 23rd Rev./*The National Formulary*, 18th Rev., Rockville, MD, pp. 1490–1491

Vidal (1995) *Dictionnaire Vidal*, 71st Ed., Paris, Editions du Vidal, pp. 1047–1048

Walash, M.I., Belal, F., Metwally, M.E. & Hefnawy, M.M. (1994) Selective fluorimetric method for the determination of some 1,4-benzodiazepine drugs containing a hydroxyl group at C-3. *J. pharm. biomed. Analysis*, **12**, 1417–1423

Zapardiel, A., Peréz Lopéz, J.A., Bermejo, E. & Hernández, L. (1988) Application of adsorptive stripping voltammetry to the determination of the psychoactive drug temazepam in urine. *Fresenius' Z. analyt. Chem.*, **330**, 707–710