having a slight odour. Soluble 1 in 8 of water, 1 in 270 of dehydrated alcohol, and 1 in 280 of chloroform; practically insoluble in acetone, in ether, and in benzene. Store in airtight containers. Protect from light.

Stability. A combination of the stabilisers hydroxyquinoline sulfate and vanillin could protect tiotixene from photodegradation.[1]

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Tiotixene is less likely to cause sedation but extrapyramidal effects are more frequent.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

◊ In 15 adequately controlled schizophrenic patients receiving oral tiotixene 15 to 60 mg daily in 2, 3, or 4 divided doses, plasma concentrations were found to be in the relatively narrow range of 10 to 22.5 nanograms/mL 126 to 150 minutes after the last daily dose despite the fourfold difference in dosage.[1] Investigations in a further 5 patients indicated that peak plasma concentrations were obtained about 1 to 3 hours after a dose, indicating rapid absorption with an absorption half-time of about 30 minutes. There was an early plasma half-life of about 210 minutes and a late half-life of about 34 hours; resurgence of drug concentrations in some subjects might have been due to enterohepatic recycling.

1. Hobbs DC, *et al*. Pharmacokinetics of thiothixene in man. *Clin Pharmacol Ther* 1974; **16:** 473–8.

Metabolism. There has been a study[1] indicating that tiotixene may induce its own metabolism.

1. Bergling R, *et al*. Plasma levels and clinical effects of thioridazine and thiothixene. *J Clin Pharmacol* 1975; **15:** 178–86.

Uses and Administration

Tiotixene is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It has a piperazine side-chain. It is used in the treatment of psychoses including schizophrenia (p.955). Tiotixene is given orally as the base or hydrochloride and by intramuscular injection as the hydrochloride. Doses are expressed in terms of the base. Tiotixene 1 mg is equivalent to about 1.2 mg of tiotixene hydrochloride.

The usual initial oral dose is 2 mg three times daily (or 5 mg twice daily in more severe conditions) gradually increasing to 20 to 30 mg daily if necessary; once-daily dosage may be adequate. In severe or resistant psychoses doses of up to 60 mg daily may be given. The usual initial intramuscular dose is 4 mg two to four times daily increased if necessary to a maximum of 30 mg daily.

Tiotixene should be given in reduced dosage to elderly or debilitated patients.

Preparations

USP 31: Thiothixene Capsules; Thiothixene Hydrochloride for Injection; Thiothixene Hydrochloride Injection; Thiothixene Hydrochloride Oral Solution.

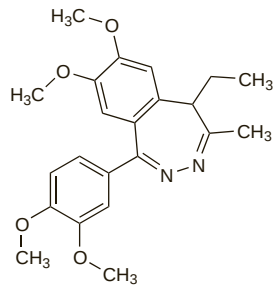
Proprietary Preparations (details are given in Part 3)
Austral.: Navane; ***Canad.:*** Navane; ***Hong Kong:*** Navane; ***Neth.:*** Navane†; ***NZ:*** Thixit; ***USA:*** Navane.

Tofisopam *(rINN)*

EGYT-341; Tofisopaami; Tofisopamum; Tofizopam. 1-(3,4-Dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5*H*-2,3-benzodiazepine.

Тофизопам

$C_{22}H_{26}N_2O_4$ = 382.5.
CAS — 22345-47-7.
ATC — N05BA23.
ATC Vet — QN05BA23.



Pharmacopoeias. In *Jpn.*

Profile

Tofisopam is a 2,3-benzodiazepine related structurally to the 1,4-benzodiazepines such as diazepam (p.986) and sharing some of the same actions. It is reported, however, to be largely lacking in the sedative, anticonvulsant, and muscle relaxant properties of the conventional benzodiazepines. Tofisopam has been given orally in the short-term treatment of anxiety disorders. The *R*-(+)-isomer, dextofisopam, is under investigation in the treatment of irritable bowel syndrome.

Preparations

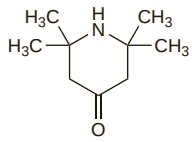
Proprietary Preparations (details are given in Part 3)
Cz.: Grandaxin; ***Hung.:*** Grandaxin; ***Jpn:*** Grandaxin; ***Rus.:*** Grandaxin (Грандаксин); ***Thai.:*** Grandaxin.

Triacetonamine Tosilate

Tempidon. 2,2,6,6-Tetramethyl-4-piperidone-toluenesulfonate.

Триацетонамина Тозилат

$C_{16}H_{25}NO_4S$ = 327.4.
CAS — 826-36-8 (triacetonamine); 29334-13-2 (triacetonamine tosilate).



(triacetonamine)

Profile

Triacetonamine tosilate has anxiolytic actions and is used in combination preparations with analgesics.

Preparations

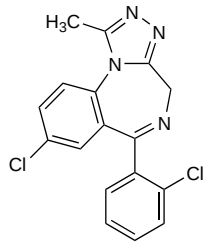
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Rus.:*** Tempalgin (Темпалгин); Tempanginol (Темпангинол).

Triazolam *(BAN, USAN, rINN)*

Clorazolam; Triatsolaami; Triazolamum; U-33030. 8-Chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine.

Триазолам

$C_{17}H_{12}Cl_2N_4$ = 343.2.
CAS — 28911-01-5.
ATC — N05CD05.
ATC Vet — QN05CD05.



Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Triazolam). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 1000 of alcohol, 1 in 25 of chloroform, and 1 in 600 of 0.1N hydrochloric acid.

Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects and Treatment

As for Diazepam, p.987.

Effects on the liver. A 44-year-old man developed severe pruritus with jaundice which subsequently proved fatal. Liver histology showed intense cholestasis. Triazolam was considered to be the most likely cause.[1]

1. Cobden I, *et al*. Fatal intrahepatic cholestasis associated with triazolam. *Postgrad Med J* 1981; **57:** 730–1.

Effects on mental function. The effects of triazolam on mental function have been controversial since van der Kroef first described in 1979 a range of symptoms including anxiety, amnesia, depersonalisation and derealisation, depression, paranoia, and severe suicidal tendencies that he had seen in 25 patients and attributed to triazolam.[1] This led to suspension of triazolam in the Netherlands (re-approved in 1990) and removal of the 1-mg tablet from other markets. Continued reporting of similar symptoms of cognitive impairment with triazolam resulted in withdrawal of the 500-microgram dosage form in several countries in 1987 and 1988 and in a gradual reduction of recommended dosage from 1 mg at night down to 125 to 250 micrograms at night. Triazolam was withdrawn from the UK[2] and some other markets in 1991. Opinion still remains divided over the adverse effects of triazolam, the main issues being its propensity to cause adverse effects relative to other benzodiazepines and whether its risk-benefit ratio is acceptable to justify its continued use.[3,4]

Others[5] have reviewed spontaneous adverse effects reported to the FDA in the USA for triazolam, temazepam, and flurazepam. Daytime sedation was noted with all three, but triazolam caused more agitation, confusion, hallucinations, and amnesia. Such effects occurred frequently with the 250-microgram dose as well as with the 500-microgram dose. Similar results were obtained after analysis of reports for triazolam and temazepam in the first 7 years of marketing, although the possibility that selection factors were producing higher reporting rates for triazolam could not be entirely excluded.[6] A study[7] gave triazolam 500 micrograms, lormetazepam 2 mg, or placebo, to groups of 40 patients for 25 nights and observed the greatest frequency of daytime anxiety, panic, derealisation, and paranoia with triazolam. Another[8] found a greater total number of reports of memory impairment or amnesia after nightly doses of triazolam 500 micrograms compared with temazepam 30 mg. Triazolam also impaired delayed, but not immediate, memory recall. Similar cases of memory impairment occurring with triazolam at doses of 125 and 250 micrograms have reportedly been submitted to the UK CSM.[2] The emergence of daytime symptoms after more than a few days' treatment with triazolam could be attributed to rebound or withdrawal phenomena occurring as a result of rapid elimination of the drug.

As regards the risk-benefit ratio of triazolam some workers have questioned the hypnotic efficacy of the drug at a dose of 250 micrograms and consider that reduction of the dose has decreased efficacy more than adverse effects.[3]

In defence of triazolam, the FDA and the manufacturers (*Upjohn*) have considered epidemiological studies which, unlike the FDA spontaneous reporting scheme, have been unable to demonstrate a substantial difference in its adverse effects compared with other benzodiazepines except, perhaps, in the incidence of amnesia.[9] Retrospective studies[10,11] claiming similar findings have been the subject of criticism.[12-14] Other workers have cited studies indicating benefit of triazolam 250 micrograms for the treatment of insomnia.[15] A review by the US Institute of Medicine found that triazolam was safe when given in a dose of 250 micrograms daily for 7 to 10 days but called for studies of lower doses and of long-term use.[16]

1. Van der Kroef C. Reactions to triazolam. *Lancet* 1979; **ii:** 526.
2. Anonymous. The sudden withdrawal of triazolam—reasons and consequences. *Drug Ther Bull* 1991; **29:** 89–90.
3. O'Donovan MC, McGuffin P. Short acting benzodiazepines. *BMJ* 1993; **306:** 945–6.
4. Ghaeli P, *et al.* Triazolam treatment controversy. *Ann Pharmacother* 1994; **28:** 1038–40.
5. Bixler EO, *et al.* Adverse reactions to benzodiazepine hypnotics: spontaneous reporting system. *Pharmacology* 1987; **35:** 286–300.
6. Wysowski DK, Barash D. Adverse behavioral reactions attributed to triazolam in the Food and Drug Administration's spontaneous reporting system. *Arch Intern Med* 1991; **151:** 2003–8.
7. Adam K, Oswald I. Can a rapidly-eliminated hypnotic cause daytime anxiety? *Pharmacopsychiatry* 1989; **22:** 115–19.
8. Bixler EO, *et al.* Next-day memory impairment with triazolam use. *Lancet* 1991; **337:** 827–31.
9. Drucker RF, MacLeod N. Benzodiazepines. *Pharm J* 1989; **243:** 508.
10. Hindmarch I, *et al.* Adverse events after triazolam substitution. *Lancet* 1993; **341:** 55.
11. Rothschild AJ, *et al.* Triazolam and disinhibition. *Lancet* 1993; **341:** 186.
12. Hawley CJ, *et al.* Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567.
13. Vela-Bueno A. Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567.
14. Kales A, *et al.* Adverse events after triazolam substitution. *Lancet* 1993; **341:** 567–8.
15. Gillin JC, Byerley WF. Diagnosis and management of insomnia. *N Engl J Med* 1990; **323:** 487.
16. Ault A. FDA advisers find no major Halcion dangers. *Lancet* 1997; **350:** 1760.

Precautions

As for Diazepam, p.988.

Hepatic impairment. Cirrhosis decreased the apparent oral clearance of triazolam to an extent depending on the severity of the liver disease.[1] An initial dose of 125 micrograms was suggested for patients with severe liver dysfunction. It was suggested that the relative lack of effect that mild to moderate cirrhosis had on the metabolism of oral triazolam might be due to some first-pass metabolism occurring in the intestinal wall.[2]

1. Kroboth PD, *et al*. Nighttime dosing of triazolam in patients with liver disease and normal subjects: kinetics and daytime effects. *J Clin Pharmacol* 1987; **27:** 555–60.
2. Robin DW, *et al.* Triazolam in cirrhosis: pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 1993; **54:** 630–7.

Renal impairment. Peak plasma-triazolam concentrations were lower in 11 dialysis patients compared with 11 controls.[1] It was postulated that a relatively high basal gastric acid secretion in dialysis patients could result in hydrolysis and opening of the ring structure of triazolam effectively reducing its systemic avail-