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.

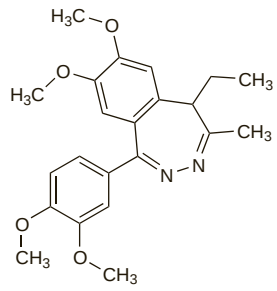
Proprietary Preparations (details are given in Part 3)
Austral.: Navane; ***Canad.:*** Navane; ***Hong Kong:*** Navane; ***Neth.:*** Navane†; ***NZ:*** Thixit; ***USA:*** Navane.

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

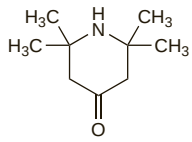
Proprietary Preparations (details are given in Part 3)
Cz.: Grandaxin; ***Hung.:*** Grandaxin; ***Jpn:*** Grandaxin; ***Rus.:*** Grandaxin (Грандаксин); ***Thai.:*** Grandaxin.

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

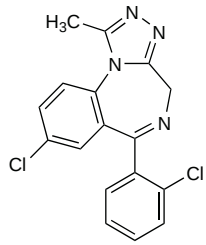
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Rus.:*** Tempalgin (Темпалгин); Tempanginol (Темпангинол).

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-

ability. Giving an antacid could reverse this effect. Renal failure had no other effect on the pharmacokinetics of triazolam which could probably be given in usual doses.

1. Kroboth PD, *et al.* Effects of end stage renal disease and aluminium hydroxide on triazolam pharmacokinetics. *Br J Clin Pharmacol* 1985; **19:** 839–42.

Interactions
As for Diazepam, p.989.

Pharmacokinetics
Triazolam is rapidly and nearly completely absorbed from the gastrointestinal tract, peak plasma concentrations being achieved within 2 hours of an oral dose. Triazolam has a plasma elimination half-life ranging from 1.5 to 5.5 hours. It is reported to be about 89% bound to plasma proteins. Hydroxylation of triazolam in the liver is mediated by the cytochrome P450 isoenzyme CYP3A4. Triazolam is excreted in the urine mainly in the form of its conjugated metabolites with only small amounts appearing unchanged.

◊ References.

1. Garzone PD, Kroboth PD. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1989; **16:** 337–64.
2. Greenblatt DJ, *et al.* Age and gender effects on the pharmacokinetics and pharmacodynamics of triazolam, a cytochrome P450 3A substrate. *Clin Pharmacol Ther* 2004; **76:** 467–79.

Uses and Administration
Triazolam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used as a hypnotic in the short-term management of insomnia (p.957) in oral doses of 125 to 250 micrograms at night for no more than 2 weeks; doses of up to 500 micrograms at night have been used for resistant cases but these may be associated with an increased risk of severe adverse effects (see Effects on Mental Function, above). Initial doses of 125 micrograms at night have been suggested for elderly or debilitated subjects, increased up to a maximum of 250 micrograms only if necessary.

Administration in hepatic or renal impairment. See under Precautions, above.

Preparations
USP 31: Triazolam Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Halcion; ***Austria:*** Halcion; ***Belg.:*** Halcion; ***Braz.:*** Halcion†; ***Canad.:*** Apo-Triazo; Halcion; ***Chile:*** Balidon; Somese; ***Cz.:*** Halcion†; ***Denm.:*** Halcion; Rilamir; ***Fin.:*** Halcion; ***Fr.:*** Halcion†; ***Ger.:*** Halcion; ***Gr.:*** Halcion; ***Hong Kong:*** Halcion; ***Irl.:*** Halcion; Trilam; ***Israel:*** Halcion; ***Ital.:*** Halcion; Songar; ***Malaysia:*** Somese; ***Mex.:*** Halcion; ***Neth.:*** Halcion†; ***NZ:*** Halcion; Hypam; ***Port.:*** Halcion; ***S.Afr.:*** Halcion; ***Spain:*** Halcion; ***Swed.:*** Halcion; ***Switz.:*** Halcion; ***Thai.:*** Halcion; Trycam†; ***USA:*** Halcion; ***Venez.:*** Somese.

Triclofos Sodium *(BANM, USAN, rINNM)*

Natrii Triclofosum; Sch-10159; Sodium Triclofos; Triclofós sódico; Triclofos Sodique. Sodium 2,2,2-trichloroethyl hydrogen orthophosphate.

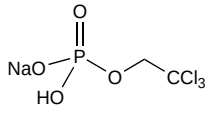
Натрий Триклофос

$C_2H_3Cl_3NaO_4P$ = 251.4.

CAS — 306-52-5 (triclofos); 7246-20-0 (triclofos sodium).

ATC — N05CM07.

ATC Vet — QN05CM07.



Pharmacopoeias. In *Br.* and *Jpn.*
BP 2008 (Triclofos Sodium). A white or almost white, odourless or almost odourless, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in ether. A 2% solution in water has a pH of 3.0 to 4.5.

Dependence and Withdrawal, Adverse Effects, Treatment, and Precautions
As for Cloral Hydrate, p.979 but causes fewer gastrointestinal disturbances. Also, triclofos sodium is not corrosive to skin and mucous membranes.

Interactions
As for Cloral Hydrate, p.979.

Pharmacokinetics
Triclofos sodium is rapidly hydrolysed to trichloroethanol, peak serum concentrations being achieved within about one hour after oral dosage. For the pharmacokinetics of trichloroethanol, see Cloral Hydrate, p.979.

Uses and Administration
Triclofos sodium has hypnotic and sedative actions similar to those of cloral hydrate (p.979) but it is more palatable and causes less gastric irritation. It is used similarly in the short-term management of insomnia (p.957) and for sedation of children before painless procedures; however, its use as a hypnotic, particularly in children, is now limited.

The usual adult dose as a hypnotic is 1 to 2 g orally at night. A suggested hypnotic dose for children 1 month to 1 year of age is 25 to 30 mg/kg; children aged 1 to 5 years may be given single doses of 250 to 500 mg, and children aged 6 to 12 years may be given single doses of 0.5 to 1 g. Although not licensed in the UK for sedation of children before painless procedures, the *BNFC* suggests that those aged 1 month to 18 years may be given 30 to 50 mg/kg (maximum of 2 g) 45 to 60 minutes before the procedure; up to 100 mg/kg (maximum of 2 g) may be used with respiratory monitoring.

Preparations
BP 2008: Triclofos Oral Solution.

Proprietary Preparations (details are given in Part 3)
India: Tricloryl; ***Irl.:*** Tricloryl†; ***Israel:*** Triclonam.

Trifluoperazine Hydrochloride

(BANM, rINNM)

Hidrocloruro de trifluoperazina; Trifluoperazin Hidroklorür; Trifluoperazin hydrochlorid; Trifluopérazine, chlorhydrate de; Trifluoperazinhidroklorid; Trifluoperazinhydroklorid; Trifluoperazini hydrochloridum; Trifluoperazino hidrochloridas; Trifluoperazyny chlorowodorek; Trifluoriperatsiinihydrokloridi; Triphthazinum. 10-[3-(4-Methylpiperazin-1-yl)propyl]-2-trifluoromethylphenothiazine dihydrochloride.

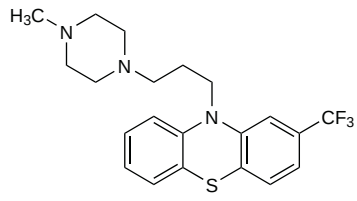
Трифлуоперазина Гидрохлорид

$C_{21}H_{24}F_3N_3S,2HCl$ = 480.4.

CAS — 117-89-5 (trifluoperazine); 440-17-5 (trifluoperazine hydrochloride).

ATC — N05AB06.

ATC Vet — QN05AB06.



(trifluoperazine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Trifluoperazine Hydrochloride). A white to pale yellow, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in ether. A 10% solution in water has a pH of 1.6 to 2.5. Protect from light.
USP 31 (Trifluoperazine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. Soluble 1 in 3.5 of water, 1 in 11 of alcohol, and 1 in 100 of chloroform; insoluble in ether and in benzene. pH of a 1 in 20 solution is between 1.7 and 2.6. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects, Treatment, and Precautions
As for Chlorpromazine, p.969. Trifluoperazine is less likely to cause sedation, hypotension, hypothermia, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects particularly when the daily dose exceeds 6 mg.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of trifluoperazine on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 29/04/04)

Interactions
As for Chlorpromazine, p.973.

Pharmacokinetics
Trifluoperazine hydrochloride is readily absorbed from the gastrointestinal tract after oral doses; peak plasma concentrations are attained 1.5 to 6 hours after ingestion and bioavailability is subject to interindividual variation. It is highly bound to plasma proteins. The elimination of trifluoperazine is multiphasic and the terminal half-life is about 22 hours. The major metabolite is the possibly active *N*-oxide. Other metabolites include the sulfoxide and the 7-hydroxy derivative. Trifluoperazine is distributed into breast milk.

Uses and Administration
Trifluoperazine is a phenothiazine antipsychotic with general properties similar to those of chlorpromazine (p.975). It has a piperazine side-chain.

Trifluoperazine is used in the treatment of a variety of psychiatric disorders including schizophrenia (p.955), severe anxiety (p.952), and disturbed behaviour (p.954). It is also used for the control of nausea and vomiting (p.1700).

Trifluoperazine is given as the hydrochloride but doses are expressed in terms of the base. Trifluoperazine 1 mg is equivalent to about 1.2 mg of trifluoperazine hydrochloride. A modified-release preparation is also available in some countries. Trifluoperazine should be given in reduced dosage to elderly or debilitated patients.

The usual initial *oral* dose for the treatment of schizophrenia and other **psychoses** is 2 to 5 mg twice daily, gradually increased to a usual range of 15 to 20 mg daily; in severe or resistant psychoses daily doses of 40 mg or more have been given. For the control of acute psychotic symptoms it may be given by deep *intramuscular* injection in a dose of 1 to 2 mg, repeated if necessary every 4 to 6 hours; more than 6 mg daily is rarely required. The initial oral dose for use in *children* is up to 5 mg daily in divided doses adjusted according to age, body-weight, and response, or 1 mg given once or twice daily by intramuscular injection.

For the control of **nausea and vomiting** the usual adult *oral* dose is 1 or 2 mg twice daily; up to 6 mg daily may be given in divided doses. *Children* aged 3 to 5 years may be given up to 1 mg daily in divided doses; this may be increased to a maximum of 4 mg daily in children aged 6 to 12 years.

When used as an adjunct in the short-term management of **severe anxiety disorders** doses are similar to those used for the control of nausea and vomiting.

Schizophrenia. A systematic review[1] of the use of trifluoperazine for schizophrenia (p.955) concluded that it appeared to be of similar efficacy to other commonly used classical antipsychotics with a similar profile of adverse effects. However, there did not appear to be good evidence for claims that it was effective for schizophrenia at low doses.

1. Marques LO, *et al.* Trifluoperazine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 17/05/05).

Preparations
BP 2008: Trifluoperazine Tablets;
USP 31: Trifluoperazine Hydrochloride Injection; Trifluoperazine Hydrochloride Syrup; Trifluoperazine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Stelazine; ***Austral.:*** Stelazine; ***Braz.:*** Stelazine; ***Gr.:*** Stelazine; Stelium; ***India:*** Trinicalm; ***Indon.:*** Stelazine; ***Irl.:*** Stelazine; ***Ital.:*** Modalina; ***Mex.:*** Flupazine; Stelazine; ***NZ:*** Stelazine; ***S.Afr.:*** Stelazine; Terflurazine; ***Spain:*** Eskazine; ***Thai.:*** Psyrazine; Triflumed; Triozine; Triplex; ***Turk.:*** Stilizan; ***UK:*** Stelazine; ***Venez.:*** Leptazine; Taclorpil†.

Multi-ingredient: ***Arg.:*** Cuait D; Cuait N; Stelapar; ***Braz.:*** Stelapar†; ***Canad.:*** Stelabid†; ***India:*** Sycot; Trinicalm Forte; Trinicalm Plus; ***Ital.:*** Parmodalin; ***Mex.:*** Stelabid.