

methyl-6*H*-thianol[3,2-*f*]-s-triazolol[4,3-*a*][1,4]diazepine, is also known as Ladormin, Lendormin, Lindormin, Noctilan, Dormex, and Sintonal.

2. Similarity to already known substances and affects on the central nervous system

Brotizolam produces pharmacological effects typical of the class of benzodiazepines. It binds with high affinity to benzodiazepine receptors. A number of studies have demonstrated the therapeutic effects of brotizolam as a short-acting hypnotic with a mean elimination half-life of 4–5 hours.

3. Dependence potential

Animal studies have shown that brotizolam has barbiturate type subjective effects. It produces alcohol-barbiturate type mild-to-severe withdrawal syndromes, and has some reinforcing effects. The few clinical studies available demonstrate the occurrence of rebound insomnia upon withdrawal of the drug. These findings collectively indicate that brotizolam has a moderate dependence potential similar to other benzodiazepine hypnotics.

4. Actual abuse and/or evidence of likelihood of abuse

In spite of its pharmacological similarity to other benzodiazepine hypnotics, and its marketing in 18 countries, actual abuse of brotizolam has been reported only in Germany and Hong Kong. In Germany, although there has been some abuse and illicit activity involving brotizolam, this was not considered serious enough to subject the drug to the distribution control measures which are applicable to controlled drugs. In Hong Kong, following its introduction to the local market in 1988, the abuse of brotizolam increased rapidly among young people, leading to the application of stricter regulatory control measures in 1990. The company withdrew the product from the market in 1992.

Based on the experiences of Germany and Hong Kong with brotizolam, it is assessed that brotizolam has an appreciable abuse liability. The problem may be more acute in situations where prescription requirements for dispensing are not effectively implemented or are not applicable.

5. Therapeutic usefulness

Brotizolam is marketed as a hypnotic in 18 countries and may be considered to have a moderate to great therapeutic usefulness.

6. Recommendation

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of brotizolam is assessed to be significant, in cases where prescription requirements are not effectively implemented or required, a situation which exists in many developing countries. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that brotizolam be included in Schedule IV of the Convention on Psychotropic Substances, 1971.

Etryptamine

1. Substance identification

Etryptamine (INN; CAS 2235–90–7), chemically 3-(2-aminobutyl)indole, is also known as α -ethyltryptamine and Monase. Etryptamine has a single chiral centre, so that two stereoisomeric forms and one racemate are possible.

2. Similarity to already known substances and affects on the central nervous system

Chemically, etryptamine is similar to hallucinogenic tryptamines, some of which are already in Schedule I of the 1971 Convention. Animal studies indicate that etryptamine produces effects similar to those produced by 3,4-methylenedioxymetamphetamine (MDMA), but its hallucinogenic effects are more pronounced than its stimulant effects. Like amphetamine, etryptamine increases locomotor activity in rodents. In a study using the behaviour pattern monitoring method, etryptamine significantly decreased investigatory behaviour, which is typical of hallucinogens and MDMA-like substances. The stimulant effects of etryptamine are slower in onset and more prolonged in duration than those of amphetamine. In addition, etryptamine inhibits monoamine oxidase.

In the early 1960s, etryptamine acetate was placed on the United States market as an anti-depressant. Soon after its release on the market, it was reported that etryptamine was associated with a high incidence of agranulocytosis, a potentially fatal condition. More recently, there were isolated reports of etryptamine being associated with the deaths of drug abusers in Germany, Spain, and the United States of America.

3. Dependence potential

Animal drug discrimination studies indicate that etryptamine has subjective effects resembling MDMA. Self-administration studies indicate that etryptamine has a moderate dependence potential, which is lower than that of cocaine.

4. Actual abuse and/or evidence of likelihood of abuse

Information available from various sources indicates that there has been some abuse of etryptamine in Germany, Spain and the United States of America. Etryptamine is estimated to have a high abuse liability.

5. Therapeutic usefulness

In view of its association with serious adverse reactions such as agranulocytosis, the therapeutic usefulness of etryptamine is assessed to be very limited, if any.

6. Recommendation

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of etryptamine is assessed to be especially serious. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that etryptamine be included in Schedule I of the Convention on Psychotropic Substances, 1971.

Flunitrazepam

1. Substance identification

Flunitrazepam (INN; CAS 1622–62–4), chemically 5-(*o*-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2*H*-1,4-benzodiazepin-2-one, is also known as Absint, Darkene, Fluninoc, Flunipam, Fluinita, Flunitrazepan-ratiopharm, Hypnodrom, Hipnosedon, Inervon, Narcozep, Parnox, Primun, Rohipnol, Rohypnol and Valsers.

2. Similarity to already known substances and affects on the central nervous system

Flunitrazepam has typical benzodiazepine effects, with a greater sedative-hypnotic potency than diazepam or chlordiazepoxide. Flunitrazepam binds with high affinity to central benzodiazepine receptors. Flunitrazepam is rapidly absorbed after oral administration. The elimination half-life of flunitrazepam following a single oral dose ranges between 9 and 25 hours in humans. Accumulation occurs with chronic administration.

3. Dependence potential

Drug discrimination, drug withdrawal and self-administration studies indicate that flunitrazepam has a dependence potential similar to other benzodiazepines. Rebound insomnia, which is considered a form of withdrawal from sedative-hypnotics, may be contributing to the tendency of continuing the medication. These data do not suggest any substantive difference between flunitrazepam and other benzodiazepine hypnotics.

However, drug preference studies in opioid users have shown that flunitrazepam and diazepam stand out from other benzodiazepines in terms of producing a strong positive reinforcing effect in these subjects.

Based on the above, flunitrazepam is estimated to have a moderate abuse potential which may be higher than other benzodiazepines. The rapid onset and longer duration of action, coupled with the strong sedative-hypnotic effects, may be contributing to its higher abuse potential.

4. Actual abuse and/or evidence of likelihood of abuse

Information available indicates that the non-medical use or abuse of flunitrazepam is widespread among drug abusers, particularly opioid and cocaine abusers. Flunitrazepam is reported to be the most widely abused benzodiazepine by opioid abusers in many large cities in Europe, Asia and Oceania. Flunitrazepam abuse is reported even in the United States of America where the drug is not marketed for therapeutic use.

Reported reasons for the abuse of flunitrazepam include potentiation of opioid effects, substitution for the opioid when it is difficult to obtain, and self-medication for opioid withdrawal. Oral intake is the most common route of administration of flunitrazepam but some abusers take the drug by intravenous injection or by smoking. Health problems associated with the abuse of flunitrazepam include deaths directly or indirectly related with the drug use, drug dependence, withdrawal syndrome, paranoia, amnesia and other psychiatric disorders.