World Health Organization

Critical pre-review report:

Zopiclone

Expert Committee on Drug Dependence

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This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

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Executive summary

Non-benzodiazepine drugs have been developed since the 1980s for the management of insomnia to replace benzodiazepines, which have an adverse effect profile. Zopiclone, commonly known as a "Z-drug", is one of these. Zopiclone was first introduced onto the market in 1986 for short-term treatment of insomnia.

Zopiclone (in pill form) is widely prescribed to patients with chronic insomnia to shorten sleep latency, decrease waking frequency and improve the duration and quality of sleep. The sedative efficacy of zopiclone is at least as good as that of long-, intermediate- and short-acting benzodiazepines. Zopiclone is generally prescribed at 7.5 mg/dose per day, purportedly with minimal adverse effects. Doses > 7.5 mg/day are prescribed when indicated, while a lower dose (3.75 mg/day) is recommended for elderly patients. Zopiclone use, particularly at higher doses or in combination with alcohol, is associated with increased risks of car accidents, psychomotor impairment, falls and fractures, especially in the elderly. Regular long-term use of zopiclone is not recommended. The manufacturers state that the treatment duration should not exceed 4 weeks, while general recommendations for hypnotic agents, including zopiclone, are that they should be used only intermittently. Nonetheless, many patients with chronic insomnia use zopiclone regularly over extended periods.

Zopiclone binds to sites on or closely linked to the benzodiazepine receptor complex and thus show benzodiazepine-like hypnotic, anxiolytic, anticonvulsant and myorelaxant properties. Specifically, zopiclone acts as a full competitive agonist at the γ-aminobutyric acid type A ($GABA_A$) receptor complex. Although zopiclone and the benzodiazepines bind to the same recognition site, differences in receptor function after binding suggest that they interact with separate binding domains and/or induce different conformational changes in the $GABA_A$ receptor complex.

Like other benzodiazepine receptor agonists, zopiclone is commonly a contributory rather than a causal agent in poisonings, although fatalities have occurred when the dose is high enough and in vulnerable people. Overdose of zopiclone is manifested by varying degrees of central nervous system (CNS) depression, ranging from drowsiness to coma, and is dose-dependent. Mild cases are characterized by prolonged sleep, drowsiness, confusion and lethargy, while more severe cases may include ataxia, hypotonia, hypotension, methaemoglobinaemia, respiratory depression and coma. Overdose in healthy individuals can be life-threatening when combined with other CNS depressants, including alcohol, especially in people with concomitant illness, debilitated patients and the elderly. Supportive treatment in an adequate clinical environment is usually sufficient to reverse toxicity.

Few data were available on the dependence or abuse potential of zopiclone in animal models; however, monkeys will self-administer zopiclone, and it has benzodiazepine-like discriminative stimulus effects that are antagonized by the $GABA_A$ antagonist, flumazenil.

Large population datasets include a fairly large number of cases of presentations to emergency departments associated with recreational use of zopiclone, although, in the majority of cases, other drugs were also consumed. Non-medical use has been established in large epidemiological studies, and there appears to be widespread access to zopiclone from various sources, including online purchase without a prescription.

Zopiclone has been identified as a significant concern to WHO Member States: 599 incidents that included zopiclone were reported between January 2020 and March 2022 through the International Operations on New Psychoactive Substances Incident Communication System (IONICS) platform of the International Narcotics Control Board by 11 governments. Zopiclone was reported through IONICS for the first time in 2020; the number of incidents involving the substance has since increased, from 36 in 2020 to 537 in 2021.

1. Substance identification

A. International nonproprietary name

Zopiclone

B. Chemical Abstracts Service registry number

Zopiclone free base: 43200-80-2

C. Other chemical names

Zopiclone free base; 5*H*-pyrrolo[3,4-*b*]pyrazine, 1-piperazinecarboxylic acid deriv. (ZCI); (±)-Zopiclone; Amoban; Amovane; Hypnor; Imoclone; Imovance; Imovane; RP 27267; Sopivan; Zimovane; Zopiclone

D. Trade names

Adco-Zopimed; Alchera; Alpaz; Amoban; Amobanters; Amvey; Datolan; Descanil; Dobroson; Dopareel; Dopareel; Eurovan; Foltran; Genclone; Good-Knight; Imoclone; Imolone; Imovane; Imozop; Imrest; Insomnium; Insopin; Jin Meng; Limovan; Losopil; Lyzop; Metorom; Milovan; Neo-Cone; Noctidem; Nocturno; Normason; Optidorm; Ozal; Piclodorm; Piklon; Qing Er Qi; Qualivane; Relaxon; Rhovane; San Chen; Senzop; Siaten; Slipvell; Somnal; Somnol; Somnosan; Sonnat; Sonoesan; Synovane; Torson; Veneco; Ximovan; z-Dorm; Zetix; Zileze; Zimoclone; Zimovane; Zolief; Zolinox; Zolium; Zolon; Zometic; Zomni; Zonix; Zoperil; Zopicalma; Zopicon; Zopigen; Zopinil.Zopinox; Zopistad; Zopitabs; Zopitan; Zopitidin; Zopitin; Zopivane; Zorclone; ACT Zopiclone; Apo-Dream; Apo-Zopiclone; Austell-Zopiclone; Chemmart Zopiclone; Docilen; DOM-Zopiclone; Dormex; Drimolin; Ecodorm; Hypnor; Jamp Zopiclone; Mar-Zopiclone; Mint-Zopiclone; Mylan-Zopiclone; Optimal; Phamzopic; Priva-zopiclone; Pro-Zopiclone; RAN-Zopiclone; ratio-Zopiclone; Riva-Zopiclone; Sandoz Zopiclone; Somnogama; Somnols; Sonlaks; Sonlax; Sonlaks; Terry White Chemists Zopiclone; Uniclone; Yi Tan Ning; Zalepla; Ziclone; Zopiclodura; Zopiclon; Zopiclona; Zopiklon; Zopitran; Zosleep-Humanity

E. Street names

Zopiclone; Z-drug; zops; zoppies *(Buckingham, 2020)*; zim-zims ("Zopiclone - Drugs.com," 2022)

F. Physical appearance

Zopiclone has been reported as a white or slightly yellowish powder *(EDQM, 2022).*

G. WHO review history

Zopiclone was pre-reviewed by the Expert Committee on Drug Dependence at its 29th meeting, when it recommended that surveillance be continued but that a critical review was not required. In view of the abuse liability of the drug and the significant number of reports of adverse drug reactions (ADRs) related to abuse reported to the WHO international drug monitoring programme, zopiclone was pre-reviewed by the Committee at its 33rd meeting, when it recommended a critical review. Zopiclone was critically reviewed at the 34th meeting, in 2006, when the Committee rated its abuse liability as low and its therapeutic usefulness considerable and recommended continued surveillance by WHO.

2. Chemistry

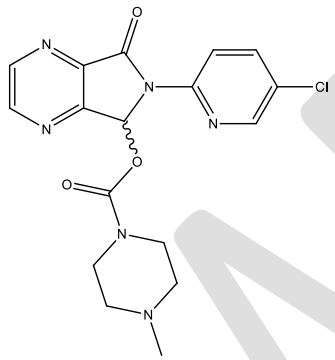
A. Chemical Name

IUPAC name: Zopiclone free base: (5RS)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate

Chemical Abstracts Service index name: Zopiclone free base: 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-*b*]pyrazin-5-yl ester (9CI, ACI)

B. Chemical structure

Free base:



Molecular formula: $C_{17}H_{17}ClN_6O_3$

Molecular weight: 388.81 g/mol

C. Stereoisomers

The presence of an asymmetric carbon atom gives rise to the (5R)- and (5S)-enantiomers of zopiclone. The racemic mixture is referred to as “zopiclone”. The (+)-(5S)- enantiomer of zopiclone is referred to as “eszopiclone”.

D. Methods and ease of illicit manufacture

Zopiclone is a nonbenzodiazepine hypnotic drug of the cyclopyrrolone class. The chemical structure is a pyrrolo[3,4-*b*]pyrazine with a 4-methylpiperazine-1-carboxyl group at the 5-position, a 5-chloropyridin-2-yl group at the 6-position and an oxo-substituent at the 7-position.

The first synthesis of zopiclone was described in a patent by Rhône-Poulenc SA *(Messer, 1972)*. The reaction of pyrazine-2,3-dicarboxylic anhydride with 2-amino-5-chloropyridine produces pyrazine-2-carboxylic acid amide, which, after ring closure with thionyl chloride, results in the 5,7-dioxopyrrolopyrazine imide derivative. Selective potassium borohydride reduction of one of the carbonyl groups leads to the chiral 6-(5-chloropyrid-2-yl)-5-hydroxy-7-oxo-5,6-dihydropyrrolo[3,4-*b*]pyrazine, which reacts with 1-chloro-carbonyl-4-methylpiperazine to produce zopiclone as a racemic mixture (scheme 1).

Alternatively, the chiral 6-(5-chloropyrid-2-yl)-5-hydroxy-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine reacts with phenylchloroformate leading to 6-(5-chloropyrid-2-yl)-7-oxo-5-

phenoxycarbonyloxy-5,6-dihydropyrrolo[3,4-b]pyrazine, which in turn reacts with 1-methylpiperazine giving the racemic mixture of zopiclone.

Other patents are for improvements of zopiclone synthesis, although they do not substantially modify the scheme described above *(Baogang, 2009; Mendelovici, 2008; Naik, 2010; Reddy, 2008; Vardanyan and Hruby, 2016)*.

All the syntheses reported in the literature, although simple, require the equipment of a chemical synthetic laboratory and qualified personnel.

E. Chemical properties

Melting-point

178 °C *(Messer, 1972)*

Boiling-point

No information was found.

Solubility

Zopiclone is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and practically insoluble in ethanol (96%). It dissolves in dilute mineral acids *(EDQM, 2022)*.

F. Identification and analysis

Synthetic zopiclone was characterized by proton and carbon nuclear magnetic resonance, mass spectrometry (MS), infra-red spectroscopy, ultraviolet (UV) spectroscopy *((Ming et al., 2007)*, fluorescence spectroscopy (Al-Attas et al., 2017) and electrochemical properties (Viré et al., 1993).

Zopiclone is available as a reference material, as are two of its metabolites, zopiclone-*N*-oxide and *N*-desmethylzopiclone, as a deuterated derivative and as (S)- and (R)-enantiomers, from commercial suppliers for routine analysis in forensic, clinical and research investigations (e.g., *(Merck, n.d.).*

Identification and analytical assays of zopiclone and of eszopiclone in bulk preparations or tablets are reported in various pharmacopoeias, such as the European Pharmacopoeia *(EDQM, 2022)*, the United States Pharmacopeia *(The United States Pharmacopoeia: The National Formulary, 2019)* and the British Pharmacopoeia *(MHRA, 2020).*

Several analytical procedures have been reported for the determination of zopiclone and its metabolites in various biological matrices *(Tonon and Bonato, 2012)*. GC coupled with MS was used to analyse urine samples (Gunnar et al., 2006; Versace et al., 2012); GC coupled to a nitrogen–phosphorous detector to analyse human post-mortem blood and plasma (Jones and Holmgren, 2012; Stanke et al., 1996); liquid chromatography (LC) coupled to a fluorescence detector to analyse zopiclone in human plasma, serum and urine (El-Shaheny et al., 2012; Gupta, 1996); LC coupled to diode array detection to analyse human plasma, blood, urine and post-mortem tissue *(Johnson and Botch, 2011; Klinke and Linnet, 2007; Tracqui et al., 1995)*; and capillary electrophoresis coupled to UV laser-induced fluorescence detection to analyse urine and saliva *(Hempel and Blaschke, 1996)*. Several human biological specimens, such as whole blood, hair, plasma, exhaled breath aerosol, serum, post-mortem liver, urine, gastric contents and meconium, were analysed by LC-MS (Ares-Fuentes et al., 2021, p.; Gottardo et al., 2020; Locatelli et al., 2021; Mestad et al., 2021; Montenarh et al., 2015; Orfanidis et al., 2020; Ristimaa et al., 2010; Van Bocxlaer et al., 1996; Wiedfeld et al., 2021).

Radioimmunoassay methods were developed for the determination of zopiclone and its metabolites in urine (*Mannaert and Daenens, 1996)*.

Various chiral analytical methods have been developed for the determination of single enantiomers of zopiclone in bulk drug, pharmaceutical preparations and biological fluids, such as capillary electrophoresis (e.g., *38*), thin-layer chromatography (e.g. *39*) and high-performance LC with chiral stationary phases (Kozlov et al., 2020; Sangaraju et al., 2009).

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

Several reviews on the general pharmacology of zopiclone were consulted *(42–45)*. Additional publications are cited when clarifications were necessary or when they provided additional information.

In the early 1980s, a new class of psychotherapeutic agents, cyclopyrrolones, was developed, of which zopiclone was the first. Zopiclone was introduced onto the market in 1986 by Rhone-Poulenc, which is now part of Sanofi-Aventis, the largest world-wide pharmaceutical manufacturer. The defining properties of this class of agents is a pharmacological profile of high efficacy and low toxicity similar to that of the benzodiazepines but purportedly with a lower dependence profile than that associated with benzodiazepines. Zopiclone binds to sites on or closely linked to the benzodiazepine receptor complex, giving benzodiazepine-like hypnotic, anxiolytic, anticonvulsant and myorelaxant properties. Specifically, zopiclone acts in a competitive manner as a full agonist at the $GABA_A$ receptor complex, where it decreased the affinity of the receptors for the $GABA_A$ antagonist flumazenil without affecting the number of binding sites (Concas et al., 1994). Although zopiclone and the benzodiazepines appear to bind to the same recognition site, enhancing the function of the $GABA_A$ receptor, differences in receptor function observed after binding suggest that zopiclone and the benzodiazepines interact with separate binding domains and/or induce different conformational changes in the $GABA_A$ receptor complex.

A. Routes of administration and dosage

In the 1980s, zopiclone was prescribed at 7.5 mg/dose per day to be taken orally 30–60 min before retiring to improve sleep, purportedly with minimal adverse effects. Doses > 7.5 mg were prescribed when indicated. No reduction of the dose was suggested for elderly patients. Clinical trials at that time found minimal “next day” effects, but patients were warned of the possibility of impaired mental alertness and psychomotor skills and were advised to exercise caution. By the 1990s, enough evidence had accumulated of “hangover effects” that a dose of 3.75 mg/day was recommended for elderly patients, which could be increased if necessary to 7.5 mg/day if the patient did not respond to the lower dose. In patients with severe or persistent insomnia, 15 mg was recommended. A new recommendation for a dose of 3.75 mg/day was added for patients with hepatic impairment or severe renal insufficiency, in whom metabolism may be slowed.

As with all hypnotics, long-term, regular use of zopiclone is not recommended. The manufacturers state that the treatment duration should not exceed 4 weeks, while the general recommendation is that zopiclone should be used only intermittently. Nonetheless, many patients with chronic insomnia use zopiclone regularly for extended periods *(Bain, 2006).*

Doses of up to 225 mg (30 tablets) were described in 20 cases of intentional zopiclone overdose. The effects included only mild drowsiness (Inman et al., 1993).

Case studies in the literature indicate instances in which higher doses were either prescribed or taken. A man was initially prescribed 7.5 mg once a day for insomnia, which was increased to 4 mg once a day *(Jones and Sullivan, 1998)*. In other cases, individuals themselves increased their dose; one woman being treated for insomnia related to depression increased her dose to 22.5 mg/day, while a woman with bipolar affective disorder increased her dose to 7.5 mg/day *(Jones and Sullivan, 1998)*. In another case, a woman with a history of recurrent depressive disorder had been prescribed zopiclone in increasing doses for insomnia and for several months was taking up to nine tablets of 7.5 mg/day in three divided doses *(Flynn and Cox, 2006)*. A review of clinical case reports of abuse or dependence indicated that some individuals took amounts that were 30–120 times greater than the recommended dose (Hajak et al., 2003). In a more recent study, Schifano et al. *(52)* cited reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions of doses of 450–2250 mg.

In a case study, a male intravenous drug user was reported to have crushed zopiclone tablets and subsequently injected them (dose unknown). The person reported relaxation followed by sleep. His use appears to have been intermittent and subject to availability, as several alternative drugs included temazepam, diazepam and dihydrocodeine *(Sullivan et al., 1995).*

B. Pharmacokinetics

At the recommended oral dose of 7.5 mg, zopiclone is rapidly absorbed (> 95% is absorbed within 1 h; peak plasma concentration, 60–70 µg/L). Its bioavailability is 80%, suggesting no significant first-pass effect. Distribution to body tissues, including the CNS, breast milk, placenta and salivary glands, is rapid and extensive, with a volume of distribution of 100 L in healthy subjects. Binding to plasma proteins is 45%. Zopiclone undergoes extensive metabolism in the liver, most biotransformation pathways involving cytochrome P450-dependent monooxygenase enzymes. Oxidation, demethylation and oxidative decarboxylation are significant mechanisms of metabolism. The *N*-oxide derivative, which is less active than the parent compound, accounts for 11% of a dose, and the inactive derivative, *N*-desmethyl zopiclone, about 15% of a dose; 4–7% is excreted unchanged in the urine. About 50% of a dose undergoes oxidative decarboxylation, and the resulting inactive metabolic products are excreted via the lungs. Neither the drug nor its metabolites are detectable in plasma 48 h after administration. In most studies, the half-life was reported to be 3.5–6 h, although it may be up to 8 h in individuals with poor liver function and the elderly. In volunteers given several oral doses of zopiclone, the elimination half-life was 6.5 h (Houghton et al., 1985). The half-life is not affected in people with poor kidney function. The elimination half-life of the active metabolite is similar to that of the parent drug. Plasma clearance of zopiclone is about 14 L/h in healthy subjects and is not affected by haemodialysis. The milk:plasma ratio in lactating women after a 7.5-mg dose is approximately 50%. Zopiclone administered intravenously undergoes biphasic elimination, with a half-life of 5 h (Gaillot et al., 1983).

In humans, rats and dogs, zopiclone kinetics are similar in males and females (Gaillot et al., 1983).

C. Pharmacodynamics

At a dose of 7.5 mg, zopiclone is efficacious in the treatment of insomnia in adults, including the elderly, who often experience insomnia (Busto et al., 2001). It is at least as effective as other benzodiazepines in improving many sleep parameters, including in patients with chronic insomnia.

Because of its action at the benzodiazepine receptor complex, zopiclone has sedative, anxiolytic, anticonvulsant and myorelaxant properties similar to those of benzodiazepines in studies in experimental animals. Zopiclone is, however, less effective than benzodiazepines against anxiety, although it has shown anxiolytic activity in clinical trials in patients with generalized anxiety disorder and insomnia. No studies on its anticonvulsant or myorelaxant properties in humans were identified.

At medically prescribed doses, people with insomnia experience some deterioration of psychomotor function 1–2 h after administration, which, however, subsides within 8–10 h. Co-administration of alcohol and 7.5 mg zopiclone has an additive effect on impairment of psychomotor function after 1.5 h, which is negligible after 8 h. Other studies showed impaired driving skills the day after a dose of 7.5 mg zopiclone in people with insomnia and residual psychomotor impairment in healthy volunteers who received zopiclone at 7.5 mg/day. In a review of 16 psychometric studies in healthy volunteers and insomniac patients given the standard dose of 7.5 mg/day, no residual effects were reported in most studies (O'Hanlon, 1995). In those studies that did find effects, they were of modest magnitude and did not persist for > 12 h after dosage. This review, which concluded that "zopiclone possesses few if any residual effects of clinical relevance", was published in 1995 and states that "the studies reviewed failed to meet current methodological standards and may have left some important questions unanswered".

Both earlier and later studies showed that at zopiclone at medically prescribed doses can cause slight immediate memory loss but little or no "morning after" amnesia *(42, 58, 59)*.

5. Toxicology

Plasma concentrations of zopiclone during therapeutic use are typically < 100 µg/L (Kratzsch et al., 2004) but are frequently > 100 µg/L in drivers arrested for impaired driving and may exceed 1000 µg/L in acutely poisoned patients *(Jones et al., 2016)*. Post-mortem blood concentrations in victims of fatal acute overdose are usually in a range 400–3900 µg/L *(Jones et al., 2016)*.

Like other benzodiazepine receptor agonists, zopiclone is generally not the only drug present in poisoning deaths, and, although it may contribute, it is generally not the causal agent. Fatalities have, however, occurred (described below) when the dose is high enough and in vulnerable populations.

In a monitoring study of prescription events in 13 177 patients, 20 cases of intentional zopiclone overdose were reported. The highest recorded dose was 225 mg (30 tablets). The effects included only mild drowsiness (Inman et al., 1993).

In early case reports, the estimated maximum dose ingested during a suicidal overdose death was 420 mg, combined with heavy alcohol use *(Pounder and Davies, 1994)*, and 450 mg in a case complicated by concomitant use of diazepam(E. Mannaert et al., 1996). In a severely debilitated elderly man, 90 mg zopiclone resulted in suicidal death *(Meatherall, 1997)*. The ingested dose was not stated in two other cases, one of which was complicated by concomitant alcohol use *(Boniface and Russell, 1996)*.

In an overview of fatalities due to overdose conducted in England and Scotland for the period 1983–1999, information was collected on fatal poisonings due to use of a single anxiolytic or sedative drug *(Buckley and McManus, 2004)*. A total of 23 deaths were attributed to zopiclone. The authors calculated a "fatal toxicity index", expressed as the number of deaths per million prescriptions for zopiclone, of 2.1, which was lower than those for flurazepam (20.5), flunitrazepam (10.8), temazepam (9.9), triazolam (4.7) and nitrazepam (3.6) but higher than those for loprazolam (1.6) and

lormetazepam (1.4). A time-course analysis presented for zopiclone with this method of assessing toxicity indicated that the fatal toxicity index of zopiclone was similar to that of the benzodiazepines as a group (> 7) within the first few years of marketing. A study conducted in New Zealand of deaths attributable to sedatives during 2001 (Reith et al., 2003), found that, of 200 deaths due to poisoning, 39 involved sedatives, of which 12 involved zopiclone, ranking it as the sixth most common cause of poisoning in New Zealand in that year. The fatal toxicity index was lower than that observed in the United Kingdom but similar for zopiclone (1.04) and all benzodiazepines (0.59).

6. Adverse reactions in humans

Few adverse reactions were found in clinical trials of 7.5 mg/day zopiclone. The most frequent events are bitter taste, dry mouth and difficulty in rising in the morning (all < 4%) *(Wadworth and McTavish, 1993)*. Nightmares, nausea and sleepiness have been reported in fewer than 1% of cases *((Wadworth and McTavish, 1993)*. For example, in a post-marketing study of 20 513 patients with insomnia, 9.2% experienced at least one adverse event while receiving zopiclone at 3.75 mg/day (elderly patients, 10.5% of the study cohort) or 7.5 mg/day for 21 days. Adverse events were reported spontaneously by patients, rather than according to a checklist. They included a bitter taste (3.6%) difficulty in waking in the morning (1.3%), dry mouth (1.6%), sleepiness (0.5%), nightmares (0.5%) and nausea (0.5%) (Allain et al., 1991). The results of other large trials are generally consistent *(Noble et al., 1998)*.

Isolated reports of adverse events after zopiclone overdose included atrioventricular block in a patient after voluntary ingestion of 127.5 mg (Wadworth and McTavish, 1993) and coma after zopiclone overdose by a psychiatric patient who was also receiving treatment with chlorpromazine, amitriptyline, trifluoperazine and procyclidine. The coma was successfully treated with flumazenil *(Ahmad et al., 1991).*

Detrimental clinical effects (such as difficulty in waking, impaired daytime well-being and reduced morning coordination) may occur the morning after hypnotic treatment if the duration of clinical action extends beyond night-time (or the normal period of sleep). These effects are lower with short-acting benzodiazepines. The results of several investigations indicate that next-day impairment is similar or superior with zopiclone to the short-acting benzodiazepine triazolam *(Noble et al., 1998)*.

Adverse effects include a withdrawal syndrome even at a medically prescribed dose of 7.5 mg/day *(4(Wadworth and McTavish, 1993)*. Withdrawal symptoms occurred 12–21 days after the last dose in healthy volunteers and included increased anxiety, morning discomfort and awake time and decreased sleep latency and quality. In patients with insomnia and generalized anxiety disorder, rebound anxiety was the most commonly reported symptom (< 1%). Nervousness and vertigo were also reported by a few subjects during zopiclone withdrawal. Most studies of zopiclone that included a withdrawal phase did not provide data on adverse events occurring during this period *(Noble et al., 1998).*

In a study of over 500 000 people, patients treated with a Z-drug (zolpidem, zopiclone, zaleplon) concomitantly with prescription opiates were at significant risk of accidental overdose in comparison with patients who were taking prescription opiates only (Szmulewicz et al., 2021).

VigiBase: VigiBase is the WHO global database of individual case safety reports (ICSRs). An ICSR is an adverse event report for a suspected medicine or vaccine in an individual patient. VigBase.As of September 2022, over 150 Member States and territories contribute to the VigiBase, and there are[insert no of icsrs] ICSRs. Given the nature of the database, VigiBase has the statement of reservations and limitations to be considered. VigiBase was searched for ICSRs reporting Drug

abuse and dependence (using Standardised MedDRA Queries[1]) with the use of zopiclone (as an active ingredient generic name) and 1348 ICSRs were extracted from 1/1/2017 – 7/27/2022 of which 1,030 (76%) were considered serious[2]: Death, 155 (11.5%); life threatening, 75 (5.6%); caused/prolonged hospitalization, 644 (47.8%); disabling/incapacitating, 10 (0.7%); congenital anomaly/birth defect, 2 (0.1%); and other medically important conditions, 324 (24%). Fatal outcomes occurred in 162 (12.0%) of all cases. Cases were reported mostly by physicians (35%), health professionals other than physician and pharmacist (35%), and pharmacists (20%).

Most cases were adults aged 18-44 (34%), 45-64 (24%), 65-and up (13%) and unknown (28%). Women accounted for 60% of all cases. Most cases occurred in France (48%), Sweden (26%), U.K. (7%), Germany (6%), Canada (4%), Australia (1%), Japan (1%), Norway (1%) and less than 1% in several other countries.

Frequently reported reactions included 406 (30%) cases of intentional overdose, 308 (23%) cases of drug dependence, 304 (23%) cases of toxicity to various agents, 204 (15%) cases of drug abuse, 126 (9%) cases of overdose, 122 (9%) cases of intentional product misuse, 67 (5%) cases of prescription form tampering, 39 cases (3%) of drug use disorder, 28 cases of intentional product use/misue (2%), 25 cases (2%) accidental overdose, 20 cases (2%) of dependence and 102 (7.4%) cases of miscellaneous origin.

Cases were co-reported with the following MedDRA terms [3]at 2% or greater: intentional self-injury, 259 (19.2%); somnolence, 168 (12.5%); suicide attempt, 79 (5.9%); fatigue, 71 (5.3%); depressed level of consciousness, 66 (4.9%); coma 57 (4.2%); loss of consciousness, 49 (3.6%); hypotension, 46 (3.4%); tachycardia, 43 (3.2%); withdrawal syndrome, 40 (3.0%); drug ineffective, 38 (2.8%); completed suicide, 34 (2.5%); confusional state, 34 (2.5%); drug interaction, 33 (2.4%).

The top 10 co-reported drugs as either suspected or concomitant were: propiomazine, 192 (14%); oxazepam, 170 (13%); diazepam, 152 (11%); promethazine, 142 (11%); alprazolam, 123 (9%); alimemazine, 90 (7%); tramadol, 84 (6%); ethanol, 80 (6%); paracetamol, 78 (6%); and pregabalin, 76 (6%).

The large number of cases in France is a concern. It is probably related to a requirement instituted in April 2017 that prescriptions for the Z-drug zolpidem be obtained on tamper-resistant, secure forms, similar to those used for narcotics (Laforgue et al., 2022). A time-series analysis of data acquired from the French national health-care system in 2018 showed a sharp decrease in prescription of zolpidem and a concomitant increase in prescription of zopiclone (Rousselot et al., 2020).

[1] Standardised MedDRA Queries (SMQs) are tools developed to facilitate retrieval of MedDRA-coded data. Over 100 SMQs have been created including "Drug abuse, dependence". The definition can be found in: https://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=20000101

[2] A serious adverse event is any event that: Is fatal, Is life-threatening, Is permanently/significantly disabling, Requires or prolongs hospitalization, Causes a congenital anomaly, Requires intervention to prevent permanent impairment or damage. Reference: Safety of Medicines A guide to detecting and reporting adverse drug reactions. WHO. 2002.

[3] MedDRA is a clinically validated international medical terminology utilized by regulatory authorities throughout the drug lifecycle process.

7. Dependence potential

A. Studies in experimental animals

Zopiclone suppressed barbital withdrawal signs in rhesus monkeys, and discontinuation of zopiclone elicited a withdrawal syndrome in crab-eating monkeys treated with the drug for several weeks *(74)*.

Zopiclone has been tested in two models of physical dependence in mice. The results in a model of dependence based on measurement of convulsant seizures suggested that it did not cause physical dependence: Zopiclone did not modify the sensitivity of the GABA receptor complex to the partial inverse agonist FG 7142 after withdrawal (Piot et al., 1990). In the other model, zopiclone did cause physical dependence, and administration of the antagonist, flumazenil, precipitated withdrawal as expressed in reduced electroshock-induced seizure thresholds in animals treated with a high dose for 3 days *(VonVoigtlander and Lewis, 1991)*. In an attempt to understand the discrepant results, the two sets of experiments are described in more detail below.

A model of a purported index of physical dependence was used to test whether zopiclone could cause dependence on the basis of the finding that chronic treatment in mice with the benzodiazepine flurazepam or midazolam enhanced their sensitivity to the proconvulsant effect of the partial inverse agonist FG 7142 after withdrawal of these compounds (Piot et al., 1990). The compounds being investigated or their vehicle were injected intraperitoneally into mice (n = 10 per dose) four times daily for 3 days, and the animals were examined 2 days after the last dose of compound. The compounds were administered at doses of 2, 4, 8, or 16 mg/kg (lorazepam and triazolam) and 4, 8, 16 or 40 mg/kg (diazepam and flunitrazepam); cyclopyrrolones were given at 4, 8, 16, 40, 80 or 400 mg/kg (zopiclone) and 4, 16, 40, 80 or 400 mg/kg (suriclone). The mice then received intraperitoneal injections of 40 mg/kg FG 7142. No convulsions were seen in the control (vehicle pretreated) mice or in mice treated with zopiclone or suriclone, whereas those treated with the benzodiazepines had seizures after administration of FG 7142.

Zopiclone caused physical dependence in the other model *(76)*, in which mice were injected subcutaneously twice a day with zopiclone at 150 mg (morning) and 300 mg (afternoon). A starting dose of 150 mg/kg per day was followed by 15 and 1.5 mg/kg per day in subsequent assays. Flumazenil (2.5 mg/kg) was given intravenously 24 h after the last dose, and the mice were tested 5 min later for electroshock seizure thresholds in an up–down titration method. Flumazenil-precipitated withdrawal was manifested by a lowering of the seizure threshold. This model was developed specifically to test the dependence potential of compounds with benzodiazepine agonist properties. The authors noted that the lowest effective dose of compounds with greater in-vivo affinity and intrinsic activity at benzodiazepine receptors, such as several of the benzodiazepine compounds and zopiclone, lowered the seizure threshold and that the effects were dose-related. In contrast, compounds with greater in-vivo affinity and intrinsic activity at benzodiazepine receptors such as zolpidem, the pyrazolopyridine tracazolate and the triazolopyridazine CL 218872 did not cause physical dependence by this criterion.

In one study of cross-tolerance to and dependence on various compounds, rats were made dependent on triazolam. Chronic triazolam treatment produced tolerance to the depressant effects of triazolam, lorazepam and zopiclone *(Cohen and Sanger, 1994)*.

B. Studies in humans

The first studies of the dependence potential of zopiclone were conducted in 2019. Only sporadic accounts of dependence were reported before then, consisting mainly of single case reports, small numbers of participants or post hoc. A common finding was that a subset of people begin treatment with zopiclone as prescribed for sleep problems, then escalate the dose over time, either because the doses lose their efficacy, to reduce anxiety, in conjunction with substance abuse and psychiatric difficulties or a combination of these reasons *(Curreen and Lidmila, 2014)*. After cessation of extreme doses, some people experienced withdrawal symptoms, including insomnia, craving, anxiety, tachycardia, tremor and occasional seizures. "Doctor shopping" to obtain more drug is common, and widespread purchase of excessive amounts has been reported *(Curreen and Lidmila, 2014)*.

An early short (4-week) clinical trial did not address the development of tolerance to the sleep-inducing effects of 7.5 mg oral zopiclone *(Goa and Heel, 1986)*. A later small 8-week trial showed that tolerance developed, while a second small 17-week trial did not. Rebound insomnia, which may indicate withdrawal, was observed after treatment in some of the trials. The general consensus in the 1980s and 1990s was that zopiclone had no abuse potential, although further study was recommended *((Goa and Heel, 1986; Noble et al., 1998; Wadworth and McTavish, 1993)*.

A study was conducted in 1983 of nine healthy male volunteers to examine the dependence liability of zopiclone. The participants were assigned in random sequence to treatment with 21 consecutive nightly oral doses of 7.5 mg zopiclone, followed by 7 nights of placebo (withdrawal period) or a 21-night treatment period with placebo, similarly followed by 7 nights of placebo. Discontinuation of zopiclone was associated with increased anxiety and lighter sleep on days 2 and 4 of withdrawal. Heart rate, systolic and diastolic blood pressure, hand tremor and measured variables in auditory-evoked electroencephalography were not significantly different from placebo during withdrawal from zopiclone. No other physical or mental symptoms were observed during zopiclone treatment. Eight participants reported subjective effects throughout the study, but only two were able to identify the period of active drug treatment correctly. The authors concluded that "similar changes occur with other hypnotic drugs of relatively low dependence liability" (Dorian et al., 1983).

Seven cases (total incidence, 0.05%) of possible dependence, none of which was confirmed, were reported during monitoring of prescription events in over 13 000 patients (Inman et al., 1993). Forms were posted to physicians in England who prescribed zopiclone between March and July 1991 enquiring about events that had occurred in patients prescribed zopiclone. An event was defined as any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction or any other complaint that was considered of sufficient importance to be entered in the patient's notes. The response rate was modest (55%).

In a review in 1999 of clinical trials of therapeutic doses of zopiclone, no significant rebound insomnia was found, and there were few withdrawal reactions. The authors concluded that the risk of dependence was insignificant, although abuse potential should be considered in people with a history of addiction or psychiatric illness *(Hajak, 1999)*.

In a review of clinical case reports of abuse or dependence in 1966–2002, 22 cases were included (Hajak et al., 2003). The proportions of males and females were similar, and cases were reported in all age groups. Extreme doses were 30–120 times the recommended dose. Most patients had a history of substance use disorder and/or other psychiatric conditions.

8. Abuse potential

A. Studies in experimental animals

Monkeys self-administered zopiclone but not a control suspension given either intragastrically or intravenously *(Yanagita, 1983)*.

In a discriminative stimulus test in monkeys trained to discriminate the benzodiazepine, midazolam, zopiclone had midazolam-like discriminative stimulus effects that were antagonized by the $GABA_A$ antagonist flumazenil *(McMahon et al., 2003)*.

In another study, rats were trained to discriminate a zopiclone-induced interoceptive stimulus (3.2 mg/kg intraperitoneally) from saline. The zopiclone discriminative stimulus could be generalized to the benzodiazepines diazepam (1.8 mg/kg), nitrazepam (10 mg/kg) and alprazolam (10 mg/kg) and was blocked by the benzodiazepine antagonist Ro 15-1788 (1 mg/kg) *(Yamamoto et al., 1989)*.

In another study, rats were trained to discriminate a dose of 5 mg/kg of the $GABA_A$ agonist chlordiazepoxide from saline. The chlordiazepoxide cue was antagonized by the $GABA_A$ antagonist flumazepil and was generalized to a variety of anxiolytic and sedative drugs, including zopiclone *(Sanger, 1988)*.

B. Studies in humans

Case reports from as early as 1995 that include subjective reports from patients suggest that zopiclone has abuse potential. One patient reported increased euphoria when zopiclone was combined with alcohol, and another reported that it induced a sense of drunkenness and well-being, also when used with alcohol *(Sullivan et al., 1995)*.

In 1999, a study in Norway (*83*, only the abstract is available in English) showed that 60% of drivers suspected of driving under the influence of drugs had concentrations of zopiclone in their blood higher than therapeutic levels, indicating misuse. Most of the drivers also tested positive for illegal drugs, prescription drugs with abuse potential or alcohol.

Widespread purchase of excessive amounts of zopiclone, an indicator of abuse potential, has been reported. A cross-sectional study of claims data from the German health insurer Gmuender ErsatzKasse was conducted to examine use of the Z-drugs zopiclone and zolpidem (*84*, only the abstract is available in English). Between July and December 2004, 6959 individuals bought at least one pack of zolpidem or zopiclone, including 21% containing 90 daily doses or more. High usage, defined as at least 180 daily doses, was identified for 501 subjects (7%).

The reinforcing properties of zopiclone (3.75 mg) and triazolam (0.25 mg) were compared in 40 recently abstinent (but not in withdrawal) alcohol-dependent inpatient men in a double-blind cross-over study *(85)*. No difference in mood or in items in the Addiction Research Centre Inventory (a standardized questionnaire for assessing subjective effects of psychoactive drugs *(National Institute on Health, 2016)*) was observed, and neither drug induced significant side-effects. However, individuals preferred triazolam to zopiclone.

A study with a similar cross-over design conducted in recently abstinent (but not in withdrawal) alcohol-dependent men was designed to determine whether a dose of zopiclone or triazolam could substitute for a drink of alcohol *(87)*. Patients were given eight doses of 0.25 mg triazolam or 3.75 mg zopiclone for 2 days each, followed by a washout period, and instructed to take one tablet whenever they wanted alcohol. The tablets of zopiclone or triazolam differed in colour. Their preference for triazolam over zopiclone was nonsignificant, and there was no difference

in subjective feelings of the intensity of the two drugs or in mood states. None of the volunteers developed a desire for zopiclone after withdrawal of the medication.

A latent class analysis was used to examine the database of a French regional health insurance organization to characterize zolpidem and zopiclone users in real-life situations and identify problem use *(88)*. Four clinical subtypes of users were identified for zolpidem: non-problematic users, users with associations with hypnotics/anxiolytics or with associated mental disorders, and problematic users. Problematic use was not identified in zopiclone users (n = 21 860).

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Zopiclone is widely prescribed and is marketed in at least 39 countries (see section 11).

Zopiclone is prescribed to patients with chronic insomnia to shorten sleep latency, decrease the frequency of waking and improve the duration and quality of sleep. It was also shown to be effective in aiding sleep the night before surgery *(Holm and Goa, 2000)*.

The sedative efficacy of zopiclone was found to be at least as good as that of the long-acting benzodiazepines nitrazepam and flunitrazepam, the intermediate-acting benzodiazepine temazepam and the short-acting benzodiazepines triazolam and midazolam *(Noble et al., 1998)*.

Louzada et al. *(90)* conducted a systematic review to compare the efficacy and safety of zopiclone to treat sleep disorders in older adults with those of other sedative-hypnotics, placebo and non-pharmacological interventions. The study was conducted according to PRISMA guidelines, and its methodological quality was assessed with the "Risk of bias" tool in the Cochrane Reviewers' Handbook. The search resulted in 12 randomized, placebo-controlled clinical trials, two open studies and two observational reports. Overall, the studies suggested that zopiclone treatment in elderly people is effective in treating insomnia by reducing sleep latency, nocturnal waking and wake time after sleep onset while increasing total sleep time, with probable effects on sleep architecture. Zopiclone was found to be reasonably well tolerated, to have few adverse effects with a non-severe impact on psychomotor or cognitive performance and to cause no major harm to overall well-being and daily living ability. The quality of most of the studies was, however, classified as low or unclear. The authors concluded that, although the studies indicate benefits of zopiclone use, high-quality trials are required on its long-term effects, tolerability and safety in the treatment of older adults.

A study of the use of zopiclone in Australia comprised almost 2 million people who had attended one of 404 Australian general practices at least three times in 2 consecutive years between 2011 and 2018. In both years, the rates of prescription of any Z-drug were lower (4.4% and 3.5%) than those for all benzodiazepines (56.6% and 41.8%) per 1000 consultations. Zopiclone prescription increased from 5.0% to 22.6% between 2011 and 2018. Repeat prescriptions for zopiclone that exceeded recommended doses increased by 31.4% during the period (Begum et al., 2021).

A study in Finland included all 408 527 legal purchases of benzodiazepines and Z-drugs between 2006 and 2014 from the Finnish Social Insurance Institution. Sedative use was defined as one or more purchases in 1 year; long-term use was defined as purchase of at least 180 daily doses and two or more separate purchases in 1 year; high-dose use was defined as purchase of at least 1000 daily doses on at least two separate occasions in 1 year. By 2014, 9.3% of the Finnish adult population used sedatives, 3.6% were long-term users, and 0.3% were high-dose users. For zopiclone, use, long-term use and high-dose use were 4.1%, 1.8% and 0.6% respectively. Overall, use of most of the benzodiazepines and Z-drugs, including zopiclone, decreased over the course of the study. Nonetheless, in each year, zopiclone was the most frequently used hypnotic substance, despite the

decrease in its use. Although long-term use of any sedative is not recommended, zopiclone use persisted for many years after initial use: 29% at 3 years, 15% at 5 years and 11% at 9 years *(*(Kurko et al., 2018).

10. Listing on the WHO Model Lists of Essential Medicines

Zopiclone is not listed on the 22nd WHO Model List of Essential Medicines or the 8th Model List of Essential Medicines for Children.

11. Marketing authorizations (as a medicinal product)

Zopiclone is marketed in at least 39 countries *(2)*:

Zopiclon Actavis, PUREN Pharma, Germany
Zopiclon AL Aliud, Pharma, Germany
Zopiclon Apotex, Apotex Nederland, Netherlands
Zopiclon Aristo, Aristo Pharma, Germany
Zopiclon Aurobindo, Aurobindo, Netherlands
Zopiclon axcount, Axcount, Germany
Zopiclon CF, Centrafarm, Netherlands
Zopiclon Focus, Focus, Netherlands
Zopiclon Genthon, Genthon, Netherlands
Zopiclon Heumann, Heumann, Germany
Zopiclon Hexal, Hexal, Germany
Zopiclon Jubilant, Jubilant, Netherlands
Zopiclon Mylan, Mylan, Netherlands
Zopiclon PCH, Pharmachemie, Netherlands
Zopiclon Sandoz, Hexal, Germany; Sandoz, Netherlands
Zopiclon Stada, STADA, Germany; STADA Nordic, Denmark; STADA Nordic, Sweden
Zopiclon Synthon, Synthon, Netherlands
Zopiclon Teva, Teva Nederland, Netherlands
Zopiclona, Humax, Colombia; Recipe, Colombia
Zopiclona Cevallos, Cevallos, Argentina
Zopiclona Genfar, Genfar SA, Costa Rica; Genfar S.A., Guatemala; Genfar S.A., Honduras; Genfar SA, Panama
Zopiclona Interpharma, Interpharma, Chile
Zopiclona La Santé, La Santé, Colombia
Zopiclona MK, MK, Colombia
Zopiclona Qualigen, Qualigen, Spain
Zopiclon-CT, AbZ-Pharma, Germany
Zopiclone Actavis UK, United Kingdom; Crescent, United Kingdom; Flamingo Pharma, United Kingdom; Generics UK, United Kingdom; Kent Pharmaceuticals, United Kingdom; Milpharm, United Kingdom; Sawai Seiyaku, Japan; Tatsumi Yakuhin, Japan; Towa Yakuhin, Japan
Zopiclone Actavis, Actavis, Denmark; Actavis, Norway; Actavis, Sweden; Actavis Group, Iceland; Teva, New Zealand
Zopiclone Alter, Alter, France
Zopiclone Aristo, Aristo, United Kingdom
Zopiclone Arrow, Arrow, France

Zopiclone Biogaran, Biogaran, France
Zopiclone Cristers, Cristers, France
Zopiclone EG, EG, Italy; EG Labo, France; Eurogenerics, Belgium
Zopiclone EG-7.5, Eurogenerics, Luxembourg
Zopiclone Eva, Eva, Egypt
Zopiclone GH, Generic Health, Australia
Zopiclone Jubilant, Jubilant, Denmark; Medical Valley, Sweden
Zopiclone Mylan, Mylan, Belgium; Mylan, France
Zopiclone Orion, Orion Pharma, Sweden
Zopiclone Ranbaxy, Ranbaxy, France
Zopiclone Sandoz, Sandoz, France
Zopiclone Sanis Health, Sanis Health, Canada
Zopiclone Sivem, Sivem Pharmaceuticals, Canada
Zopiclone Synthon, Synthon, Singapore
Zopiclone Teva, Teva Pharma Belgium, Belgium
Zopiclone Teva Sante, Teva Santé, France
Zopiclone Tianping, Tianping, China
Zopiclone Zentiva, Sanofi-Aventis, France
Zopiclone Zentiva 7.5mg, Helvepharm, Switzerland
Zopiclone Zydus, Zydus, France
Zopiclon-neuraxpharm 3,75mg, neuraxpharm Arzneimittel, Germany
Zopiclon-neuraxpharm 7,5mg, neuraxpharm Arzneimittel, Germany
Zopiclon-ratiopharm, ratiopharm, Germany; Ratiopharm GmbH, Netherlands
Zopiclon-Takeda, Takeda, Bulgaria
Zopicon, Intas, India
Zopigen, Xixia, South Africa
Zopigen 7.5 mg, Generics, Hungary
Zopiklon, Mylan, Norway
Zopiklon Mylan, Mylan, Iceland; Mylan, Norway; Mylan, Sweden
Zopiklon Pilum, Pilum Pharma, Sweden
Zopinox, Orion Pharma, Finland
Zopistad 7.5, Stada-VN JV, Viet Nam
Zopitidin 7.5 mg, Vitabalans, Hungary
Zopitin, Vitabalans, Czechia; Vitabalans, Estonia; Vitabalans, Lithuania; Vitabalans, Latvia; Vitabalans, Norway; Vitabalans, Slovakia; Vitabalans Oy, Poland
Zopitran, Alembic, India
Zopivane, Cipla Medpro, South Africa
Zosleep-Humanity, Celogen, Georgia

12. Industrial use

There does not appear to be any industrial use for zopiclone.

13. Non-medical use, abuse and dependence

In the early 1990s, there was some indication of voluntary non-medical use, abuse and physical dependence on zopiclone. Wadsworth and McTavish *(43)* reported a review of 239 cases of voluntary overdose *(93,* (abstract, full text not available)*)* in which CNS depression was the most frequently

reported event. Other reported adverse effects of overdose included hyperkalaemia, hyperglycaemia and slight hyperbilirubinaemia. Isolated reports of physical dependence described symptoms of anxiety (Thakore and Dinan, 1992) and convulsions (Aranko et al., 1991) during withdrawal from zopiclone at doses up to 90 mg/day in patients with a history of substance abuse. In a case study in 1991, recurrence of physical and psychological symptoms of craving for opioids was reported after ingestion of a single dose of 7.5 mg zopiclone by a patient who had withdrawn from the opioid pethidine 12 months previously. The craving led to a full narcotic relapse. The patient was a medical practitioner with insight into the significance of this event *(Sutherland, 1991).*

Early reports of non-medical use were substantiated later. Bannan et al. *(97)* examined the prevalence of non-medical use of zopiclone (and other drugs) in 158 clients attending a methadone maintenance programme in Dublin, Ireland. Thirty-seven (23%) clients tested positive for zopiclone. Re-testing at 4–5 months indicated persistent non-medical use of zopiclone in 17%. Benzodiazepines were the most popular drug used concomitantly, followed by heroin and other opiates. None of the clients had injected zopiclone, although the majority had injected other drugs (Bannan et al., 2007).

Zopiclone is readily available without prescription on the Internet. Ho et al. *(98)* conducted an internet snapshot survey with the methods of the European Monitoring Centre for Drugs and Drug Addiction. Thirty-seven websites that sold zopiclone tablets in quantities of up to 2000 daily doses were identified. Most (24) provided information or warnings about dosage. A prescription for purchase was not required on 22 of the websites, 14 did not mention whether a prescription was necessary, and 1 stated that a prescription was necessary.

Schifano et al. *(52)* examined reports on Z-drugs to the *E*uropean Medicines Agency Database of Suspected Adverse Drug Reactions, providing systematic data for identification and analysis of zopiclone misuse, abuse, dependence and withdrawal. Of the total number of ADRs, 9283 (14%) were related to zopiclone misuse, abuse, dependence or withdrawal. Most of those related to zopiclone were reported by physicians in countries outside the European Economic Area (45.8%); pharmaceutical companies were the usual reporting agencies (51.4%). The most common ADRs were intentional overdose (30%), overdose (23%) and drug use disorder (23%). Most were found in women. Of these cases, 24% involved only zopiclone, 21% involved concomitant use of benzodiazepines, 15% antidepressants, 11% antipsychotics and 3% opiates or opioids. A few cases included use of other drugs (cannabis, 12; cocaine, 6; and methamphetamine, 1). Suicidal behaviour was reported in 27% of the cases. When doses were reported, they were > 15 mg in 577 cases (360 individuals), including 205 ADRs (120 cases) in which the dose ingested was 450–2250 mg.

Several online forums were consulted for information on the misuse, abuse and dependence potential of zopiclone.

Bluelight is a web forum and research portal dedicated to harm reduction in drug use for people aged ≥ 13 years. As of May 2022, it claimed over 455 000 registered users. Between April 2020 and July 2022 there were only three threads (conversations) on zopiclone *(Bluelight.org, 2021)*, which involved only a few commenters. Most used it medicinally for sleep, although a few used it at high doses (~ 30 mg) to hallucinate, in combination with other drugs. The commenters cautioned others not to stop zopiclone abruptly and offered titrating schedules. Some comments described tolerance, withdrawal symptoms and rebound insomnia after daily use for as little as 2 weeks. Several commenters mentioned the bitter taste, and some provide antidotes.

Erowid is a publicly available Internet resource on psychoactive plants and chemicals (“Erowid,” 2022). Anyone can submit a report; however, reports are reviewed and are required to be descriptive, informative and written at a level of at least 8th grade (13–14 years). Over 2 million people use Erowid every month to post reports of their experience with a drug, including whether they combined it with

other drugs. Between 1995 and 2022, there were 43 reports on zopiclone, in the following categories: general, 6; first use, 5; combination with other psychoactive substances, 19; experiences, 3; addiction, 3; and medical use to sleep, 10. Most of the reports are from 2005–2010. In contrast, 334 and 426 reports included the search terms "caffeine" and "heroin", respectively, during the same period.

Reddit is the largest Internet forum on which people discuss and comment and provide news and information on drugs ("reddit," 2022). Zopiclone has its own online forum (i.e., "subreddit"); however, the only posts are by the advertiser, Zopic.co.uk., an online pharmacy that purportedly fills prescriptions for sleep medications, including zopiclone. Zopiclone is mentioned in a few other forums, most discussions centring on its medical use for insomnia; others include how to avoid withdrawal and the optimal dose for sleep. About 10% of the comments are on non-medical use, and about 20% of the comments are from the advertiser, Zopic.co.uk.

Drugs-forum.com is a forum for discussion of all aspects of medical and recreational drug use ("Drugs-Forum Home," 2022). As of 26 July 2022, there were 1.7 million contributions and 285 000 members. A keyword search on zopiclone for 26 July 2021–26 July 2022 resulted in 18 zopiclone-related comments (withdrawal, 6; sleep, 4; dependence, 3; tolerance, 0; dose, 3; addiction, 2; weaning, 0; titrating, 0), whereas a search on caffeine and heroin during the same period resulted in 27 and 140 comments, respectively.

Thus, although zopiclone is widely prescribed throughout the world, there has been very little discussion on online forums on its medical or non-medical use.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

A meta-analysis was conducted in 2005 of studies of the risks and benefits of sedative hypnotics in older people with insomnia. The objective was to quantify and compare potential benefits (subjective reports of sleep variables) and risks (adverse events and morning-after psychomotor impairment) of short-term treatment with sedative hypnotics. Statistically significant improvements in sleep were found with sedative use, but the effect was small. The risk of adverse events was statistically significantly increased and potentially clinically relevant in older people at risk of falls and cognitive impairment. The authors concluded that the ratio of benefit:risk is small, particularly if the patient has additional risk factors for cognitive or psychomotor adverse events (Glass et al., 2005). The analysis did not distinguish among different sedatives however, and is included here only to provide historical background.

Nishtala and Chyou *(104)* conducted a population-based, case-crossover study in New Zealand of the use of zopiclone and the risk of fractures in 74 787 elderly people with a first fracture between 1 January 2005 and 31 December 2015. The risk of fracture was found to be significantly higher (RR = 1.45) with use of zopiclone than with non-use and remained significant after adjustment for concomitant use of α blockers, antipsychotics, β blockers, benzodiazepines and tricyclic antidepressants. The effect increased with age.

A systematic review and meta-analysis of the risk of vehicle accidents associated with use of psychoactive drugs, which included zopiclone, found that zopiclone increased the risks of an accident involving only property damage, a fatal accident and an accident involving only injury *(Elvik, 2013).* These findings were substantiated in a descriptive review of studies on driving and zopiclone use and studies on psychomotor performance in general *(59)*. The author concluded that patients who took zopiclone have over twice the risk of motor vehicle collisions than unexposed drivers and that

psychomotor impairment, falls and hip fractures are more likely, especially at higher (15 mg) doses and when zopiclone is mixed with other psychoactive substances, including alcohol.

15. Licit production, consumption and international trade

Zopiclone is widely used throughout the world as a sedative hypnotic. A search identified 119 trade names (see section 1.D), and there are probably more. Zopiclone is manufactured by 70–100 pharmaceutical companies (see section 11).

16. Illicit manufacture and traffic and related information

The Medicines and Healthcare Products Regulatory Agency in the United Kingdom estimated that between 2013 and 2016 up to £200 million worth of prescription medicines, including diazepam and zopiclone, had been diverted to the criminal market for supply (Gov.uk, 2018).

Only one incidence of suspicious shipment of, trafficking in or manufacture or production of zopiclone before 2006 has been reported to IONICS, in which zopiclone was diverted to illicit channels and abused in Argentina *(International Narcotics Control Board, 2022)*.

In a report to WHO prepared by the Organe international de contrôle des stupéfiants (International Agency for Drug Control) of the International Narcotics Control Board, zopiclone was identified as a significant concern to Member States throughout the world: 599 incidents involving zopiclone between January 2020 and March 2022 were communicated through IONICS by 11 governments in Africa, East and South-East Asia, West Asia, Oceania, West and Central Europe and North America. The previous report included 58 incidents between January 2019 and March 2021 communicated by eight governments in West Asia, Oceania and West and Central Europe, indicating the spread of zopiclone to other regions of the world.

The 24 countries or territories of origin of the incidents between January 2020 and March 2022 were in nine regions (Africa, East and South-East Asia, South Asia, West Asia, Oceania, West and Central Europe, North America, Central America and the Caribbean, and South America). The previous report (January 2019–March 2021) identified eight countries in five regions (Africa, South Asia, Oceania, Southeast Europe, and West and Central Europe) as the origins of incidents.

Zopiclone was reported through IONICS for the first time in 2020. The number of communicated incidents involving the substance increased from 36 incidents in 2020 to 537 in 2021.

17. Current international controls and their impact

Zopiclone is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

See Annex 1.

19. Other medical and scientific matters relevant for a recommendation on scheduling of the substance

No other matters were identified.

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