

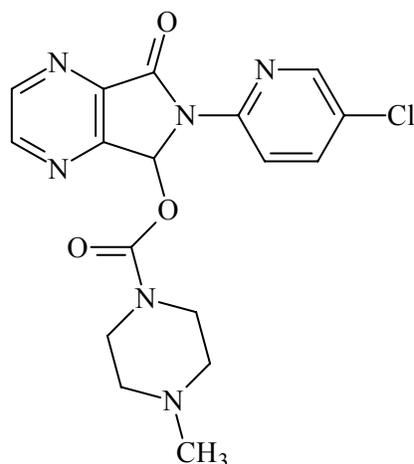
Assessment of zopiclone

1. Substance Identification

- A.** International Nonproprietary Name (INN): zopiclone
- B.** Chemical Abstracts Service (CAS) registry number: CAS 43200-80-2
- C.** Other Names: eszopiclone (the S(+)-enantiomer of zopiclone)
- D.** Trade Names: (these trade names might include trade names for eszopiclone preparations): Alchera, Alpaz, Amoban, Amovane, Ansium, Clonil, Datolan, Ezolin, Flazinil, Hypnoclone, Hypnor, Imolon, Imovance, Imovan, Imovane, Imozop, Imrest, Insorel, Limovan, Losopil, Mozop, Normason (!?), Nuctane, Piclodromin, Rhovane, Sedolox, Sedorm, Sedorn, Siaten, Somnal, Somnol, Somnols, Somnogamn, Somnol, Sonnat, Sonovan, Sopivan, Sucedal, Ximovan, Zedax,, Zetix, Zileze, Zimovane, Zimoclone, Zometic, Zonap, Zonix, Zopi, Zopicalma, Zopicon, Zopimed, Zopinil, Zopinox, Zopitan, Zorclone,
- Trade names for eszopiclone preparations:
Lunesta, Estorra
- Street name: Zim-zims
- E.** Identification Characteristics:
Zopiclone is a white to light-yellow crystalline solid. It is very slightly soluble in water, slightly soluble in ethanol, and soluble in phosphate buffer (pH 3.2).
- F.** WHO Review History:
Zopiclone was pre-reviewed by the 29th meeting of the WHO Expert Committee on Drug Dependence in 1994, which recommended continued surveillance but not a critical review. For the 33rd meeting in Geneva September 17-20, 2002, the Secretariat of the ECDD proposed zopiclone for another pre-review, and the ECDD recommended the critical review of zopiclone.

2. Chemistry

- A.** Chemical Name: 6-(5-chloro-2-pyridyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo-[3,4-*b*]pyrazin-5-yl-4-methylpiperazine-1-carboxylate; 4-Methyl-1-piperazinecarboxylic acid ester with 6-(5-chloro-2-pyridyl)-6,7-dihydro-7-hydroxy-5*H*-pyrrolo[3,4-*b*]pyrazin-5-one.

B. Chemical Structure:

Formula: C₁₇H₁₇ClN₆O₃
 Molecular Weight: 388.82

Zopiclone has a single chiral centre.

3. General Pharmacology***Preclinical:***

Zopiclone was the first compound developed which is chemically unrelated to benzodiazepines yet binds with high affinity to benzodiazepine receptors (Blanchard et al., 1979). In a manner similar to benzodiazepine anxiolytics, zopiclone has anti-anxiety, anticonvulsant, sedative, muscle relaxant and antiaggressive properties in rodents (Julou et al., 1983; Sanger et al., 1985). At rather high doses, zopiclone elicited a weak antinociceptive effect in mice in the hot-plate assay, which was sensitive to yohimbine; clinical relevance of this effect is doubtful (Pick et al., 2005).

Zopiclone, a cyclopyrrolone, is a non-benzodiazepine derivative that binds at the BZD-ionophore: chloride channel complex. Its absorption time is approximately 2 hours with a bioavailability of 70% and the elimination half-life is 5 hours. Metabolites of zopiclone have similar elimination half-lives to that of the parent compound. Renal excretion occurs after enterohepatic cycling.

Clinical trials in sleep laboratories have shown that zopiclone leads to an increase in total sleep duration, a decrease of stage 1 sleep and increases of stages 2, 3 and 4 sleep. Few side effects with this drug have been reported, however, some patients have complained of a modification of taste with buccal bitterness. As with other hypnotics, side effects as headache, asthenia and drowsiness have also been reported with zopiclone. (Bourin M. et al. 2001)

Between 1987 and 1989, the different protein subunits that make up the receptor for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) were identified. (Bourin M., 2004)

These make up the alpha, beta, gamma and delta families, for each of which exist several subtypes. This receptor is the molecular target of modern hypnotic drugs (i.e. benzodiazepines, zopiclone, zolpidem and zaleplon). Receptor subtype specificity of hypnotics has been explained in terms of differential affinity for receptors containing different alpha subunits, which are expressed in different brain regions. Zolpidem and zaleplon bind preferentially to alpha1-containing receptors, whereas benzodiazepines and zopiclone are

aspecific. Different sets of subunits are encoded in contiguous 'cassettes' on the genome, and the transcription of each set appears to be regulated coherently. The predominant GABAA receptor composition found in the brain is $\alpha 1\beta 2\gamma 2$, which are all encoded on human chromosome 5. Targeted gene disruption has provided clues to the physiological functions served by GABAA receptors containing different subunits. Receptors containing $\gamma 2$ appear to have a vital role in maintaining appropriate central inhibition; $\beta 3$ -containing receptors may also be important determinants of excitability in certain brain regions, whereas a clear role for $\alpha 5$ -, $\alpha 6$ - and $\gamma 3$ -containing receptors has not yet been established by these techniques. Site-directed mutagenesis has indicated that benzodiazepines bind to a cleft on the GABAA receptor surface at the interface between the α and γ subunits. Other drugs (flumazenil, zopiclone, zolpidem) also bind to the α subunit, but interact with amino acids in different binding domains to the benzodiazepines. The molecular mechanism of hypnotic dependence has been explored, and seems to involve downregulation of transcription of the normally prevalent $\alpha 1$, $\beta 2$ and $\gamma 2$ subunits, and the reciprocal upregulation of the expression of rarer subunits. (Doble A., 1999)

So, finally, zopiclone could be considered as a conventional benzodiazepine profile drug regarding its binding properties on GABAA receptor subunit:

- classic benzodiazepines (e.g. diazepam, temazepam) and zopiclone have non-specific activation of all α subtypes
- non-benzodiazepine BZD-receptor agonists (e.g. zolpidem, zaleplon) have high affinity for $\alpha 1$ subtype

In drug discrimination studies, zopiclone shares discriminative stimulus properties with benzodiazepines in rodents (Julou et al., 1983). In both rats and baboons, food-maintained lorazepam discrimination procedures have been developed to predict compounds which are benzodiazepine receptor agonists (Ator and Griffiths, 1992). Zopiclone, zaleplon and zolpidem, three non-benzodiazepine hypnotics, all made the animals to respond as if they had received the benzodiazepine, while a number of other substances, including barbiturates, chloral hydrate, but also the compounds that bind to GABA_A receptors but not to the $\alpha 1$ -containing subtypes, failed to do so (Ator, 2005). In an operant study on squirrel monkeys, the effect of zopiclone on punished responding but also on unpunished responding and responding maintained by food or shock presentation was very similar to that of chlordiazepoxide, all of its effects being either shifted to the right on the dose-response graphs or completely blocked by flumazenil, a benzodiazepine receptor antagonist, dependent on the dose of the latter (Barrett et al., 1986). The discriminative stimulus properties of stereoisomers of zopiclone were recently compared to that of the parent drug in rhesus monkeys (McMahon et al., 2003). Both (R)-zopiclone and (S)-zopiclone substituted for midazolam with similar potencies, whereas the inactive stereoisomer of zopiclone had a weak substitutive effect even at very high doses, and this limited effect could possibly be explained by stereoconversion of the compound into the (S)-isomer in vivo (see below). This study also found that (S)-desmethylzopiclone, a metabolite of zopiclone that has been described to have anxiolytic-like effects in rats in tests based on both spontaneous exploratory behaviour and conflict situation (Carlson et al., 2001), did not possess any benzodiazepine-like or benzodiazepine antagonist-like discriminative stimulus properties, and thus the effects of this metabolite should be related to other mechanisms than benzodiazepine receptors. (S)-desmethylzopiclone has similar subunit affinity profile as the parent compound but is weaker at GABA_A receptors. It does inhibit activity at nicotinic acetylcholine receptors in recombinant systems, but this relatively weak effect is shared by zopiclone and benzodiazepines (Fleck, 2002).

While the above findings suggest that zopiclone exerts its effects through the same recognition sites as benzodiazepines, there are minor differences between the behavioural effects of benzodiazepine drugs and zopiclone (Barrett et al., 1986). These may be related to the dissimilarities in receptor binding reported to occur between benzodiazepines and zopiclone (Blanchard et al., 1979). Thus, it has been found that GABA and barbiturates do not increase zopiclone binding while they enhance benzodiazepine binding. Zopiclone binding to benzodiazepine receptors is also differently affected by photoaffinity labeling (Davies et al., 2000). The γ -subunit of the GABA receptor complex may contribute differently to the binding pocket of zopiclone compared to that of the benzodiazepines. In turn, zopiclone appears to enhance GABA_A receptor

binding similarly to benzodiazepines, and has the same subunit requirements. Zopiclone and diazepam, a prototypic benzodiazepine, have a similar effect on cGMP levels, which is also blocked by the benzodiazepine receptor antagonist flumazenil in a similar manner (Möhler et al., 1981). Zopiclone binds with roughly equal affinity to GABA_A receptors containing different α subunits (Sanger, 2004) and thus can not discriminate the GABA-dependent behavioural pharmacological effects by selective action via GABA_A receptors containing α subunits specifically related to sedation, anxiolysis and other effects (Möhler et al., 2002). This is also consistent with data indicating the similarity of behavioural effects of zopiclone and benzodiazepines currently in use.

Zopiclone suppressed barbitol withdrawal signs in rhesus monkeys and, in crab-eating monkeys treated with the drug for several weeks, elicited a withdrawal syndrome upon discontinuation of the drug described to be less severe than with diazepam but similar to nitrazepam (Yanagita, 1983). Cross-tolerance with benzodiazepines was demonstrated in an experiment in which rats were administered triazolam for two weeks via osmotic minipumps: this treatment caused a reduction of the sedative effect of zopiclone (Cohen and Sanger, 1994). Zopiclone was found to produce tolerance in a test developed to assess benzodiazepine receptor-related physical dependence in mice: administration of flumazenil precipitated withdrawal as expressed in reduced electroshock-induced seizure thresholds in animals treated with a high dose of zopiclone for three days (von Voigtlander and Lewis, 1991).

A most reliable preclinical predictor of abuse of a psychoactive compound in humans is self-administration of this substance in animals. There is limited evidence regarding self-administration of hypnotics compared to many other drugs of abuse, but self-administration of benzodiazepines can be demonstrated in monkeys. Self-administration of zolpidem has also been demonstrated by Griffiths et al. (1992) in a study on baboons: one or two weeks of self-administration of the drug caused tolerance to its sedative and ataxic effects, and withdrawal symptoms upon cessation of the substance. In similar conditions, zaleplon has also been found to be self-administered by baboons, but zopiclone has not been studied (Ator, 2005). However, in the study by Yanagita (1983), self-administration of zopiclone by rhesus monkeys was reported to occur “relatively frequently” by the intravenous route. Intragastric self-administration was also described: this occurred infrequently, but more frequently than with diazepam. It is relevant to the drug abuse pattern in humans that while naive monkeys do not self-administer benzodiazepines in many laboratory settings, this can be more readily obtained in animals that have previously been treated with other sedative drugs (Woods and Winger, 1995) which may augment the reinforcing effects of benzodiazepines in self-administration paradigms (Ator et al., 2005).

Clinical:

Benzodiazepine receptor agonists have among the experts been considered the preferred drugs to promote sleep and suggested for use of transient and short-term insomnia, restricting the length of the intake period, and applying the drugs mainly on an as-needed basis (NIMH Consensus Development Conference, 1984; Lader and Russel, 1993; Kirkwood, 1999). In practice, long-term use of hypnotics for chronic insomnia is not uncommon, and many patients with insomnia, as well as their physicians favour daily administration of hypnotics even over periods of many weeks or months (Busto et al., 2001).

Zopiclone was introduced during the second half of eighties (sold in France since 1987) and has been proven to be an effective hypnotic (Noble et al., 1998). Zopiclone has been found to prolong non-REM (rapid eye movement) stage 2 and 4 sleep with a significant decrease in total REM sleep (Hemmeter et al., 2000). Zopiclone has also been reported to reduce stage 1 sleep and increase stage 3 sleep (Stone et al., 2002). Its effects on sleep architecture as measured by polysomnography are, however, quite variable and inconsistent (Wagner and Wagner, 2000). In comparative studies, zopiclone in the standard dose of 7.5 mg (3.75 mg for the elderly) demonstrated hypnotic efficacy similar to many benzodiazepines and has, by increasing sleep efficiency, improved patients’ daytime functioning in comparison with placebo (Wagner and Wagner, 2000). Zopiclone is equal to lorazepam in sleep and cognitive function measures also in patients with stroke and brain injury (Li Pi Shan and Ashworth, 2004). Zopiclone is usually classified as a

short-acting hypnotic drug, but considering the duration of action it has been suggested as an agent rather suitable for maintaining a complete night's sleep than sleep induction (Drover, 2004). Zopiclone can successfully substitute for benzodiazepines in patients who have chronically used these drugs (Wagner and Wagner, 2000). Its regular use is common and concerns have been expressed that sleep disorders such as sleep apnoea and periodic limb movements in sleep remain unnoticed in such patients who rely on the drugs: A small study on patients taking hypnotics daily for at least a year (17 of 19 were taking zopiclone), found that most of them were experiencing sleep disorders (Sivertsen et al., 2004).

Zopiclone is undergoing chiral switch as eszopiclone, the active (S)-enantiomer of zopiclone, has arrived in the market. Eszopiclone is supposed to have equivalent efficacy with racemic zopiclone and possibly an improved side effect profile (Anonymous, 2005a). The recommended dosing to improve sleep onset and maintenance is 2-3 mg for adult patients and 1-2 mg for the elderly. Double-blind studies have shown its efficacy as compared to placebo, and a six-weeks treatment was reported not to lead to tolerance or rebound insomnia and to any detrimental effects on next-day psychomotor performance as measured by the Digit-Symbol Substitution Test (DSST) (Zammit et al., 2004). (S)-desmethylzopiclone, an enantiomer of the active metabolite of zopiclone, has been reported to be under development as an antianxiety drug (Gal, 2002).

Appropriate studies which could provide rationale for the use of hypnotics over prolonged periods have been lacking. Until recently any controlled study did not extend to more than to 2-3 weeks and very exceptionally beyond that (Wagner and Wagner, 2000; Walsh, 2004). This need has become to be met with new studies initiated in association with the launch of eszopiclone. A recent randomized multicenter study compared eszopiclone (3 mg daily) given for 6 months to 593 patients aged 21 to 69 years with primary insomnia and placebo (n=195) (Krystal et al., 2003). About 60% of the subjects in both placebo and eszopiclone arm completed the study. Eszopiclone significantly improved all self-reported measures of sleep: reduced sleep latency, increased total sleep time, reduced the number of awakenings, and improved sleep quality compared with the patients given placebo, without any evidence for tolerance.

Most studies involving small numbers of healthy volunteers have not detected any next-day residual effects of zopiclone on psychomotor performance (Wagner and Wagner, 2000), while some investigators have detected impairment in a coordination test (Billiard et al., 1987) and in performance of skilled tasks (Nicholson and Stone, 1982) after the 7.5 mg dose next morning.

Both the sleep-inducing efficacy and impact on psychomotor performance of zopiclone (7.5 mg) have been compared with zaleplon (10 mg), temazepam (15 mg) and melatonin (6 mg, time-released preparation) immediately after administration (Paul et al., 2003; Paul et al., 2004) in a placebo-controlled crossover study which attempted to mimic a situation in which a subject would be required to awaken from sleep and to return to normal performance, which could occur e.g., in military operational settings. Zopiclone was the strongest sleep-inducing treatment of the four in terms of both subjective drowsiness and sleep recorded by EEG during 4-min eyes-closed rest periods, and its impairing effects in demanding psychomotor tests (including tasks to simulate information processing characteristics of flight performance) were still significant six hours after administration.

Recently an attempt was made to compare zaleplon, zolpidem and zopiclone, the "Z-drugs", with benzodiazepines in terms of clinical efficacy and cost-effectiveness in a systematic review of the literature (Dündar et al., 2004). Twenty-four studies were identified for review, including 13 with data on zopiclone, but were found provide a confusing diversity of possible comparisons, outcome measures, and interpretations of the rarely standardized outcomes, making the authors to state explicitly the need for further adequate long-term follow-up studies to support a more cohesive database. Given the available data, the conclusion of the authors was that there is no major difference between the drug groups either in their efficacy or safety. Zopiclone was, though, possibly associated with less effect on daytime alertness than nitrazepam in four studies out of eight. The recommendations of the National Institute for Clinical

Excellence of U.K. that followed this analysis and suggested to prefer a hypnotic drug with the lowest purchase cost has elicited a vigorous argumentation about the advantages of the "Z-drugs", but this discussion has discriminated zopiclone as a longer-acting drug as compared to the other members of this group (e.g., Lader, 2005).

In the study which examined the effect of administration of eszopiclone (3 mg daily) for a period of 6 months (Krystal et al., 2003), patients' rating on daytime alertness while taking the hypnotic were actually better than with placebo, and adverse event rates after discontinuation of medication were not different from the placebo group.

Immediately after administration of zopiclone, memory is disturbed; this effect peaks at 1-2 h after administration and resolves by 6-8 h (Subhan and Hindmarch, 1984). A double-blind, placebo-controlled three-way crossover study compared the effect of zopiclone (7.5 mg) and brotizolam (0.25 mg) on memory storage during sleep (Silva et al., 2003). While neither drug was associated with residual sedation next morning as measured with the DSST, zopiclone but not brotizolam impaired the morning recall of a standard word list presented before bedtime. This experimental finding was linked by the authors to the suppressant effect of zopiclone on the theta band in EEG (Kim et al., 1993).

Hypnotics are often prescribed to the elderly, but postural control and memory functions which may be worsened by sedative drugs are also a particular concern in this age group. A double-blind, randomised cross-over study compared the effect of three hypnotics, including zopiclone, and placebo after a single usual starting dose for the elderly in 49 healthy volunteers aged ≥ 65 years (Allain et al., 2003). All active drugs increased body sway in the clinical stabilometric platform test and the mean reaction time in the Sternberg memory scanning test. The effects of zopiclone (3.75 mg on evening) persisted as significant for 8-9 hours, thus suggesting a reduction of function after awakening in the morning. Attention as assessed by measuring simple reaction time and critical tracking was not affected. This study mimicked the conditions of use of the drug among the population and thus assessed indirectly the potential risk of accidents in the elderly due to inconsiderate use of a the hypnotic.

No study has explicitly examined the ability of zopiclone to produce euphoria. However, reports on zopiclone dependence cited below point out that polydrug users may use zopiclone for producing euphoria. This may occasionally happen also in subjects without history of psychiatric disorders or psychoactive substance abuse (Kahlert and Brune, 2001). A 59-year-old female patient increased her dose of zopiclone per day to 150 mg within the period of three years, and the dose increases were associated with euphoria and subjectively improved fitness.

The effect zopiclone on driving abilities on the morning after a night on drug has been thoroughly examined in both laboratory conditions and actual driving conditions. In a specific task of simulation of anticipation of collision at intersection, zopiclone (7.5 mg) had no residual effect in ten healthy experienced drivers 10 h after taking the drug (Berthelon et al., 2003); zolpidem (10 mg) and flunitrazepam (1 mg) did not produce residual effects either. Vermeeren et al. (2002) found in a placebo-controlled study that a single dose of zopiclone (7.5 mg), when taken at bedtime, caused marked residual impairment in a highway driving test and on divided attention and memory, which was larger than that observed after alcohol drinks leading to blood levels 0.3 g/l. The authors concluded that patients on zopiclone should be advised to avoid driving the morning after zopiclone administration. Comparative analysis of this effect of zopiclone, as expressed in experimental conditions in the Standard Deviation of Lateral Position (i.e., the weaving of the car), have consistently shown that in the standard dose, zopiclone impairs driving ability 10-11 h after intake to a comparable extent to alcohol levels above common legal blood limits for driving (Verster et al., 2004). A recent study examined the effect of single and repeated (seven days) zopiclone administration on simulated driving in 23 patients with DSM-IV primary insomnia, and found that 9-11 h after intake of the drug zopiclone impaired performance compared to placebo (increase in the number of "collisions"), and EEG was at this time still altered by zopiclone in a similar way as by lormetazepam (Staner et al., 2005).

Patients are cautioned about using zopiclone when having hepatic and renal impairment, and history of drug use or psychiatric illness. Myasthenia gravis, respiratory failure, severe sleep apnoea syndrome, severe hepatic impairment, pregnancy and breast-feeding are contraindications to the use of zopiclone.

4. Toxicology, Including Adverse Reactions in Humans

Sedative hypnotics active through the benzodiazepine receptors are known for their low fatal toxicity. Anxiolytics and hypnotics are contributory factors rather than primary substances in poisoning deaths. Probably the lowest fatal dose known for zopiclone has been 90 mg which was taken in a successful suicide attempt by an elderly man with lung cancer and much weakened physical condition (Meatherall, 1997). A recent study in New Zealand attempted to compare fatal toxicity indices of zopiclone and benzodiazepines (Reith et al., 2003). The authors used a chemical injury database which included 200 poisoning deaths in 2001, and 39 of these cases involved sedative hypnotics, amongst them 12 cases with zopiclone. The age of subjects was in the range 15-29 years in one, 30-59 years in 7, and ≥ 60 in 4 cases. When the relative rates of death per prescription and DDD were compared, the fatal toxicity of zopiclone was similar to that of benzodiazepines as a group. It should be acknowledged that benzodiazepine receptor agonists are rarely the only drug present in poisoning deaths, and act rather as contributory factors than primary substances. In another overview of fatalities due to overdose, in England and Scotland in the period of 1983-1999, information was collected only for fatal poisonings due to a single anxiolytic or sedative drug (Buckley and McManus, 2004). This analysis identified 23 cases of death attributed to zopiclone. The fatal toxicity index as expressed in the number of deaths per one million of descriptions for zopiclone was found to be 2.1 (95% CI 1.4-3.2), which was similar to zolpidem (2.3) and, in comparison with sedative benzodiazepines, lower than for flurazepam (20.5), flunitrazepam (10.8), temazepam (9.9), triazolam (4.7), and nitrazepam (3.6; 95% CI 3.2-4.1), but tended to be higher than for loprazolam (1.6) and lormetazepam (1.4). A time-course analysis was presented for zopiclone to demonstrate that this method of assessing toxicity estimated the fatal toxicity index of zopiclone to be similar to the benzodiazepines as a group (>7) within the first few years of marketing. However, this analysis also includes some benzodiazepine formulations that have been withdrawn from the market.

Most frequently reported adverse effects are bitter or metallic taste and dry mouth (Wadworth and McTavish, 1993); the former can occur in approximately 10% of recipients. Some sources have preferred to characterize the effects of zopiclone in more general terms as changes in taste perception (Ratrema et al., 2001). Other frequent side effects include nausea and dizziness (Allain et al., 1991). Increase in sweating, and headache have been reported (Allain et al., 2003). Due to the potentiation of inhibitory neurotransmission in the CNS, sedation, somnolence and tiredness are expected side effects (Musch and Maillard, 1990). Adverse cognitive and psychomotor events and daytime fatigue appear more frequently in older people treated for insomnia (Glass et al., 2005). As of mid-December 2005, Uppsala Monitoring Centre had recorded 4923 adverse drug reactions.

Benzodiazepine receptor agonists have the potential to cause severe withdrawal reactions, including convulsions. Aranko and colleagues (1991) described a case of a 36-year-old man who repeatedly misused zopiclone in daily doses of 60-90 mg and suffered from convulsions on two occasions following abrupt withdrawal of the substance. It is relevant to mention that this subject also used alcohol, trimipramine and promazine.

A study in Finland analysed the presence of a number of psychotropic drugs and alcohol in 1995-2000 in fatal poisonings, and found that while fatal toxicity indices of benzodiazepines were relatively low, benzodiazepines were detected in slightly more than half of the 1006 cases (Koski et al., 2003). The additional presence in case of alcohol poisonings of a number of psychotropic drugs, including zopiclone, was associated with significantly lower median postmortem blood alcohol levels as compared to alcohol

poisonings without involvement of other drugs. Zopiclone was present in 38 cases and had been considered by pathologist to be the primary cause of death in 21 cases.

The WHO Uppsala Monitoring Centre (UMC) reported, out of 4927 reported adverse effects of world wide PMS-data 13 cases of death (0.3%) and 7 cases of sudden death (0.1 %) (unpublished, communication to WHO, 2005).

Central Nervous System Effects

Sedation and amnesia: Zopiclone as a sedative hypnotic reduces CNS functions, including memory. Anterograde amnesia is dose dependent (Gouille and Anger, 2004). Asthenia and fatigue, ataxia, impairment of concentration, and somnolence can occur (UMC, 2005). Evidence for mild, transient memory impairment by the chirally selective eszopiclone has also been reported (Anonymous, 2005b).

Sensory: Changes in taste perception; paraesthesias; abnormal vision (UMC, 2005).

Movement: Hyperkinesia, dyskinesia, involuntary muscle contractions (UMC, 2005).

Psychosis: Hallucinations, nightmares, and behavioural disturbances, including agitation and aggression have been reported (Wagner and Wagner, 2000; UMC, 2005).

Affect: Irritability, confusion, depressed mood (UMC, 2005).

Suicide: Sedative hypnotics acting through benzodiazepine receptors play a role in fatal drug poisoning despite of their relative safety in overdose. Particular significance among the elderly has been suggested (Carlsten et al., 2003). While the compounds most frequently associated with suicide among the elderly in Sweden are flunitrazepam and nitrazepam, zopiclone is on the rise quite in parallel with its increasing sales. Thus, the annual fatality ratios calculated as the number of drug-associated suicides divided by millions of sold DDDs appears a relative stable measure for any of these drugs, and was the highest with flunitrazepam, but similar for nitrazepam and zopiclone (Carlsten et al., 2003).

Other effects:

Gastrointestinal effects: Nausea and vomiting (Wagner and Wagner, 2000), abdominal pain, diarrhoea, dyspepsia; hepatitis (UMC, 2005).

Kidney/genitourinary: A case of acute interstitial nephritis with anuric renal failure in a young, otherwise healthy man has been described (Hussain et al., 2003).

Respiratory: Increase in viral infections (UMC, 2005).

Dermatologic effects: Hypersensitivity reactions, including urticaria and rashes have been reported (UMC, 2005).

Drug interactions: Concurrent use of zopiclone with other CNS depressant drugs, including alcohol, is contraindicated.

Erythromycin accelerates absorption of zopiclone, as demonstrated in a placebo-controlled study on ten healthy volunteers (Aranko et al., 1994). Erythromycin given orally 500 mg t.i.d. for six days increased plasma concentration of zopiclone (after administration of 7.5 mg) 4-fold at 0.5 h and 2-fold at 1 h. The peak time of zopiclone plasma levels was brought by erythromycin treatment from 2 h after administration to 1 h; the total area under curve of zopiclone increased by 80%, the peak levels by 40%. This facilitation of

zopiclone absorption increased the pharmacodynamic effect of zopiclone on saccadic latency and in the digit symbol substitution test for the period 0.5 – 2 h after administration of the hypnotic.

One report described a possible interaction of zopiclone and nefazodone (Alderman et al., 2001). A 86-year-old woman was treated with nefazodone for depression and zopiclone was added to manage insomnia; subsequently the patient experienced morning drowsiness and when nefazodone was discontinued the plasma levels of zopiclone decreased markedly (from 107 to 16.9 ng/mL and from 20.6 to 1.45 ng/mL for (S)- and (R)-enantiomer, respectively). Nefazodone is a relatively potent inhibitor of CYP3A4, which is a hepatic isoenzyme important in the metabolic elimination of zopiclone. Previously an attempt had been made to elucidate the possible effect of CYP3A4 inhibition on zopiclone pharmacokinetics: in a double-blind crossover study by Jalava et al. (1996), healthy young volunteers received during four days either placebo or 200 mg of itraconazole, a potent inhibitor of CYP3A. Itraconazole significantly increased the maximal blood levels (from 49 to 63 ng/ml) and area under curve of zopiclone, and prolonged the plasma half-life value from 5 to 7 h. However, no significant difference was observed in the pharmacodynamic effects of zopiclone after CYP3A4 inhibition, and it was concluded that at least in young adults, such a pharmacokinetic interaction would be of limited clinical importance. It thus appears that, for zopiclone use, CYP3A4 inhibition can be clinically relevant together with coinciding additional factors. Conversely, another experimental study from the same laboratory using similar design demonstrated that when a strong CYP3A4 inducer is administered, then zopiclone pharmacokinetics can be greatly changed (Vilikka et al., 1997). Rifampicin (600 mg) for five days reduced the peak plasma levels of zopiclone threefold and total area under curve values more than fivefold; significant reduction in the effects of zopiclone on tests assessing psychomotor abilities was also observed, suggesting that CYP3A4 inducers such as rifampicin, phenytoin and carbamazepine have a potential to interfere with the clinical effects of zopiclone.

5. Pharmacokinetics

Absorption: Oral bioavailability of zopiclone is about 75-80% (Gaillot et al., 1983). Time to peak plasma concentration is 1 - 2 h (Dündar et al., 2004; Vermeeren, 2004), the absorption rate constant is 1.3 h^{-1} and maximum plasma concentration after administration of 7.5 mg is 131 $\mu\text{g/l}$ (Drover, 2004). Half-life associated with the absorption rate constant is 0.52 h (Drover, 2004). High-fat meal preceding drug administration does not change absorption as measured by area under the curve, but reduces peak plasma levels and delays its occurrence and may thus delay the onset of effect of the drug.

Distribution: Zopiclone is weakly bound to plasma proteins (52-59%), the blood-to-plasma ratio is less than one, indicating no selective uptake by red blood cells. Zopiclone is rapidly and widely distributed in body tissues including the brain (Fernandez et al., 1995). In animal experiments, the highest accumulation is in muscle, lung, liver, fat tissue and kidney (Yurt et al., 1999). Apparent volume of distribution is 132 l (Drover, 2004). Terminal plasma half-life in healthy individuals is on average 5 hours (Vermeeren, 2004), in the range of 3.5-6.5 h. In elderly subjects the half-life increases, being on average 7 h (Goa and Heel, 1986). In healthy adults, the drug does not accumulate with once-daily administration of the recommended dose.

Metabolism: Zopiclone is extensively metabolized by the liver. Metabolites are formed by N-demethylation and N-oxidation; the principal plasma metabolites are zopiclone-N-oxide and N-desmethyl zopiclone (Le Liboux et al., 1987). The latter is an active metabolite. Decarboxylation also plays a role (Drover, 2004). Hepatic enzymes playing the most significant role in zopiclone metabolism are CYP3A4 and CYP2E1. In vitro, zopiclone was shown not to inhibit such isoenzymes as CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Excretion: Zopiclone is mainly (80%) excreted by the kidneys, primarily as the active and inactive

metabolites (5-10% as the parent drug) (Noble et al., 1998). Mean $t_{1/2}$ is approximately 6 h, elimination rate constant 0.203, and half-life associated with the elimination rate constant 3.41 h ((Drover, 2004).

Sex and race have not been found to interact with pharmacokinetics of zopiclone. In subjects aged >65 years, the bioavailability is higher and plasma levels of zopiclone also remain higher in time as compared to healthy adults, the area under curve measure being about 40% higher and $t_{1/2}$ about 9 h. These changes are attributed to a gradual decline in organ function and change in volume of distribution with increasing age (Gaillot et al., 1987).

The large degree of first-pass metabolism of zopiclone leads to a significant decrease in its clearance in patients with liver failure (Parker and Roberts, 1983; Gaillot et al., 1987). In severe chronic renal failure, the area under the curve value for zopiclone was larger and the half-life associated with the elimination rate constant longer, but these changes were not considered to be clinically significant (Viron et al., 1990).

Zopiclone and its main metabolites contain chiral centres, and (S)-zopiclone binding at benzodiazepine recognition sites is about 50-fold higher than of the (R)-zopiclone (Fernandez et al., 1995), and the pharmacokinetics of the enantiomers varies between individuals differently (Leonard, 2001). In rats, there is no stereoconversion from (S)- to (R)-zopiclone, whereas (R)-zopiclone converts to (S)-zopiclone, which is preferentially distributed into the brain (Fernandez et al., 2002).

6. Dependence Potential

The occurrence of dependency after therapeutic doses of benzodiazepines has been a subject of controversy, and hidden in unsystematic and inconsistent use of terms such as withdrawal symptoms, rebound, discontinuation symptoms. This also holds for other hypnotics, and in the absence of placebo control the pill discontinuation per se may serve as a cause of rebound insomnia (Hajak, 1999).

Since the beginning of its therapeutic use, zopiclone has been found to cause rebound insomnia and anxiety, as reviewed by Lader in 1992. For example, a placebo-controlled study on healthy volunteers revealed a detectable increase in state anxiety and a decrease in sleep depth on a few days after zopiclone withdrawal after three-week treatment with the standard dose 7.5 mg (Dorian et al., 1983). Nevertheless, the incidence of withdrawal symptoms after discontinuation of doses of zopiclone advised for clinical use has been suggested to be negligible or considerably lower than that of benzodiazepines (Lader, 1998a, 1998b; Wagner and Wagner, 2000). Withdrawal from zopiclone as measured by polysomnography was less severe than from triazolam (Voderholzer et al., 2001). Zopiclone dependency has been reported to occur mainly in patients with a history of drug abuse (Wadworth and McTavish, 1993; Ayonrinde and Sampson, 1998; Hajak, 1999). In some instances, other mental health problems such as depression have appeared more important predictors of developing dependence on the hypnotic (Strohle et al., 1999). A review of laboratory sleep studies and clinical trials monitoring discontinuation of zopiclone administration described no significant rebound effect on sleep and few withdrawal effects (Bianchi and Musch, 1990). The main withdrawal symptoms were anxiety and vertigo. A prescription-event monitoring study by Inman and colleagues (1993) found withdrawal reactions like headache, anxiety or agitation only in 0.05% individuals (7 out of 13 177). Nevertheless, quotations of these studies supporting very limited potential for dependence of zopiclone and related drugs go in current literature hand-in-hand with cautioning about the as yet unclear potential for dependence of this compound (Bauer, 2001; Terzano et al., 2003). As noted by Dündar and colleagues (2004), dependence with hypnotics becomes a greater issue when the drug is used outside its licence, which is more difficult to study. Any comparison of the Z-drugs with benzodiazepines has to take into consideration the fact that benzodiazepines were introduced in an era with a different attitude and were used at that time with less caution than is usual at present. By the time the Z-drugs arrived there was much more vigilance towards this issue.

The Medline database has been systematically searched for single case reports on abuse and dependence occurrence with zopiclone and zolpidem between 1966-2002, and the outcome reviewed (Hajak et al., 2003). The authors were able to identify 22 reports on zopiclone and 36 reports on zolpidem. For almost all patients the typical features of dependence were reported: dose increases over time, tolerance, and withdrawal symptoms. Reported symptoms of zopiclone withdrawal usually occurred when the dosing had been increased or the use prolonged, and included anxiety, tachycardia, tremor, sweating, rebound insomnia, flushes and palpitations, derealisation, and convulsions. The number of reports, when compared to the world-wide prescription frequency, suggests similar incidence of reported cases of dependence for the two drugs, or a slightly higher incidence for zopiclone. This incidence would be lower than for many benzodiazepines. This analysis presented detailed information about individuals in all cases in tabulated form. However, it did not make use of information from any reports which included more cases as identified among consecutively admitted patients of addiction clinics or other practices, in which the subjects were not always individually described. Some reports of the latter type are reviewed below.

Although the occurrence of zopiclone dependence has been believed to occur mainly in subjects with history of psychiatric disorders, there are exceptions to this. Jones and Sullivan (1998) described four patients aged 26-49 who increased their daily dose to 22.5-30 mg over prolonged periods and experienced anxiety and insomnia when trying to stop taking the medication. Physical symptoms such as tachykardia, tremor, sweating, flushes, palpitations were also reported, as well as a strong craving for the drug. Of these four cases, only one had been dependent on benzodiazepines previously.

Kahlert and Brune (2001) have presented a case of a 59-year-old female patient with primary zopiclone dependence: This patient with no record of psychiatric disorders or abuse of psychoactive substances increased in the period of three years her daily intake of zopiclone to 150 mg. Any attempt to discontinue zopiclone made her to suffer from anxiety and inner restlessness, but she was suffering from fatigue and forgetfulness when on the medication. After withdrawal of zopiclone the patient experienced inner restlessness, psychomotor agitation, vague abdominal pain and hypertension, and these symptoms subsided after administration of diazepam.

Another recently published case report on zopiclone dependence (Kuntze et al., 2002) described a patient who used up to 337.5 mg of the drug per day; the study did not however include any pharmacokinetic information. The patient was not taking other psychotropic drugs except social use of alcohol. He had no history of drug abuse.

A case of delirium caused by zopiclone withdrawal was recently reported in a 74-year-old woman, who had been admitted to hospital due to congestive heart failure which was successfully managed (Wong et al., 2005). The patient had an extended medical history including hypertension, diabetes mellitus, hypercholesterolaemia, renal impairment, gout and primary hyperparathyroidism, and was taking several medications, but had never drunk alcohol or smoked. While in hospital, she developed confusion and disorientation two days after admission, which were not explained by any possible cause considered. Only several days later her husband provided information that the patient had been taking high-dose zopiclone (112.5) daily and had done so "for more than 20 years". When zopiclone (30 mg daily) was resumed, the patient's mental condition normalized over the next few days.

Dependence on legal and illicit psychoactive drugs among alcoholics was recently studied in a Swedish sample (Johansson et al. 2003), using a questionnaire based on DSM-IV. Alcoholic patients were much more often dependent on legal psychotropic drugs than healthy controls, and institutionalized patients were more frequently dependent than those studied in the open care setting. Dependence on zopiclone was reported for 5% of the 153 subjects, compared to 15% for benzodiazepines, 5% for codeine, and 3% for zolpidem and dextropropoxyphene, the use/dependence quotient being roughly similar for benzodiazepines, zolpidem and zopiclone. Also, number of cases of zopiclone dependence was identified amongst Australian Vietnam War veterans treated at a psychiatry department (Alderman et al., 2000). The

issue that withdrawal effects and dependence may be underreported in databases for zopiclone has been raised because these figures appear, at least in New Zealand, not match to the number of patients seeking assistance from addiction services (<http://www.medsafe.govt.nz>).

Duration of zopiclone treatment seems less a factor in dependence than increasing the dose, as the only adequate long-term study which was quoted above (Krystal et al., 2003) did not find any evidence for systematic adverse effects when eszopiclone (3 mg daily) was abruptly discontinued after six months of treatment.

There is no withdrawal syndrome when patients discontinue their treatment with zopiclone abruptly. There is no more tolerance when they are treated chronically, than there is dependency in abuse patients for other drugs. (Extracted from the report of the CEIP of Nantes for the French Drug Agency)

7. Epidemiology of Use and Abuse, with an Estimate of the Abuse Potential

While the liability for abuse of hypnotics has been considered low among the general population, in drug abusers and alcoholics the risk of abuse of hypnotics has been estimated as particularly significant (Busto et al., 1986; Woods, 1998). A survey was carried out by Jaffe and collaborators (2004) among 297 drug addicts who were consecutively admitted to addiction treatment centres at three sites in United Kingdom. Subjects were given 14 questions to assess their exposure, medical use and abuse liability regarding five benzodiazepines, zolpidem and zopiclone, three antidepressants and two antihistamines. The subjects were past and current users of different types of addictive substances, so the authors attempted to control for a possibly distinct pattern of responses in the subjects with past or current abuse of alcohol or hypnotic sedative drugs. However, history of alcohol or hypnotic sedative abuse did not differentiate the participants, which seems to indicate that drug abuse per se is more important in relation with hypnotic sedative drugs than earlier experience with this group of substances. Slightly more than half of the subjects had used zopiclone, which ranked fourth in this respect among drugs after diazepam, temazepam and nitrazepam. About 80% of zopiclone users had obtained the drug through a prescription, but 42% reported having purchased it on street. In most cases (88.5%) the users took zopiclone for sleep, but 56.7% answered affirmatively to a question about taking the drug to feel better, and 22.9% reported taking it to get high. In comparison, for the frequently used benzodiazepines the latter proportion was slightly more than 50%. About half of zopiclone users said they like the effect of the drug (this proportion was about 80% for the three benzodiazepines). To the questions whether they need the drug, feel addicted to it, or think they might become addicted, the positive answers for zopiclone were given by 28.0, 5.1, and 19.8%, respectively. Feeling the need of the drug was similar for zopiclone and the three benzodiazepines; addiction to benzodiazepines was felt more frequently, but zopiclone maintained its rank above other drugs under investigation.

Practitioners have warned about the misuse of zopiclone since mid-nineties, and worries were expressed that the drug had, in Wales, obtained a certain reputation and become widely available on streets, being used together with alcohol (Clee et al., 1996; Sullivan et al., 1995). In a Letter to the Editor of "Addiction", Sikdar and Ruben (1996) reported that among one hundred consecutive patients attending the methadone maintenance programme in Liverpool six subjects admitted zopiclone abuse. Their average daily dose of zopiclone was 105 mg divided into 2-3 oral doses. All had previously abused temazepam in high doses and reported that they had switched to zopiclone because of the strong amnesic action of the benzodiazepine. These methadone-treated patients admitted to using heroin and cocaine intermittently. The six patients had initially used zopiclone for sleep, but later developed tolerance to the sedative effects. Among the withdrawal effects, very strong craving for zopiclone 6-8 h after the last dose was reported, leading to self-medication. Another letter described prevalence of zopiclone use among participants in a methadone program in Ireland (Rooney and O'Connor, 1998). A total of 38 patients out of 55 had taken zopiclone; of these, 16 were reported to "misuse it to experience various degrees of tranquillization". One of the subjects

had attempted to inject the substance. The authors commented that the main attraction of zopiclone to drug misusers is the similarity of its effects to benzodiazepines while the compound not being monitored during the drug treatment programme. Comments on the abuse potential have also been posted by users on websites (e.g., <http://www.rsdalert.co.uk/drugs/Zopiclone.htm>).

Zopiclone has been mentioned in the context of hypnotic sedative use in drug-facilitated crimes such as sexual assaults or robbery (Kintz et al., 2005), and because of the recent increase in attention to this concern, forensic testing for zopiclone use pattern in hair has been developed (Villain et al., 2004). A report has described a car theft followed by a road traffic accident in which case the two detainees were found in possession of a few tablets of zopiclone and reported of having taken 8-9 tablets with alcohol before the events which they claimed not to remember because of the effect of the drugs (Walter and Samtani, 1998): No information about blood levels of the drug was apparently possible to include to support or refute the claim of drug-induced anterograde amnesia.

In France, there are more and more people taking zopiclone using false prescriptions. Therefore, it could be considered as a substance of abuse. Zopiclone is in France in the "top ten" of false prescriptions. It used in injection by the abusers in some cases. Fifteen per cent of the regular users take zopiclone for another goal than hypnotic use, mainly to present with euphoria, stimulation and even to desinhibit an anxiolytic effect. (Extracted from the report of the CEIP of Nantes for the French Drug Agency)

In the 2005 WHO Questionnaire, six countries report abuse:

Belgium: has five reports of abuse

China (no further comment)

France: the abuse is comparable with zolpidem and most of the abusers are polydrug users

Iceland: the substance is probably overused

Sweden: the substance is frequently found in the urine of drug abusers

Switzerland: In 6 out of 832 cases of poisoning it was abuse; 52 out of 832 were possible abuse (1997-2005) 3 of the abuse cases were cases of multidrug use: (alcohol, heroin, midazolam)

Data from UMC: As of December 2005, the ADR database of UMC contains out of 4927 reports for zopiclone, 18 reports of drug abuse (0.3 %), 89 reports of drug dependence (1.8%), 83 reports of withdrawal syndrome (1.7 %), 2 reports of withdrawal convulsions (0,04 %) and 1 report of withdrawal arrhythmia (0,02 %) (unpublished, communication to WHO, 2005).

8. Nature and Magnitude of Public Health Problems

Zopiclone became highlighted in a case-crossover study conducted in the U.K. which examined the association of road accidents with use of antidepressants, anxiolytics and hypnotics (Barbone et al., 1998). Prescription records of more than four hundred thousand individuals were linked to police records of car crashes, in which almost 20 000 drivers were involved. It was found that while there were moderately increased risks with anxiolytic use and no significant increase of accident risk associated with the use of hypnotics as a group, the odds ratio for zopiclone was 4.0. Altogether 14 cases of zopiclone association with road accident were identified This finding is in line with the studies of Volkerts and O'Hanlon (1988) and Vermeeren et al. (2002) on the residual effects of zopiclone on driving simulation and real car driving. The finding of particular risks with zopiclone may also be related to the possible misuse of this drug. A forensic toxicology study in Norway revealed that of the 101 suspected intoxicated drivers who tested positive for zopiclone, 60 % had blood concentrations of zopiclone above the levels normally observed after intake of therapeutically recommended doses, and 80% had blood levels higher than expected 8 h after intake of therapeutic doses (Bramness et al., 1999).

9. National Control

In the United States, zopiclone and its isomers were placed into the Schedule IV of the U.S. Controlled Substances Act on April 4, 2005 by Drug Enforcement Administration. This decision was based on the conclusions that zopiclone has a low potential for abuse relative to the drugs or other substances in CSA Schedule III, has a currently accepted medical use in the U.S. (eszopiclone was approved for marketing by the Food and Drug Administration on December 15, 2004), and that abuse of zopiclone may lead to limited physical or psychological dependence relative to the drugs or other substances in Schedule III (Federal Register, 2005).

Other countries that put the substance under control are France (1999), Mauritius and Turkey.

10. Therapeutic and Industrial Use

Zopiclone is among the most frequently prescribed hypnotics in Europe (Ohayon and Lader, 2002) which, at usual therapeutic doses, decreases sleep latency and the number of nocturnal awakenings, increases total sleep time and improves sleep quality (Wagner and Wagner, 2000).

11. Production, Consumption and International Trade

Zopiclone is an authorized medicine in 34 countries out of 59 that answered the questions for the substance. In one country it used to be authorized, but it was withdrawn from the market by the company.

12. Illicit Manufacture and Illicit Traffic, and Related Information

There are very few reports of illicit activities on zopiclone. The most serious is that France reported that it is on the top-ten of most falsified prescriptions. 4 % of users obtains zopiclone from other people or from dealers since 2000.

Sweden reported 96 - 117 seizures annually (2002 - 2005). The United States of America reported only one seizure (4 tablets) in the period from 1995 to 2004.

13. Current International Controls in Place and their Impact

Zopiclone is not under international control at present. In the WHO 2005 Questionnaire, 9 countries said that bringing it under control would have impact on its availability:

Australia	there is not sufficient information to warrant any further regulation. Scheduling would be a minor burden for industry; there would be additional controls on supply and distribution to end users
Bangladesh	It will take more time than before. Due to the two-tier system more time will be required which will hamper its medical availability in the country
Cabo Verde	(no comment)
China	The placement of zopiclone under control will result in the change of its mode of circulation, thereby affecting its medical availability
India	It will restrict medical availability
Japan	It would impact its medical availability very much. Doctors will not tolerate the inconvenience.
Jordan	The specific regulation may effect on the import of the substance and its preparations (notice that Jordan answered that the substance is not used)
Myanmar	Medical availability will become limited in remote areas of the country and

Poland in places where authorized professionals are not available
Restriction because of storage and administrative requirements

Mauritius remarked, that since it scheduled zopiclone, the drug is used in a rational way.

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