

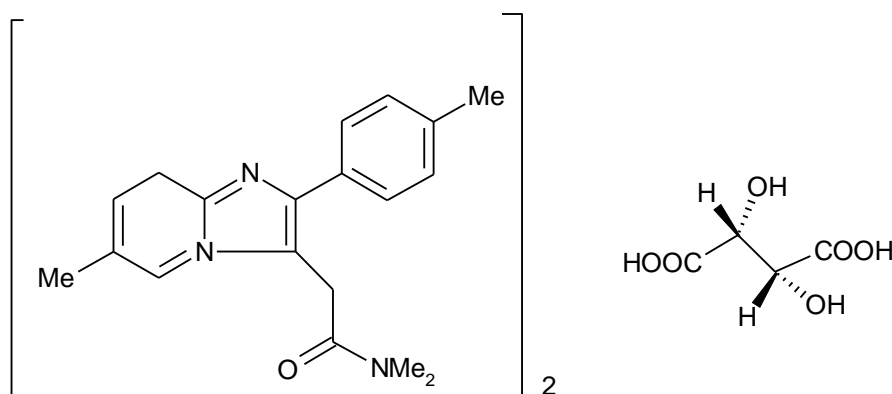
# PRODUCT INFORMATION

## DORMIZOL

(zolpidem tartrate)

**WARNING: Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleep walking, sleep driving and other bizarre behaviours. Zolpidem is not to be taken with alcohol. Caution is needed with other CNS depressant drugs. Limit use to four weeks maximum under close medical supervision.**

### DESCRIPTION



Zolpidem tartrate is a white to off white colourless, crystalline powder, sparingly soluble in water. Its chemical name is 2-(4-methylphenyl)-N,N,6-trimethylimidazo [1,2,a] pyridine-3-acetamide hemitartrate.

Its molecular formula is (C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O)<sub>2</sub>, C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>. MW is 764.9.

CAS numbers are 99294-93-6 (zolpidem tartrate) and 82626-48-0 (zolpidem).

Each tablet contains zolpidem tartrate 10 mg with lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycollate and magnesium stearate. The coating on the tablets consists of hypromellose, titanium dioxide and macrogol 400.

### PHARMACOLOGY

#### Pharmacodynamics

Zolpidem belongs to the imidazopyridine group of compounds and is structurally unrelated to other hypnotic agents. Zolpidem selectively binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which is the alpha unit of the GABA-A receptor complex. Whereas benzodiazepines non-selectively bind all three omega receptor subtypes, zolpidem preferentially binds the omega-1 subtype. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem i.e. the preservation of deep sleep (stage 3 and 4 slow wave sleep).

These effects are reversed by the benzodiazepine antagonist flumazenil.

In animals: The selective binding of zolpidem to omega-1 receptors may explain the virtual absence at hypnotic doses of myorelaxant and anti-convulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.

In humans: The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem. All identified effects of zolpidem are reversed by the benzodiazepine antagonist flumazenil.

## Pharmacokinetics

### Absorption

DORMIZOL has both a rapid absorption and onset of hypnotic action. Peak plasma concentration is reached at between 0.5 and 3 hours. Following oral administration, bioavailability is 70% due to a moderate first-pass metabolism.

The elimination half-life is short, with a mean value of 2.4 hours (+ 0.2 h) and a duration of action of up to 6 hours. DORMIZOL pharmacokinetic profile is linear in the therapeutic dose range, and is not modified upon repeated administration.

### Distribution

Protein binding amounts to approximately 90%. The distribution volume in adults is  $0.54 \pm 0.02$  L/kg and decreases to  $0.34 \pm 0.05$  L/kg in the very elderly.

### Metabolism

The main cytochrome P450 enzyme involved in the hepatic biotransformation of zolpidem is CYP3A4. CYP1A2 and CYP2D6 contribute minimally to the metabolism of zolpidem (see **INTERACTIONS WITH OTHER MEDICINES**).

### Excretion

All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%). Furthermore, they do not interfere with zolpidem plasma binding.

### Effect of Food

A food-effect study in 30 healthy male volunteers compared the pharmacokinetics of zolpidem 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food, mean AUC and  $C_{max}$  were decreased by 15% and 25%, respectively, while mean  $T_{max}$  was prolonged by 60% (from 1.4 to 2.2 hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, DORMIZOL should not be administered with or immediately after a meal.

### Special Populations

Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks. In the elderly, the recommended dose for DORMIZOL is 5 mg (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). This recommendation is based on several studies in which the mean  $C_{max}$ ,  $T_{1/2}$  and AUC were significantly increased when compared to results in young adults.

Zolpidem did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

The pharmacokinetics of DORMIZOL in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20 mg oral zolpidem dose, mean  $C_{max}$  and AUC were found to be two times (250 vs 499 ng/mL) and five times (788 vs 4,203 ng.hr/mL) higher, respectively, in hepatically-compromised patients.  $T_{max}$  did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normals of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected. Zolpidem has been shown to be non-dialysable.

## CLINICAL TRIALS

### Insomnia in non-elderly adults

Short term (1 to 2 nights) placebo controlled studies in 620 volunteers showed that DORMIZOL 2.5 to 10 mg decreased the latency of persistent sleep in a dose dependent manner. No further increase in efficacy was seen in doses up to DORMIZOL 40 mg.

The efficacy of DORMIZOL 2.5 - 20 mg was investigated in 11 placebo-controlled studies in 1606 (513 received DORMIZOL 10 mg) non-elderly insomniacs over a period of 2-35 nights. DORMIZOL 10 mg was superior to placebo using both objective (polysomnography) and subjective methods of assessment. DORMIZOL 20 mg showed little increase in efficacy.

### Insomnia in the elderly

Four studies in 145 elderly (>65 years) patients showed, using objective (2 studies) and subjective (4 studies) methods of assessment that DORMIZOL 5 mg was the dose giving the optimum efficacy/safety ratio.

*Next-day residual effects:* There was no evidence of residual next-day effects seen with DORMIZOL in several studies utilising the Multiple Sleep Latency Test (MSLT), the Digit Symbol Substitution Test (DSST), and patient ratings of alertness. In one study involving elderly patients, there was a small but statistically significant decrease in one measure of performance, the DSST, but no impairment was seen in the MSLT in this study.

*Rebound Effects:* Although there were no studies to exclude this effect, there was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of DORMIZOL. There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

*Memory Impairment:* Two small studies (n=6 and n=9) using objective measures of memory yielded little evidence for memory impairment following the administration of DORMIZOL. There was subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of DORMIZOL, predominantly at doses above 10 mg.

*Effects on Sleep Stages:* In studies that measured the percentage of sleep time spent in each sleep stage, DORMIZOL has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

The hypnotic efficacy and safety of DORMIZOL has not been assessed in children and pregnant women.

## INDICATIONS

DORMIZOL is indicated for the short-term treatment of insomnia in adults (see **DOSAGE AND ADMINISTRATION**).

## CONTRAINDICATIONS

- Sleep apnoea.
- Known hypersensitivity to zolpidem or other ingredients in the tablet.
- Myasthenia gravis.
- Severe hepatic insufficiency.
- Acute and/or severe pulmonary insufficiency.
- Prior or concomitant intake with alcohol.
- DORMIZOL should not be prescribed for children.

## **PRECAUTIONS**

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed.

The failure of insomnia to remit after a 7-14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re-evaluated at regular intervals.

### **Withdrawal, Rebound, Dependence and Tolerance**

#### Tolerance

Continuous long-term use of DORMIZOL is not recommended and should not exceed four weeks.

Some loss of efficacy to the hypnotic effects of sedative/hypnotic agents may develop after repeated use for a few weeks.

#### Dependence

Use of sedative/hypnotic agents may lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. These patients should be under careful surveillance when receiving hypnotics.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

#### Rebound insomnia

A transient syndrome whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form, may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur when the medicinal product is discontinued.

There are indications that, in the case of sedative/hypnotic agents with a short duration of action, withdrawal phenomena can manifest within the dosage interval, especially when the dosage is high.

When DORMIZOL is used in accordance with the recommendations for dosage, duration of treatment and warnings, the risk of withdrawal symptoms or rebound phenomena occurring is minimal.

#### Severe injuries

Due to its pharmacological properties, zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

### **Patients with Long QT syndrome**

An in vitro cardiac electrophysiological test showed that under experimental conditions, using very high concentration and pluripotent stem cells, zolpidem may reduce the hERG related potassium currents. As a precaution, the benefit/risk ratio of zolpidem treatment in patients with known congenital long QT syndrome should be carefully considered.

### **CNS effects**

As with all patients taking CNS-depressant medications, patients receiving DORMIZOL should be warned not to operate dangerous machinery or motor vehicles until it is known that

they do not become drowsy or dizzy from DORMIZOL therapy. Patients should be advised that their tolerance for other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of DORMIZOL. Prior or concomitant intake with alcohol is contraindicated (see **CONTRAINDICATIONS**).

### **Respiratory function**

Both animal and human pharmacology studies performed with DORMIZOL have not observed any effect on the respiratory centre. However, as other sedative/hypnotics have the capacity to depress respiratory drive, caution is advised when DORMIZOL is administered to patients with respiratory insufficiency. (See **CONTRAINDICATIONS**)

### **Use in the Elderly or Debilitated Patient**

Elderly and debilitated patients may be particularly sensitive to the effects of DORMIZOL, therefore a 5 mg dose is recommended. This dose should not be exceeded in these patients. (See **DOSAGE AND ADMINISTRATION**).

### **Hepatic impairment**

As clearance and metabolism of zolpidem is reduced in hepatic impairment, dosage should begin at 5 mg with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated. (See **PRECAUTIONS 'Use in the Elderly'** and **DOSAGE AND ADMINISTRATION**). Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy.

### **Renal Impairment**

Dosage reduction is not necessary in patients with renal impairment, however, as a general precaution, these patients should be monitored closely (see **DOSAGE AND ADMINISTRATION**).

### **Memory Impairment**

Sedative/hypnotic agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours.

### **Suicidality, Depression, Psychosis and Schizophrenia**

Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including zolpidem. DORMIZOL is not recommended as primary therapy in patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary as depression may increase in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Pre-existing depression may be unmasked during the use of DORMIZOL. Suicidal tendencies may be present or uncovered and protective measures may be required. Intentional overdose is more common in this group of patients: therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

### **Other Psychiatric and Paradoxical Reactions**

Other psychiatric and paradoxical reactions such as acute rage, restlessness, insomnia exacerbated, agitation, irritability, aggression, delusions, anger, nightmares, hallucinations, stimulation or excitement, abnormal behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like DORMIZOL. Should such reactions occur, DORMIZOL should be discontinued. These reactions are more likely to occur in the elderly.

## **Somnambulism and Associated Behaviours**

Sleep walking and other associated behaviours such as “sleep driving”, preparing and eating food, making phone calls or having sex, with amnesia for the event, have been reported in patients who had taken zolpidem and were not fully awake. The use of alcohol and other CNS depressants with zolpidem appears to increase the risk of such behaviours, as does the use of DORMIZOL at doses exceeding the maximum recommended dose. Discontinuation of DORMIZOL should be strongly considered for patients who report such behaviours (for example, sleep driving) due to the risk to the patient and others (see **Interactions and ADVERSE EFFECTS**). These events can occur in sedative-hypnotic naive as well as sedative-hypnotic experienced patients.

## **Interactions with Alcohol**

Prior or concomitant intake with alcohol is contraindicated (see **CONTRAINDICATIONS**). Patients should be advised that their tolerance for alcohol and other CNS depressants might be reduced and have an additive effect on psychomotor performance (see **PRECAUTIONS ‘Somnambulism and Associated Behaviours’** above).

## **Risks from Concomitant use with Opioids**

Concomitant use of sedative-hypnotic drugs, including zolpidem, with opioids may result in sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and zolpidem for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe zolpidem concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. (see **INTERACTIONS WITH OTHER MEDICINES**).

## **Psychomotor Impairment**

The risk of psychomotor impairment, including impaired driving ability, is increased if zolpidem is taken within less than 7-8 hours before performing activities that require mental alertness, a dose higher than the recommended dose is taken, or zolpidem is co-administered with other CNS depressants, alcohol, or with other drugs that increase the blood levels of zolpidem.

## **Severe Anaphylactic and Anaphylactoid Reactions**

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

## **Geriatric or Debilitated Patients**

Such patients may be particularly susceptible to the sedative effects of the medication and associated giddiness, ataxias and confusion, which may increase the possibility of a fall.

## **Epilepsy**

Abrupt withdrawal of CNS-depressant drugs in persons with convulsive disorders has been associated with a temporary increase in the frequency and or severity of seizures.

As with other sedative/hypnotics, caution is advised when DORMIZOL is used in these patients.

## **Abuse**

Caution must be exercised in administering DORMIZOL to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

## **Effects on Ability to Drive and use Machinery**

This preparation is to aid sleep. Patients should not drive or operate machinery for 8 hours after taking DORMIZOL.

Adverse effects including drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision, reduced alertness and/or impaired driving may continue the following day. In order to minimise this risk a full night of sleep (7-8h) is recommended. After ingesting the medicine, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor co-ordination such as operating machinery or driving a motor vehicle, including potential impairment of the performance of such activities that may occur the day following ingestion of DORMIZOL. Furthermore, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such effects. Patients should be warned not to use alcohol or other psychoactive substances when taking zolpidem.

## **Carcinogenicity, Mutagenicity, Impairment of Fertility**

### Mutagenic Potential

Zolpidem was not genotoxic in assays for gene mutations (*Salmonella typhimurium* histidine reversion assay, L5178Y mouse lymphoma assay), for chromosomal aberrations (human lymphocytes, mouse micronucleus assay) and for DNA repair assays (in human fibroblasts and rat hepatocytes). The mutagenic activity of zolpidem and/or its metabolites was equivocal in a Chinese hamster V79/HRPT gene mutation assay in the presence of metabolic activation.

### Carcinogenic Potential

Two year dietary carcinogenicity studies on zolpidem were conducted in rats and mice. No evidence of carcinogenic potential was observed in mice at plasma concentrations (AUC) of zolpidem and its major human metabolite of about 2 and 7-12 times, respectively, the anticipated clinical exposure at the maximum recommended clinical dose. An increased incidence of renal liposarcomas was observed in male rats (6% cf. 0 in controls) at plasma concentrations (AUC) of zolpidem and its major metabolite of at least 22 and 9 times, respectively, the anticipated human exposure.

## **Use in Pregnancy**

### Category B3

This drug has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is uncertain in humans. As a precautionary measure, it is preferable to avoid the use of zolpidem in pregnancy.

### Teratogenic effects

In reproductive toxicity studies, rats treated with oral zolpidem with estimated exposures (AUC) to zolpidem and its major metabolite of 41 and 15 times, respectively, the anticipated clinical exposure did not exhibit teratogenic effects but post-implantation survival index and postpartum viability of the offspring were significantly reduced. In rats, delayed ossification of foetal skull bones occurred at zolpidem and metabolite exposure levels of 8 and 3 times, respectively, the anticipated clinical exposure.

Rabbits treated with oral zolpidem with estimated exposure to zolpidem of 0.6-2.6 times the anticipated clinical exposure did not exhibit teratogenic effects, but there was increased post-implantation loss.

Although animal studies have not shown any teratogenic effects with zolpidem, the safety of zolpidem in human pregnancy has not been established.

#### Non-teratogenic effects

Cases of severe neonatal respiratory depression have been reported when zolpidem was used with other CNS depressants at the end of pregnancy.

Infants born to mothers who took hypnotics chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

#### **Use During Lactation**

The use of DORMIZOL in nursing women is not recommended as small quantities of zolpidem are excreted into breast milk.

### **INTERACTIONS WITH OTHER DRUGS**

#### CNS depressants

Co-administration of DORMIZOL with other CNS depressants should be exercised with caution since the central depressant effect may be additive. CNS depressants include alcohol, benzodiazepines, barbiturates, sedative/hypnotics, anxiolytics tricyclic antidepressants, MAOIs, antipsychotics, phenothiazines, skeletal muscle relaxants, antihistamines, neuroleptics, antiepileptic drugs, narcotic analgesics or anaesthetics. Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability. In the case of narcotic analgesics enhancement of euphoria may also occur.

#### Opioids

The concomitant use of sedative-hypnotic drugs, including zolpidem, and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of zolpidem and opioids (see **PRECAUTIONS 'Risks from Concomitant use with Opioids'**).

#### Alcohol

Prior or concomitant intake with alcohol is contraindicated (see **CONTRAINDICATIONS**). Patients should be advised that their tolerance for alcohol and other CNS depressants might be reduced and have an additive effect on psychomotor performance. The use of alcohol and other CNS depressants with zolpidem appears to increase the risk of somnambulism and associated behaviours (see **PRECAUTIONS 'Somnambulism and Associated Behaviours'**).

#### Imipramine

The sedative effects of imipramine 75 mg and zolpidem 20 mg were shown to be additive when the two compounds were given concomitantly in healthy volunteers. No pharmacokinetic interaction was shown between zolpidem and imipramine or its metabolite, desipramine.

#### Chlorpromazine

The combination of zolpidem 10 mg and chlorpromazine 50 mg in healthy volunteers produced an addition of effects seen in psychometric tests and decreased alertness and psychomotor performance. No pharmacokinetic interaction was observed.



### Haloperidol

No evidence of pharmacokinetic interaction between zolpidem 20 mg and haloperidol 2 mg was seen when they were given concurrently to healthy volunteers.

### Caffeine

No change in the sleep inducing effect of zolpidem was seen when 300 mg caffeine was given in the evening 45 minutes before administration of zolpidem 20 mg to 8 healthy volunteers.

### Warfarin

Prothrombin times were not prolonged in healthy adults when zolpidem 20 mg was administered for 4 consecutive nights concomitantly with warfarin. Warfarin had been given for at least 10 days previously to produce a 1.5 times prolongation of baseline prothrombin time in the volunteers. Zolpidem does not appear to modify the anticoagulant activity of warfarin.

### Digoxin

The concurrent administration of zolpidem 10 mg once daily and digoxin 0.25 mg in healthy volunteers did not show any alteration of the pharmacokinetic or pharmacodynamic profile of digoxin.

### H<sub>2</sub> - antagonists

Simultaneous administration of zolpidem 20 mg and cimetidine 200 mg tds and 400 mg at night or ranitidine 150 mg bd did not cause any significant change in psychometric tests from those produced by zolpidem alone. No change in the pharmacokinetics of zolpidem were caused by concomitant administration of either cimetidine or ranitidine.

### Hepatic enzyme inhibitors and inducers

Zolpidem is metabolized via several hepatic cytochrome P450 enzymes: the main enzyme being CYP3A4 with the contribution of CYP1A2. Compounds which inhibit or enhance certain hepatic enzymes (particularly cytochrome P450) may increase or decrease the activity of some hypnotics. The pharmacodynamic effect of zolpidem is decreased when it is administered with a CYP3A4 inducer such as rifampicin and St John's Wort. Co-administration of St John's Wort may decrease blood levels of zolpidem, therefore concurrent use is not recommended. Ketoconazole has a significant but only quantitatively modest reduction in zolpidem clearance, with an increase in its pharmacodynamic effects. Patients should be advised that use of zolpidem with ketoconazole may enhance the sedative effects of zolpidem. However, when zolpidem is administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

Fluvoxamine is a strong inhibitor of CYP1A2 and a moderate to weak inhibitor of CYP2C9 and CYP3A4. Co-administration of fluvoxamine may increase blood levels of zolpidem, concurrent use is not recommended.

Ciprofloxacin has been shown to be a moderate inhibitor of CYP1A2 and CYP3A4. Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

## **ADVERSE EFFECTS**

### **Clinical trials data**

There is evidence of a dose-relationship for adverse effects associated with DORMIZOL use, particularly for certain CNS events. These occur most frequently in elderly patients.

### Associated with discontinuation of treatment

Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in US premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from US trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 6% of 1,320 patients who received zolpidem at all doses (5 to 50 mg) in similar European trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.6%), amnesia (0.6%), dizziness (0.6%), headache (0.6%) and nausea (0.6%).

### Incidence in controlled clinical trials

*Most commonly observed adverse events in controlled trials:* During short-term treatment (up to 10 nights) with DORMIZOL at doses up to 10 mg, the most commonly observed adverse events associated with the use of DORMIZOL and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of DORMIZOL patients), dizziness (1%), and diarrhoea (1%). During longer-term treatment (28 to 35 nights) with DORMIZOL at doses up to 10 mg, the most commonly observed adverse events associated with the use of DORMIZOL and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

*Adverse events observed at an incidence of  $\geq 1\%$  in controlled trials:* The following tables enumerate treatment-emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received DORMIZOL in US placebo-controlled trials. Events reported by investigators were classified utilising a modified World Health Organisation (WHO) dictionary of preferred terms for the purpose of establishing event frequencies.

The following table was derived from a pool of 11 placebo-controlled short-term US efficacy trials involving DORMIZOL in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

#### Incidence of Treatment-Emergent Adverse Experiences in Short-term Placebo-Controlled Clinical Trials (Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem (<10 mg) (N=685)	Placebo (N=473)
<b>Central and Peripheral Nervous System</b>		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
<b>Gastrointestinal System</b>		
Nausea	2	3
Diarrhoea	1	-
<b>Musculoskeletal System</b>		
Myalgia	1	2

\*Events reported by at least 1% of DORMIZOL patients are included.

The following table was derived from a pool of three placebo-controlled long-term efficacy trials involving DORMIZOL (zolpidem tartrate). These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem at doses of 5, 10 or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

**Incidence of Treatment-Emergent Adverse Experiences in  
Long-term Placebo-Controlled Clinical Trials**  
(Percentage of patients reporting)

<b>Body System/ Adverse Event*</b>	<b>Zolpidem (&lt;10 mg) (N=152)</b>	<b>Placebo (N=161)</b>
<b>Autonomic Nervous System</b>		
Dry Mouth	3	1
<b>Body as a Whole</b>		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Fatigue	1	2
<b>Cardiovascular System</b>		
Palpitation	2	-
<b>Central and Peripheral Nervous System</b>		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Anxiety	1	1
Nervousness	1	3
Sleep disorder	1	-
<b>Gastrointestinal System</b>		
Nausea	6	6
Dyspepsia	5	6
Diarrhoea	3	2
Abdominal pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
<b>Immunologic System</b>		
Infection	1	1
<b>Musculoskeletal System</b>		
Myalgia	7	7
Arthralgia	4	4
<b>Respiratory System</b>		
Upper respiratory infection	5	6

Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
<b>Skin and Appendages</b>		
Rash	2	1
<b>Urogenital System</b>		
Urinary tract infection	2	2

\*Events reported by at least 1% of patients treated with DORMIZOL

## Post Marketing Data

### Gastrointestinal

Common: Diarrhoea, nausea, vomiting, abdominal pain

### Neurological

Common: Dizziness, somnolence, headache, exacerbated insomnia, anterograde amnesia (amnestic effects may be associated with inappropriate behaviour)

Uncommon: Paraesthesia, tremor

Rare: Ataxia, dysarthria, disturbance in attention, depressed level of consciousness\*

### Visual

Uncommon: Diplopia, vision blurred  
Visual impairment has been reported

### Psychiatric

Common: Drowsiness, hallucinations, agitation, nightmare

Uncommon: Confusion, memory disturbances, reduced alertness, irritability

Rare: Perceptual disturbances, restlessness, aggravated insomnia, libido disorder, aggressiveness, delusion, rages, inappropriate behaviour, somnambulism (see **PRECAUTIONS – ‘Somnambulism and Associated Behaviours’**), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation)\*, other adverse behavioural effects, depression, euphoric mood  
Anger and abnormal behaviour have been reported

### Immune system

Rare: Angioneurotic oedema

### Respiratory, thoracic and mediastinal

Respiratory depression has been reported

### Skin and subcutaneous tissue

Rare: Hyperhidrosis, rash, pruritis, urticaria

### Musculoskeletal and connective tissue

Common: Back pain

Uncommon: Arthralgia, myalgia, muscle spasms, neck pain

Rare: Muscular weakness

### Hepatobiliary

Elevated liver enzymes, hepatocellular, cholestatic and mixed liver injury have been reported

### Infections and infestations

Common: Upper respiratory tract infection, lower respiratory tract infection

**General disorders and administration site conditions**

Common: Fatigue  
Rare: Fall, ataxia/gait disturbances, drug tolerance\*.

**Metabolism and nutritional disorders**

Uncommon Appetite disorder

**DOSAGE AND ADMINISTRATION**

DORMIZOL acts rapidly and should therefore be taken immediately before retiring, or in bed. DORMIZOL should be taken in a single intake and not be re-administered during the same night. As with all hypnotics, long-term use of zolpidem is not recommended and a course of treatment should not exceed four weeks.

For oral use only.

**Discontinuation of treatment:** see **ADVERSE EFFECTS** section.

**Withdrawal Effects:** see **PRECAUTIONS**

Recommended Dosage:

**Adults**

10 mg to be taken at night. The lowest effective daily dose of DORMIZOL should be used and must not exceed 10mg.

**Elderly or Debilitated Patients**

5 mg to be taken at night. This dose should not be exceeded.

**Hepatic Impairment**

5 mg to be taken at night. In adults, less than 65 years, the dosage may be increased if the clinical response is inadequate and the drug is well tolerated.

**Renal impairment**

No dosage adjustment is necessary in these patients, although they should be closely monitored.

**Children**

The use of DORMIZOL in children under 18 years is contra-indicated.

**OVERDOSAGE**

**Signs and Symptoms:** In reports of overdose with DORMIZOL alone or with other CNS depressant agents (including alcohol), impairment of consciousness has ranged from somnolence to coma and more severe symptomatology, including fatal outcomes have been reported. Fatalities have occurred when overdoses of multi CNS depressants were taken.

**Recommended Treatment:** General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Sedative drugs should be withheld, even if excitation occurs.

Zolpidem has been shown in trials to be non-dialysable.

Use of flumazenil may be considered when serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms, such

as convulsions, since zolpidem does not exhibit the anticonvulsant effects of benzodiazepines.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

### **PRESENTATION AND STORAGE CONDITIONS**

DORMIZOL 5mg tablets are round, white film coated tablets\*.

DORMIZOL 10 mg tablets are oblong, scored, white, film-coated tablets marked "SN10".

Store below 30°C.

\*Not Marketed

### **NAME AND ADDRESS OF SPONSOR**

sanofi-aventis australia Pty Ltd

12-24 Talavera Road

Macquarie Park, NSW 2113

### **POSITIONS SCHEDULE OF THE MEDICINE**

Prescription Medicine (Schedule 4).

### **DATE OF FIRST INCLUSION IN THE ARTG**

14 June 2005

### **DATE OF MOST RECENT AMENDMENT**

11 October 2017