VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Zolpidem is used for short-term treatment of serious sleep problems that incapacitate or cause people extreme distress. Zolpidem is a hypnotic, a class of drugs used to help people to sleep.

Overview of disease epidemiology
Sleep problems are defined as a disturbance of normal night sleep that adversely affect the person's functioning during the day. People with sleep problems may have difficulty falling asleep or difficulty maintaining sleep (waking up frequently during the night or in the early morning).
Sleep problems are common and affect about 30–40% of the population every year. They are usually classified by the duration of their symptoms:
-Transient sleep problems are caused by acute stress related to a situation or an environment (jet lag, change in environment) and last 2 to 3 nights.
-Short-term sleep problems are caused by temporary environmental stress (illness, loss of a job) and typically last for up to 3 weeks.
-Chronic sleep problems last longer than 3 weeks and are often attributed to an underlying medical condition, psychiatric problem, drugs that are taken simultaneously, or chronic abuse of drugs or alcohol.
The cause of the sleep problems should be clarified if possible, and particularly if the problems are chronic. The underlying causes should be treated before prescribing a hypnotic.

VI.2.2 Summary of treatment benefits

Zolpidem tratrate is a well-known drug and has been used in the treatment of short-term insomnia for many years. Zolpidem tartrate is an imidazopyridine that is reported to have similar sedative properties to the benzodiazepines, but minimal anxiolytic, muscle relaxant, and anticonvulsant properties. It has a rapid onset and short duration of action, and the usual dose is 10 mg taken by mouth immediately before retiring.
Non-benzodiazepines like zolpidem generally cause less disruption to normal sleep patterns than benzodiazepines and fewer problems with dizziness and poor memory, especially in comparison with longer-acting benzodiazepines. Sometimes recurrence of sleep problems and withdrawal symptoms occur after stopping taking non-benzodiazepines, but these symptoms tend to be less common and milder than those experienced after stopping certain benzodiazepines.
The choice of hypnotic should be based on the patient's primary sleep problem, health history and adverse effects. If the sleep problem is not relieved after a treatment course of 7 to 14 days, this may indicate a psychological or physical problem that should be evaluated.

VI.2.3 Unknowns relating to treatment benefits

The information about the benefit of using zolpidem in children below 18 years and during pregnancy and breastfeeding is not sufficient. A review of worldwide literature supports the information given about age, elderly people, children, pregnancy, nursing/breastfeeding and patients with liver or kidney problems in the proposed SmPC.

Elderly	Elderly people have been found to benefit from zolpidem if they take a lower dose of 5 mg per day.
Children	There is no systematic information about treatment of children below 18 years as this use is off-label. Children should only be treated with caution and under surveillance by medical doctor.
Pregnancy/breastfeeding	Zolpidem passes into the milk during breastfeeding, and there are indications that it crosses the placenta. Using zolpidem during pregnancy or breastfeeding, especially during the first three months of pregnancy should be avoided.
Organ problems (organ impairment)	Although it is not necessary to adjust the dose in patients with kidney failure, such patients should take zolpidem only with caution. Benzodiazepines and benzodiazepine-like drugs like zolpidem are not recommended for treating patients with serious liver problems as they could cause brain damage. The initial dose in this patient group should therefore be 5 mg, and special attention should be paid to elderly patients.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Next morning residual effect	Patients may feel drowsy in the morning after using zolpidem in the evening. Some patients experience next-morning impairment of activities that require alertness, including driving.	To minimize this risk, a full night's sleep (7-8 hours) is recommended after taking zolpidem. Use the lowest dose for the patient and respect the recommended dose according to the patient's age and condition.
Tolerance	Zolpidem may lose some of its hypnotic effects if it is used for several consecutive weeks.	The treatment with zolpidem should not exceed the recommended duration and should be as short as possible.
Dependence	Use (even at therapeutic dosages) may lead to physical dependence: when stopping the therapy, patients may experience withdrawal or the sleep problems may reappear. There have been reports of abuse in patients who use multiple drugs (polydrug abusers). Patients who have a history of alcohol and drug abuse should take zolpidem with caution as they risk getting psychologically dependent on and addicted to it.	Patients who have a history of alcohol and drug abuse should be monitored carefully when they take Zolpidem Dune as they risk getting psychologically dependent on and addicted to it.

Risk	What is known	Preventability
	The higher the dose and the longer the duration of treatment with zolpidem, the higher the risk of dependence. If the patient has become physically dependent and stop taking zolpidem suddenly, the patient ill experience withdrawal symptoms.	
Rebound effect	After the patient stop the treatment, the patient may experience a so-called rebound effect, a passing syndrome where the symptoms which led to the prescription of a treatment with a benzodiazepine or a benzodiazepine-like drug like zolpidem reappear in a stronger form. The rebound effect may be accompanied by other reactions including mood changes, anxiety and restlessness. The patient are more likely to experience withdrawal when the dose is high, and there is a higher risk that the patient will experience withdrawal/that symptoms will reappear if the patient stop the treatment suddenly.	It is important that the patient are aware that the symptoms may reappear and be as calm as possible about their appearance after stopping taking the drug. To reduce the risk of rebound effects, the patient are recommended to use the lowest effective dose and to decrease the dose gradually.
Poor memory (amnesia)	Zolpidem may cause poor memory (anterograde amnesia) when it is used at recommended doses. The risk increases at higher doses. Poor memory may cause inappropriate behaviour.	To reduce the risk, patients should ensure that they get 7-8 hours of uninterrupted sleep.
Psychiatric and abnormal reactions	When using zolpidem, the patient may experience reactions like restlessness, agitation, irritability, aggressiveness, delusions, rages, nightmares, hallucinations, mental breakdowns (psychosis), sleep walking, inappropriate behaviour, renewed sleep problems and other adverse effects on the behaviour. These reactions are more likely to occur in elderly people.	If the patient experience such reactions, the patient should stop taking the product.
Sleep walking and associated behaviour	Patients taking zolpidem have reported sleep walking, "sleep driving", preparing and eating food, making phone calls or having sex and not remembering any of these events (amnesia). If the patient use zolpidem simultaneously with alcohol and other depressants of the central nervous system or at doses higher than the maximum recommended dose, the risk of such behaviour increases.	It should be evaluated if patients who sleep walk or have other associated behaviour (e.g. "sleep driving") should stop taking zolpidem because they might be a danger to themselves and others.
Additive effect of zolpidem due to interaction between zolpidem and other depressants of the	Drugs that have a depressant effect on the central nervous system, i.e. CNS depressants (e.g. drugs for mental problems (antipsychotics/neuroleptics), drugs for sleep problems (hypnotics),	Simultaneous use of zolpidem with CNS depressants may increase the depressant effect of zolpidem on the central nervous system.

Risk	What is known	Preventability
central nervous system	drugs for anxiety (anxiolytics), drugs for easing agitation and permitting sleep (sedatives), muscle relaxant drugs, drugs for depression (antidepressants), painkillers for relief of severe pain (narcotic analgesics), antiepileptic drugs, drugs used in surgery (anaesthetics) and drugs for hay fever, rashes and other allergies that can make people sleepy (sedative antihistamines)), as well as alcohol: Simultaneous use with zolpidem is likely to increase their depressant effect on the central nervous system. Use of painkillers affecting the central nervous system, i.e. centrally acting analgesics (opioids) together with zolpidem may also cause increased happiness and excitement (euphoria) and might lead to an increase in psychological dependence.	Simultaneous use with alcohol might increase its sedative effect. This will affect the patients ability to drive or use machines.
Drug interactions: Following medicines can increase the chance of you getting side effects when taken with zolpidem or can make zolpidem work less well.	To be able to remove zolpidem from the body zolpidem is broken down by several cytochrome P450 enzymes in the liver. Substances blocking the liver enzymes that break down zolpidem (cytochrome P450) may increase the effect of zolpidem. Some other substances has the opposite effect on the same liver enzymes and do there for increase the rate which zolpidem is removed from the body which make zolpidem work less well. The following medicine can make zolpidem work less well: -Rifampicin (an antibiotic) – for infections The following medicine can increase the chance of the patient getting side effects when taken zolpidem. To make this less likely, the patients doctor may decide to lower the dose of zolpidem: -Some medicines for fungal infection such as ketoconazole. Other medicines for fungal infection like itraconazole and fluconazole do not affect the breakdown of zolpidem in the liver, so preference should be given to these drugs. There are no reports of significant interactions when zolpidem is administered together with warfarin, digoxin, ranitidine, or cimetidine.	Depending on the degree of interaction and the clinical consequences, certain drugs should not be taken simultaneously with zolpidem, while others may require different doses and/or monitoring for adverse events. Patients should read the package insert before and during treatment for potential drug interactions. The patient should consult his/hers doctor if experiencing any adverse events and take zolpidem together with other drugs. This might be due to drug interaction.

Risk	What is known	Preventability
	The combination of zolpidem and muscle relaxants can increase the muscle relaxant effect.	
Difficulty or slower breathing (respiratory depression)	Zolpidem has not shown to cause difficult or slower breathing in studies with healthy patients, but since sleep disorder drugs are capable of reducing respiration control, the patient should take precautions when zolpidem is prescribed to patients with breathing difficulties.	The patients doctor should consider the risk before prescribing zolpidem to patients with breathing difficulties, including pauses in breathing or shallow breathing during sleep (sleep apnoea) and muscle weakness (myasthenia gravis).
Overdose	In cases of overdose of zolpidem alone or with other CNS depressants (including alcohol), there are reports of blacking out, ranging from drowsiness to light coma and death. Individuals have fully recovered from zolpidem overdoses of up to 400 mg, 40 times the recommended dose.	If the patient takes too much zolpidem or overdose, the patient should seek emergency treatment immediately.
Illegal use	As there is a potential for abuse of the drug, there might be an illegal market for zolpidem.	The patients doctor should not prescribe more zolpidem than needed.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in elderly	There is evidence of a connection between dose and reactions associated with the use of zolpidem, especially certain reactions of the central nervous system which occur mostly in elderly patients. In theory, there should be fewer such reactions if the patients take zolpidem immediately before going to bed. As elderly or frail patients may be particularly sensitive to the effects of zolpidem, a dose of 5 mg is recommended, and the total dose should not exceed 10 mg. Due to the muscle relaxing effects of zolpidem, patients – in particular, elderly patients – risk falling and consequently breaking their hips when they get up at night. Benzodiazepines and benzodiazepine-like drugs like zolpidem are not recommended for treating patients with serious liver problems as they could cause brain damage. The initial dose in this patient group should therefore be 5 mg, and special attention should be paid to elderly patients. Psychiatric and abnormal reactions such as restlessness, agitation, irritability, aggressiveness, delusions, rages, nightmares, hallucinations, mental breakdowns (psychosis), sleep walking, inappropriate behaviour, renewed sleep problems and other adverse effects on your behaviour are more likely to occur in elderly patients. If the patient experience such reactions, the patient should stop taking the product.
Use in patients with liver problems	Benzodiazepines and benzodiazepine-like drugs like zolpidem are not recommended for treating patients with serious liver problems as they could cause brain damage. The initial dose in this patient group should therefore be 5 mg, and special attention should be paid to elderly patients.

Risk	What is known (Including reason why it is considered a potential risk)
Hallucinations, agitations and nightmares	Patients may experience agitation, nightmares, and hallucinations when taking zolpidem. If these reactions occur, the patient should stop taking the product. These reactions are more likely to occur in the elderly. The patient should also take into consideration that anxiety or agitation is described as a sign of untreated breathing problems in patients who suffer from chronic breathing problems.
Worsening of pre-existing depression.	The use of zolpidem may reveal or worsen a pre-existing depression. Zolpidem should be administered with caution in patients who have symptoms of depression. Such patients may show suicidal tendencies. Zolpidem should not be used alone for treating depression or anxiety associated with depression (this may lead to suicide in such patients).

Missing information

Risk	What is known
Use in children.	Children under 18 years should not take zolpidem as there are insufficient data about its safety and efficacy in children.
Use during pregnancy.	Since there are too little data to assess the safety of zolpidem during pregnancy and breastfeeding, patients should not use zolpidem during pregnancy. Although animal studies have shown no toxic or adverse effects on the foetus, safety in pregnancy has not been established in humans. Patients should not use zolpidem during pregnancy, especially during the first three months of the pregnancy. Women of childbearing potential taking the product, should contact their doctor about stopping the product if intending to get or having suspicion about being pregnant. If zolpidem is prescribed during the late phase of pregnancy, or during childbirth for serious medical reasons, the newborn may experience effects like low body temperature (hypothermia), low muscle tone (hypotonia) and moderately slower breathing (respiratory depression) because of the action of the product. There have been reports of cases of serious respiratory depression in newborns when zolpidem was administered simultaneously with other drugs that suppress the central nervous system in the later stage of pregnancy. Infants born to mothers who took benzodiazepine or benzodiazepine-like drugs like zolpidem chronically during the latter stages of pregnancy may develop physical dependence and may be at some risk of developing withdrawal symptoms after birth.
Use during nursing/breastfeeding.	Zolpidem is passed into human milk. At present, there are too little data to assess zolpidem safety during pregnancy and breastfeeding. The use of zolpidem in nursing mothers is therefore not recommended as the effect on the child has not been determined.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the

form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Zolpidem Dune can be found in the Zolpidem Dune's EPAR page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies are a condition of the marketing authorisation.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	**Date**	**Safety Concerns**	**Comment**
1.0	10-04-2013	Important identified risk: Next moning effect described by US FDA.	No update of the proposed SmPC is recommended. No risk minimisation activities is recommended or implemented.
2.0	01-04-2014	Evaluation of several Identified Risks, Potential Risks and Missing information requested by DKMA during the DCP procedure: DK/H/2309/001-002/DC	No update of the proposed SmPC is recommended. No risk minimisation activities is recommended or implemented.
3.0	05-08-2014	Evaluation of several Identified Risks, Potential Risks and Missing information requested by DKMA during the DCP procedure: DK/H/2309/001-002/DC And PRAC and CMD(h) reccomendations.	SmPC is updated according to recommendations by PRAC and CMD(h).
4.0	15-09-2014	Updated according to comments from RMS DKMA during the DCP procedure: DK/H/2309/001-002/DC (Day 180).	SmPC and PL is updated according to correct MedDRA, detailed address of MAH added and correction of frequency of ADRs.
5.0	25-09-2014	Updated according to comments from RMS	

Version	Date	Safety Concerns	Comment
		DKMA during the DCP procedure: DK/H/2309/001-002/DC (Day 201).	