VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Diazepam is used in the treatment of anxiety, muscle spasms including those caused by cerebral spasticity (Muscle rigidity caused by Brain damage), for symptoms of alcohol withdrawal, and to provide sedation before operations (premedication).

Anxiety

Anxiety is a general term for several disorders that cause nervousness, fear, apprehension, and worrying. The prevalence of anxiety disorders was obtained from 87 studies across 44 countries. Estimates of current prevalence ranged between 0.9% to 28.3% and past-year prevalence between 2.4% to 29.8%. The global current prevalence of anxiety disorders was 7.3% (4.8–10.9%) and ranged from 5.3% (3.5–8.1%) in African cultures to 10.4% (7.0–15.5%) in Euro/Anglo cultures. Analyses of the largest prevalence studies of psychiatric illnesses in the United States find that anxiety disorders afflict 15.7 million people in the United States each year, and 30 million people in the United States at some point in their lives.

Alcohol withdrawal

The World Health Organization (WHO) estimates that 38.3% of the world population consumes alcohol, with 16.0% of drinkers aged over 15 years engaging in heavy episodic alcohol

consumption. In the US, 6.2% of adults (ages> 18 years) and 2.5% of youths (ages 12-17 years) suffer from alcohol use disorder. It is estimated that of these alcohol-dependent patients, approximately 50% will experience symptoms of alcohol withdrawal upon reduced alcohol intake.

VI.2.2 Summary of treatment benefits

Diazepam is used in the treatment of short-term (2-4 weeks) symptomatic treatment of anxiety that is severe, disabling or subjecting the individual to extreme distress and also for symptomatic treatment of acute alcohol withdrawal.

The benzodiazepines (Group of drugs- including diazepam, generally used as anxiety alleviating agents) seem to be useful and powerful anxiolytic (Removing anxiety) agents and are generally accepted as such, at least in short-term usage. Unfortunately, close evaluation of the available data shows even this efficacy to be surprisingly limited. One analytical study from Australia examined 81 studies mainly of benzodiazepines in anxiety, as compared to a placebo (Dummy product), and in some studies, to no treatment at all. Useful therapeutic effects were apparent in the study but half of this improvement was placebo-related, i.e. non-specific. A large number of short-term trials (up to 28 nights) attest to the effectiveness of benzodiazepines in the treatment of insomnia. Thus, they shorten time to sleep onset, usually prolong sleep time, and reduce the number of arousals in the night. These effects can be seen both with objective brain activity recordings in the sleep laboratory and subjectively with rating scales completed each morning. Although these two sets of data correlate at an extremely low level, the rating of "a good night's sleep" usually reflects infrequent nocturnal arousals. The effects generally wane beyond 28 nights and even before that time.

VI.2.3 Unknowns relating to treatment benefits

Data on use of diazepam in children below age of 6 months and pregnant women is not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Loss of memory; inability to create new memory (Anterograde amnesia)	Memory loss is uncommon side effect of diazepam and may affect up to 1 in 100 people. It is more likely to occur when taking high doses of diazepam. The condition occurs most often several hours after ingesting the product.	To reduce the risk you should ensure that you will be able to have a continuous sleep of 7 to 8 hours during the treatment with diazepam. Inform your doctor or nurse or pharmacist for experiencing memory loss during the treatment with diazepam.
Physical and mental addiction (Physical and Mental Dependence)	When taking this medicine there is a risk of (addiction) dependence, which increases with the dose and duration of treatment.	You should take this medicine for as short period of time as possible. Doctor should take special care when using this medicine in patients with a history of alcoholism and drug abuse. Doctor should stop the treatment gradually.
Very slow and/or shallow breathing/increase the sedative effects and make you very sleepy when taken with alcohol.(CNS inhibition	Respiratory depression (very slow and/or shallow breathing) is uncommon and may affect up to 1 in 100 people. Alcohol may increase the sleeping effects of this medicine and make	Take special care when using this medicine. Tell your doctor if you notice these side effects or notice any other effects. Do not drink alcohol while you

Risk	What is known	Preventability
(Respiratory/CNS depression) and enhanced sedation with Concomitant use of alcohol/CNS depressant)	you very sleepy.	on treatment with diazepam. Do not take diazepam if you have acute intoxication with alcohol or other CNS active substances (e.g. hypnotics, analgesics, antidepressants, antipsychotics).
Mental side effects such as agitation, hyperactivity, restlessness, aggressiveness, nightmares or hallucinations (Psychiatric and paradoxical reactions)	Mental side effects such as excitation, agitation, restlessness, irritability, aggressiveness, memory loss, delusion, rages, psychoses, nightmares or hallucinations are rare and may affect 1 in 1,000 people. May be or become serious. These side effects are more likely to occur in children or the elderly.	Talk to your doctor if you developed any symptoms of mental side effect during the treatment with diazepam. Doctor should immediately discontinue the treatment of diazepam in case of occurrence of such symptoms as it may require immediate medical treatment.
Withdrawal symptoms with recurrence of insomnia and anxiety (Withdrawal symptoms with rebound insomnia and anxiety)	Treatment should be gradually withdrawn. Withdrawal symptoms occur with this medicine even when normal doses are given for short periods of time. It may be accompanied by other reactions including headache, mood changes, anxiety or sleep disturbances and restlessness. The risk of withdrawal	It is recommended that the dosage is decreased gradually.

Risk	What is known	Preventability
	phenomena/rebound phenomena is greater after abrupt discontinuation of treatment. In severe cases, derealisation, depersonalisation, increased sensitivity to sound and light, numbness, tingling of activity and fit.	
Interaction with other medicines which are broken down in body by specific chemical CYP3A and/or CYP2C19. (Interactions with medicines metabolized via CYP3A4 and/or CYP2C19)	The medicine which slows down the activity of chemicals like CYP3A4 and/or CYP2C19, such medicines can give rise to increase in amount of diazepam blood, while medicines which increase the activity of such chemicals can result in decrease in amount of diazepam in blood.	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.
Brain disorders that occurs when the liver is unable to remove toxins from the blood (Hepatic encephalopathy in patients with severe hepatic insufficiency)	Patient with severe liver problem should not be treated with diazepam as it may cause brain dysfunction.	Do not take diazepam if you have severe liver disorders. If you suffer from liver problems or abnormalities, inform your doctor who may reduce the dose.
Suicidal behaviour (Precipitation of suicide)	Diazepam or these types of drugs (benzodiazepines) should not be used alone to treat depression or	Take special care with this diazepam and talk to your doctor before taking this

Risk	What is known	Preventability
	anxiety associated with depression as suicide may be precipitated in such patients.	medicine if you have suicidal thoughts.
Drug interaction with oral contraceptives leading to breakthrough bleeding	As oral contraceptives can slow down the removal of diazepam from the body and increase its effect. Breakthrough bleeding can occur when taking diazepam and oral contraceptives together, but the contraceptive protection is not reduced.	Do not take diazepam and oral contraceptive together as breakthrough bleeding can occur. You should tell your doctor if you are taking or have recently taken oral contraceptives.
Severe allergic reaction (Hypersensitivity)	People taking diazepam tablets may experience an uncommon (up to 1 in 100 people) side effect like allergic skin reactions in the form of itching, skin redness and swelling and skin rash. People taking diazepam tablets may experience a very rare (up to 1 in 10,000 people) side effect like Anaphylaxis (severe allergic reaction) with symptoms such as sudden wheezing, swelling of your lips, tongue and throat or body, rash, fainting or difficulties to swallow.	Do not take diazepam if you are allergic (hypersensitive) to diazepam or to other benzodiazepine medicines or to any of the other ingredients of this medicine. You should tell your doctor if you are taking or have recently taken antihistamine medicines to treat allergies.

Risk	What is known	Preventability
Use in patients with severe respiratory insufficiency or reduction or pause of breathing (airflow) during sleep. (Use in patients with severe respiratory insufficiency or sleep apnoea syndrome)	People taking diazepam tablets may experience a rare (up to 1 in 1,000 people) side effect like respiratory arrest (cessation of breathing) People taking diazepam tablets may experience an uncommon (up to 1 in 100 people) side effect like respiratory depression (slow and/or shallow breathing).	Do not take diazepam if you have acute respiratory depression (slow and/or shallow breathing). A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression (slow and/or shallow breathing).
Use in a patient with weakness of the skeletal muscles of the body (Use in patients with myasthenia gravis)	People taking diazepam tablets may experience an uncommon (up to 1 in 100 people) side effect like muscle weakness. Signs of an overdose include loss of coordination of muscle movements and muscle weakness. If you suddenly stop taking diazepam, you may experience muscle spasms	Do not take diazepam if you have a condition called myasthenia gravis which causes muscles to weaken and tire easily. Diazepam affect on your muscles work hence do not take diazepam during driving. You should tell your doctor if you are taking or have recently taken muscles relaxants (e.g. suxamethonium, tubocurarin).
Abnormal usage of drug (Diazepam abuse and misuse)	Diazepam should be used with extreme caution in patients with a history of drug abuse. Treatment with diazepam can	Talk to your doctor before taking this medicine if you have a history of drug abuse. Do not take diazepam as abuse

Risk	What is known	Preventability
	result in mental or physical dependency. The risk increases with dose and duration of treatment; it is also greater in patients with a history of drug abuse. There is also risk of seizures if you have a drug abuse problem and suddenly stop taking this medicine.	of benzodiazepines has been reported. Regular monitoring in drug abuse patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually. Discontinuation should be gradual in order to minimise the risk of withdrawal symptoms.
Use in patients with mental condition characterized by anxiety disorder or hallucinations, delusions, and thought disorder. (Use in patients with phobic or obsessional states or chronic psychosis)	People taking diazepam tablets may experience a rare (up to 1 in 1,000 people) side effect like hallucinations, delusions, aggressiveness and excitation. People taking diazepam tablets may experience a common (up to 1 in 10 people) side effect like psychosis delirium and anxiety.	Do not take diazepam if you have a condition called psychosis, delirium and anxiety. Do not take diazepam if you have anxiety disorder or hallucinations, delusions, and thought disorder.

Important potential risks

Risk	What is known

Capable of causing malformations in a fetus - developing baby still inside the mother's body (Teratogenicity)	If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. If you take this medicine late in pregnancy or during labour, your baby might have a low body temperature, floppiness and breathing difficulties. If taken regularly during late pregnancy, your baby may develop withdrawal symptoms. Moreover, animal study shown that exposure to diazepam in the first trimester produces an increased risk of cleft lip and palate (mice), CNS abnormalities and permanent functional disorder in the offspring (rats).
Affecting the ability to get pregnant or carry a baby to term. (Impairment of fertility)	Studies in animals have shown a decrease in pregnancy rate and reduced number of surviving new born at high doses. There are no human data. Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of diazepam prior to and during mating and throughout gestation and lactation.
Risk of falls and consequently hip fractures in elderly and energy or strength impaired patients. (Risk of falls and consequently hip fractures in elderly and debilitated patients)	If you are elderly, talk to your doctor before taking this diazepam because this medicine can cause confusion and have effects on muscles causing falls and injuries. If you are elderly or frail (weak/delicate) you are likely to be more sensitive to the effects of diazepam hence your dose needs to be reduced.

Missing information

Risk	What is known
Use in children (Use in Paediatric patient)	Diazepam is not recommended for treatment of anxiety and acute alcohol withdrawal in children and adolescents as safety and efficacy have not been established. No data are available.
Use in pregnant women	There are limited amount of data from the use of diazepam in pregnant women. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. If you take this medicine late in pregnancy or during labour, your baby might have a low body temperature, floppiness and breathing difficulties. If taken regularly during late pregnancy, your baby may develop withdrawal symptoms.

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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concern	Comment
4.0	17-Nov-2017	In this RMP, name of missing information "Use in Paediatric patient below 6 months of age" have been modified to "Use in Paediatric patient".	RMP has been updated as per revised SmPC and PIL as per RMS and CMS recommendation per day 206.
3.0	09-Nov-2017	No change in safety concerns	RMP has been updated as per revised SmPC and PIL as per RMS and CMS recommendation.
2.0	17-Feb-2017	Below safety concerns have been included in the RMP: **Important identified risks** • Hypersensitivity • Use in patients with severe respiratory insufficiency or sleep apnoea syndrome • Use in patients with myasthenia gravis • Diazepam abuse and misuse • Use in patients with phobic or obsessional states or chronic psychosis **Important potential risks** • Risk of falls and	The safety concerns and relevant sections have been changed based on Day 70 Preliminary RMP assessment report of diazepam (UK/H/5974/01-03/DC) dated 21 April 2015.

Version	Date	Safety Concern	Comment
		consequently hip fractures in elderly and debilitated patients Below safety concerns have been removed from this RMP: **<u>Important identified risks</u>** • Use in patient with hereditary problem of galactose intolerance. Below safety concerns have been modified to important identified risk from important potential risk in the RMP: • Hepatic encephalopathy in patients with severe hepatic insufficiency • Severe sedation • Precipitation of suicide Below safety concerns have been merge in important identified risk (CNS inhibition (Respiratory/CNS depression) and enhanced sedation with concomitant use of	

Version	Date	Safety Concern	Comment
		alcohol/CNS depressant) in the RMP: **<u>Important potential risks</u>** Severe sedation Below safety concerns have been modified in the RMP: **<u>Important identified risks</u>** • Anterograde amnesia	