Desitin Arzneimittel GmbH

Addendum to Module 2.5

The summary of product characteristics (SmPC) and the package leaflet (PL) of Diazepam Desitin Rectal solution have been reviewed and in consequence both documents have been updated, especially in the safety relevant sections. Therefore, further SmPCs of Diazepam rectal solutions currently approved in UK, the guideline published by EMA "Summary of product characteristics for benzodiazepines as anxiolytics or hypnotics" (referred to as "EU-SmPC" throughout the text) as well as additional medical and scientific literature were taken into account to update the informative texts according to the current state of knowledge.

The potential of Diazepam to cause **tolerance, dependence and drug withdrawal effects** is well known[1]. It may already occur at therapeutic doses and after use for short periods. Patients with a history of alcohol or drug abuse are at particular risk of dependence[1].
Dependence and withdrawal effects are already addressed in section 4.4 and 4.8 of the SmPC. However, these effects or the respective consequences have to be addressed in more detail throughout the SmPC. The duration of treatment with Diazepam should always be kept to a minimum and the risk to experience drug withdrawal effects is reduced when the dose is tapered gradually. Since Diazepam Desitin rectal solution due to its special pharmaceutical form is particularly suitable for acute intervention and its use should be limited to single or few doses, a respective passage was furthermore added to section 4.2, including information on the possibility of withdrawal effects with a reference to sections 4.4 and 4.8, where this information was already given:

> *The medicinal product is particularly suitable for acute clinical intervention and is less suitable for chronic therapy. The duration of administration should be limited to single doses or to a few days in cases of acute illness.*
> *When longer-term treatment with diazepam (lasting more than 1 week) is to be discontinued, the dose should be reduced gradually. In this case, temporary development of withdrawal effects should be considered (see section 4.4 and 4.8).*

Since the risk of developing dependence is more pronounced in patients with a history of alcohol or drug abuse (see above), administration of Diazepam should not be used in these patients. This fact has only been reflected by a warning in section 4.4 to use Diazepam with special caution in these patients, which was considered insufficient. Instead, it was added as a contraindication to section 4.3:

> *Addictive disorders (alcohol, prescription medications, illegal drugs)*

In section 4.4, a warning concerning the development of tolerance was included:

> *<u>Development of tolerance</u>*
> *Loss of efficacy (tolerance) can occur following long-term and repeated benzodiazepine intake over a period of weeks.*

The risk of dependence was mentioned in section 4.4 as being low when limited to short term use. This however is considered as insufficient information giving an impression of false security. In line with recommendations of the MHRA on Addiction to benzodiazepines and codein, treatment duration should not exceed 4 weeks[2]. Therefore, information on development of dependence was rephrased and amended as follows:

Development of dependence
Benzodiazepine use can lead to the development of psychological and physical dependence. This applies not only to abuse of particularly high doses but also within the therapeutic dose range. The risk of drug dependence increases with the dose and duration of treatment. This risk is also increased in patients with a history of dependence on alcohol or medicinal products or drug abuse.
Long-term administration should be avoided unless there is a compelling indication and the therapeutic benefit has been carefully weighed up against the risk of tolerance and dependence. In all cases, the duration of treatment should not exceed 4 weeks.

If physical dependence has developed, abrupt withdrawal of treatment is accompanied by withdrawal symptoms (see below).
[…]
The patient should be informed at the beginning of treatment about the limited duration of treatment and the gradual dose reduction should be precisely explained. It is also important that the patient is made aware of the risk of rebound phenomena, in order to reduce anxiety about such symptoms should they occur during withdrawal of the medicinal product.

To provide conclusive information on the topic of tolerance/dependence/withdrawal, the existing passage on withdrawal symptoms was amended by the reported effects sleep disturbances[1], increased dreaming[1], sweating, trembling[1], mood changes and confusional state.

Diazepam is known to interact with **alcohol and other CNS depressant drugs**, either pharmacologically by addition of CNS depressant effects, such as sedation, respiratory or cardiovascular depression, or pharmacokinetic resulting in increase of certain plasma levels[3]. In case of overdose/intoxication with these drugs, major consequences may result from additional intake of benzodiazepines, e.g. fatal outcome in patients abusing opioid analgesics[3]. As intoxication with the above mentioned substances might even provoke symptoms (such as agitation, irritability, seizures) where administration of a benzodiazepine appears indicated, it is of special importance to alert physicians to the risk of co-administration. Therefore, a respective contraindication was added to section 4.3:

Acute intoxication with alcohol, hypnotics, analgesics or psychopharmaceuticals (neuroleptics, antidepressants and lithium)

As not all of these substance groups are already addressed as interacting in section 4.5 of the SmPC, it was also updated by adding analgesics and lithium to the subsection “Pharmacodynamic interactions”.

Furthermore, the existing warning in section 4.4 on enhanced effects of other CNS depressants and information on interaction with alcohol in section 4.5 were expanded to represent the issue more precisely.

Diazepam should not be used concurrently with alcohol and/or drugs with a central depressant effect. Concurrent intake may enhance the effects of other CNS depressants as well as the effects of diazepam and may possibly lead to profound sedation and clinically relevant cardiovascular and/or respiratory depression (see section 4.5).
[…]

This applies particularly when the product is used in combination with alcohol which may alter or potentiate the effects in an unpredictable manner.

Since interaction with alcohol additionally affects the ability to drive and use machines even further, respective amendments were also made to section 4.7:

If insufficient sleep duration occurs as well as when alcohol is taken at the same time, the likelihood of impaired alertness may be increased.

Due to the well known centrally depressant effects of diazepam, which may lead to effects such as hypotension or circulatory depression, special precautions are required if diazepam has to be administered to patients in **shock**. If hypovolaemia exists in these patients, measures to correct the volume deficiency have to be undertaken to avoid additional negative effects on circulation. Furthermore, kinetics of diazepam may be affected by hypovolaemia since diazepam has a high distribution volume and lipophilic properties. Therefore the following warning was amended in section 4.4:

Patients in shock may be treated with Diazepam only if measures are concurrently undertaken to correct the volume deficiency.

As currently stated in the SmPC of Diazepam Desitin rectal solution, it should only be used with special caution in patients with closed angle **glaucoma**. However, the rational for this recommendation is unclear[1]. The Pharmacovigilance Working Party performed a review on the benzodiazepine prazepam and patients with glaucoma in 2012. Besides their recommendation to delete the contraindication in SmPC and PL of prazepam, they stated that "[…] there was insufficient evidence to require a contraindication for glaucoma in the summary of product characteristic (SmPC) of any benzodiazepine." The information in the SmPC of Diazepam Desitin rectal solution was therefore adapted accordingly by deleting the precaution in section 4.4.

In patients with renal or hepatic dysfunction, chronic pulmonary insufficiency, organic brain changes as well as elderly patients and children, diazepam should only be used with particular caution. This is already reflected in the current SmPC. However, additional information on special monitoring and precautions to be taken, if diazepam is administered in these patients was added:

At the beginning of therapy, individual patient response to the medicinal product should be monitored, in order to ensure prompt recognition of any relative overdose due to accumulation. This particularly applies to elderly and debilitated patients, children and adolescents as well as patients with organic brain changes, circulatory or respiratory insufficiency and impaired renal or hepatic function. Furthermore, the patient should be given specific instructions with reference to his/her daily routine according to particular circumstances (e.g. occupation). […] In long-term therapy, monitoring of the blood count and hepatic function is recommended.

In accordance with recommendations of the NICE guideline on generalised anxiety disorder and panic disorder in adults[4], where drug treatment is only included in the third step of treatment, the following information was added to reflect importance of alternative means besides drug treatment in patients with anxiety:

Not all states of tension, agitation or anxiety require drug treatment. They are often a manifestation of physical or mental disorders and can be managed by alternative means or by specific treatment of the underlying disease.

Due to the muscle relaxing effects of benzodiazepines, these medicinal products bear a risk of **falling**. This is especially true for elderly people with impaired ability to walk, when getting up at night and it is more pronounced for the longer acting benzodiazepines such as diazepam. The correlation of benzodiazepine intake and increased incidence of falls is discussed in the literature and even an increased risk of fractures may result[1,5]. Since this is not yet addressed and reflected properly in the SmPC, amendments were performed as follows:

Section 4.4
Elderly patients (≥ 65 years)
Caution is advised in elderly patients due to the risk of falling, particularly when getting up at night.
Section 4.8
General disorders and administration site conditions
Not known: Risk of falls, fractures

This particularly applies in combination with other muscle relexants, therefore the existing interaction in section 4.5 was also amended:

Concurrent administration of muscle relaxants can potentiate the muscle-relaxant effect, particularly in elderly patients and at higher dosage (risk of falls!).

Amnesia is a known adverse reaction to diazepam, which is already presented in the SmPC as warning in section 4.4 as well as in section 4.8. However, the risk of amnesia can be reduced by an uninterrupted sleep of 7–8 hours. This is stated in the EU SmPC, as well as in current SmPCs of Diazepam rectal solutions in UK[6,12] and was accordingly added to the SmPC:

Benzodiazepines 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 (see section 4.8).

It is well known that Diazepam affects the patients' reaction time and may lead to sedation and drowsiness. It therefore impairs the ability to drive and use machines, as already addressed in section 4.7. However, these effects may also pose a risk to outpatients receiving Diazepam as a sedative in minor surgical or dental procedures. These patients should only be allowed home one hour after administration and accompanied. Therefore, a respective warning was added to section 4.4 and 4.7.

Diazepam undergoes hepatic metabolism, mainly mediated by CYP3A4 and CYP2C19 and therefore bears potential for **pharmacokinetic interactions** with other substrates, inhibitors or inducers of these isoenzymes[1,3]. Certain examples of affected active substances are already given in section 4.5 of the SmPC, however, detailed information on the background of pharmacokinetic interactions and the involved CYP isoenzymes is lacking. The section

was therefore updated by a general introduction on pharmacokinetic interactions, and further affected active substances were added in line with the current state of knowledge: fluvoxamine[3], fluoxetine[3], HIV protease inhibitors[3]

Pharmacokinetic interaction via CYP enzymes is also relevant with respect to some azole antifungals[3]. This is reflected in the current SmPC of Stesolid rectal tubes (diazepam, MAH Actavis Group PTC ehf.) in UK[6], and a respective passage was added accordingly:

> *Itraconazloe, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiapines. The effects of benzodiapines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.*

As already addressed in the current SmPC, diazepam may potentiate the effect of phenytoin, which is also metabolised by CYP3A4 and is furthermore an inducer of CYP enzymes. However, reports on interaction of benzodiazepines and phenytoin are inconsistent. Phenytoin concentrations may either be increased, reduced or remain unchanged. Furthermore, phenytoin may reduce diazepam concentrations. The SmPC was updated to reflect the situation more precisely:

> *Phenobarbital and phenytoin may accelerate the metabolism of diazepam.*
> *Phenytoin concentrations may either be increased, decreased or remain unaltered by co-administration of diazepam.*

Concerning phenobarbital as known inducer of hepatic enzymes, a reduction of diazepam plasma concentrations may be anticipated and is mentioned in the current SmPC of Phenobarbital Thornton & Ross 15mg/5ml Elixir (MAH THORNTON & ROSS LTD) in UK[7].

As already addressed in the current SmPC, narcotic analgesics may enhance respiratory and cardiovascular depression if given with diazepam. According to Stockley's Drug Interactions, concurrent use of opioids and benzodiazepines may result in both beneficial analgesic effects and enhanced sedation and respiratory depression. Current SmPCs of the opioid analgesic buprenorphine even report of cases of death due to respiratory depression if combined with benzodiazepines. Therefore, besides the existing general information on co-administration of narcotic analgesics, a passage on interaction with buprenorphine was added:

> *Concurrent administration of buprenorphine (a potent analgesic) can lead to respiratory arrest and circulatory collapse.*

According to the current SmPC of Stesolid rectal tubes (diazepam, MAH Actavis Group PTC ehf.) in UK[6], diazepam may enhance the effects of sodium oxybate. This is furthermore addressed in the current EPAR product information of Xyrem[8] (sodium oxybate) and was accordingly added to the SmPC:

> *Given the possibility of increasing the risk of respiratory depression, the concomitant use of benzodiazepines and sodium oxybate should be avoided.*

Since diazepam is slowly eliminated over a period of 1 or 2 days, with its main active metabolite nordazepam having a half-life of even 2 to 5 days, interactions must even be expected after discontinuation of diazepam. This information was added to section 4.5:

> *Due to the slow elimination of diazepam, possible interactions must be anticipated even after discontinuation of treatment with diazepam.*

In the current SmPC it is stated, that after administration of diazepam in the third trimenon or during labour, moderate respiratory depression may occur in the neonate. However, since benzodiazepines are well known for their respiratory depressant effects and may even lead to respiratory arrest (as stated in section 4.8), this statement is considered too weak. Therefore, to alert the attending physician to this risk in the neonate, the term “moderate” was deleted and the possibility of respiratory insufficiency as well as a remark on the possible need for artificial ventilation in the newborn was added.

As already stated in section 5.2, metabolism in neonates is markedly slower than in children and adults. This is also relevant with respect to breast-feeding during treatment with diazepam and was accordingly added to section 4.6. Hence, since treatment with diazepam cannot be avoided, breast-feeding should be discontinued. The section was updated as follows:

> *Diazepam is metabolised significantly more slowly in the neonate than in children or adults. For this reason, if diazepam therapy is essential, breast-feeding should be terminated in order to avoid undesirable effects in the breastfed infant.*

According to the literature diazepam may impair **reaction time**, has pro**arrhythmic** properties and may cause **hangover effects**[1]. These reactions were therefore added to the SmPC.

Besides monitoring of the current literature and spontaneous reports, SmPCs of other medicinal products containing diazepam were checked for further relevant undesirable effects. This resulted in addition of the following undesirable effects in line with either the current SmPC of Stesolid rectal tubes (diazepam, MAH Actavis Group PTC ehf.)[6] in UK or the current SmPC of Diazemuls (diazepam, MAH Actavis Group PTC ehf.)[9] in UK:

- loss of libido, increased libido (previously mentioned as “changes of libido”)
- dysarthria
- blurred vision and nystagmus
- vertigo
- bradycardia
- heart failure, including cardiac arrest
- respiratory arrest
- increased salivation
- pruritus
- muscle spasm
- myasthenia
- incontinence
- fatigue
- changes of hepatic parameters (elevation of ALT, AST, alkaline phosphatase).

The existing paragraph on **paradoxical reactions** was updated in line with the literature as well as the current SmPC of Diazepam RecTubes (MAH Wockhardt UK Ltd) by adding **excitation**, **anxiety**, **insomnia** and **hostility**. The risk of precipitating **suicidal tendencies** is already addressed in section 4.4 of the SmPC and was therefore also added to the listing. As

already stated in section 4.4, in case of paradoxical reactions, diazepam should be **discontinued**; this was also added to section 4.8.

As already addressed in the SmPC, overdose with diazepam is usually manifested by degrees of central nervous system depression and only very rarely proves fatal. In line with information in the literature on overdose and toxicity of diazepam[1,10], the risk of fatalties especially exists in combination with other drugs or alcohol while overdose with diazepam alone is not generally life-threatening. This is furthermore in line with the EU SmPC for diazepam[11] and the current SmPC of Diazemuls (diazepam, MAH Actavis Group PTC ehf.)[9] in UK. To present this more clearly in the SmPC, section 4.9 was updated as follows:

> *Effects of overdose are more severe when taken with centrally-acting drugs, especially alcohol.*
>
> *...*
>
> *Overdose with diazepam alone is not generally life-threatening, unless combined with other CNS depressants (including alcohol).*

Furthermore, the current literature on diazepam toxicity as well as SmPCs of diazepam in UK and the EU SmPC for diazepam revealed further relevant symptoms of diazepam toxicity, which were added to the SmPC:

- somnolence[10]
- dysarthria[9,10]
- nystagmus[9]
- areflexia[9]
- apnoea[9,10]
- cardiorespiratory depression[9]

Special patient groups, i.e. elderly patients and patients with pre-existing respiratory disturbances, need particular attention in case of overdose with diazepam. Therefore, the SmPC was amended to point this out to the attending physician:

> *If coma occurs, this only lasts for a few hours; it can, however, be prolonged and periodic, particularly in elderly patients. The respiratory depressant effect of benzodiazepines enhances pre-existing respiratory disturbances in patients with respiratory disease. In case of severe intoxication, depression of vital functions can occur, particularly of the respiratory centre (cyanosis, respiratory arrest, cardiac arrest; monitoring in an intensive care unit is required!).*

According to the literature[1] and in line with the current SmPC of Diazepam RecTubes (MAH Wockhardt UK Ltd)[12], in the abatement phase of intoxication agitation and insomnia may develop, possibly with major convulsions. The SmPC was amended accordingly:

> *As drug levels fall severe agitation, insomnia and, possibly, major convulsions may develop.*

As already stated in the SmPC, management of intoxication is mainly symptomatic with respect to cardiovascular and respiratory function. This was further specified:

> *Symptomatic treatment of cardiorespiratory and central nervous system effects may be particularly necessary. Hypotension can be treated with sympathomimetics. If respiratory insufficiency occurs, which can also be the result of reduced peripheral muscle tone, assisted respiration is necessary.*

In line with information in the literature, dialysis is not effective to eliminate diazepam[10]. This also applies to forced diuresis, and is mainly due to diazepam's high protein binding and large volume of distribution. The SmPC was amended accordingly:

> *Note: To date, neither haemodialysis nor peritoneal dialysis has been described in the scientific literature. Following overdose with diazepam alone, forced diuresis and dialysis measures are unlikely to be very effective, due to diazepam's high plasma protein binding and large volume of distribution.*

Concerning management of intoxication, it is stated in the current SmPC that flumazenil is indicated to counteract the central depressive effect of benzodiazepine. However, according to the current state of knowledge, administration of flumazenil is not generally indicated[1,10]. It is rarely required and must be used with special care since it not only antagonizes the sedative effects but also anticonvulsive and anxiolytic effects. This is of particular importance in case of mixed overdoses involving active substances lowering the seizure threshold (e.g. tricyclic antidepressants). Therefore, the SmPC was amended as follows:

> *In order to cancel out the CNS-depressant effects of benzodiazepines it may rarely be necessary to use the specific benzodiazepine antagonist flumazenil. The patient must be closely monitored, as flumazenil not only antagonises the sedative effect, but also the anticonvulsive and anxiolytic effects, for example. Due to the short half-life of approximately 1 hour, patients must be kept under continuous monitoring after the effect of flumazenil has worn off. Flumazenil is contraindicated if there is concurrent administration of drugs that lower the seizure threshold (e.g. tricyclic antidepressants). For further information on correct administration, please see the Summary of Product Characteristics for flumazenil.*

[1] Brayfield A (ed), Martindale: The Complete Drug Reference. [online] London: Pharmaceutical Press <http://www.medicinescomplete.com/> (accessed on 29-Oct-2015).
[2] MHRA. Drug Safety Update. Addiction to benzodiazepines and codein. July 2011. https://www.gov.uk/drug-safety-update/addiction-to-benzodiazepines-and-codeine (accessed on 05-Nov-2015).
[3] Baxter K, Preston CL (eds), *Stockley's Drug Interactions*. [online] London: Pharmaceutical Press http://www.medicinescomplete.com/ (accessed on 29-Oct-2015).
[4] NICE guidelines [CG113] Generalised anxiety disorder and panic disorder in adults: management. January 2011. http://www.nice.org.uk/guidance/cg113/chapter/Key-priorities-for-implementation (accessed on 19-Nov-15).
[5] Neutel CI, Hirdes JP, Maxwell CJ, Patten SB. New evidence on benzodiazepine use and falls: the time factor. Age Ageing. 1996 Jul;25(4):273-8.
[6] Summary of product characteristics – Stesolid rectal tubes 5 mg. October 2014. http://www.medicines.org.uk/emc/medicine/24296 (accessed on 11-Nov-15).
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[8] EPAR product information – Xyrem -EMEA/H/C/000593 -R/0054. November 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000593/WC500057103.pdf (accessed on 11-Nov-15)
[9] Summary of product characteristics – Diazemuls, Diazepam Actavis 5mg/ml Emulsion for injection. January 2015. http://www.medicines.org.uk/emc/medicine/520 (accessed on 13-Nov-15).
[10] IPCS INCHEM Poisons information monographs archive. Diazepam (PIM 181). http://www.inchem.org/documents/pims/pharm/pim181.htm (accessed on 17-Nov-2015).
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[12] Summary of product characteristics – Diazepam RecTubes 10 mg Rectal Solution. April 2009. http://www.medicines.org.uk/emc/medicine/12170 (accessed on 18-Nov-15).