Medicines & Healthcare products Regulatory Agency

M E D I C I N E S N O T I F I C A T I O N

CLASS 4 MEDICINES DEFECT INFORMATION

Caution in Use
Distribute to Pharmacy / Wholesaler Level

Date: 13 December 2023 EL(23)A/43 Our Ref: MDR 008-11/23

Dear Healthcare Professional,

Atnahs Pharma UK Limited

Clobazam Atnahs 5mg/5ml Oral Suspension PL 43252/0010

SNOMED Code 37471711000001108

Batch Number	Expiry Date	Pack Size	First Distributed
230001	01.2025	5mg/5ml	15.06.2023

Clobazam Atnahs 10mg/5ml Oral Suspension PL 43252/0011

SNOMED Code 37471111000001107

Batch Number	Expiry Date	Pack Size	First Distributed
230002	03.2025	10mg/5ml	19.07.2023

Active Pharmaceutical Ingredient: Clobazam

Brief description of the problem
Atnahs Pharma UK Ltd has informed the MHRA that the batches of Clobazam Atnahs 5mg/5ml and 10mg/5ml Oral Suspension listed in this notification do not contain the most up to date safety information. The Summary of Product Characteristics (SmPC) and the Patient Information Leaflets (PIL) present in the pack are missing significant information. This is in relation to the use of the product in children (contraindicated), pregnancy, depression, drug dependence, numerous interactions and adverse effects, which are missing from the PIL present in the pack and in the SmPC.

Please see below for an extract of the key information that was missing in the leaflets packed in the batches affected. Healthcare professionals and patients should note that the full details for information missing in the SmPC and in the PIL for these batches are listed in the appendices within this notification.

Healthcare professionals should note that the information in the PIL and SmPC has already been updated and the relevant links can be found in the following sections of this notification.

Summary of key missing information from the SmPC:

Section 4.3
"As there is no age appropriate formulation to enable safe and accurate dosing, no dosage recommendations can be made in children under 6 years of age (see section 4.2)"

Section 4.4
"Depression and personality disorders
Some epidemiological studies suggest an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including clobazam. However, a causal relationship has not been established (see section 4.8)."

"Dependence
These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur; derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually."

"Risks from concomitant use of opioids and benzodiazepines
Concomitant use of Clobazam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Clobazam with opioids should be reserved for patients for whom alternative treatment options are not possible.
If a decision is made to prescribe Clobazam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2). The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5)"

Section 4.5
"Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Clobazam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4)"

"Cannabidiol
When cannabidiol and clobazam are co-administered, bi-directional PK interactions occur. Based on a healthy volunteer study, elevated levels (3- to 4-fold) of N-desmethylclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition.
Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions.

Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation. Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with cannabidiol."

Section 4.6
"Pregnancy
Nevertheless, a large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of major malformations following exposure to benzodiazepines during the first trimester of pregnancy, although incidences of cleft lip and palate were reported in certain case-control studies.

Clobazam is not recommended during pregnancy and in women of childbearing potential not using contraception. Clobazam crosses the placenta. Animal studies have demonstrated reproductive toxicity (see section 5.3). Women of childbearing potential should be informed of the risks and benefits of the use of clobazam during pregnancy. Women of childbearing potential should be informed to contact her physician regarding discontinuation of the product if they are pregnant or intend to become pregnant. If clobazam treatment is continued, it should be used at the lowest effective dose. Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during childbirth, effects on the neonate, such as respiratory depression (including respiratory distress and apnea), sedation signs, hypothermia, hypotonia, and feeding difficulties in the newborn (so-called "floppy infant syndrome") are to be expected"

Section 4.8
The following significant side effects were not included in the PIL (in order of frequency):

- "Common side effects: depression, drug tolerance
- Uncommon side effects: anxiety, delusion, memory impairment, amnesia (including anterograde amnesia)
- Not known (frequency cannot be estimated from available data): dependence, psychotic disorder, suicidal ideation, hallucinations, cognitive disorder, respiratory depression & failure, Steven Johnsons Syndrome, toxic epidermal necrolysis, hypothermia"

Advice for healthcare professionals
There is no risk to product quality because of this issue, therefore the affected batches are not being recalled. Healthcare professionals are advised to check if patients belong to any of the groups at risk and provide advice accordingly or do not prescribe and/or dispense this product. Where appropriate, healthcare professionals should provide a copy of the PIL when supplying any remaining stock to patients.

A copy of the correct SmPC and PIL can be found in the following links:

- SmPC Clobazam Atnahs 5mg/5ml Oral Suspension:
  https://www.medicines.org.uk/emc/product/721/smpc

- SmPC Clobazam Atnahs 10mg/5ml Oral Suspension:
  https://www.medicines.org.uk/emc/product/7618/smpc

- PIL Clobazam Atnahs 5mg/5ml &10mg/5ml Oral Suspension:
  https://www.medicines.org.uk/emc/files/pil.7618.pdf

Atnahs Pharma UK Ltd has also confirmed that all remaining packs of the impacted batches will not be distributed and that all future batches will contain the updated PIL. Upon request, the manufacturer will post hard copies of the updated PIL to wholesalers and pharmacies so that any remaining stock in the dispensary can be supplemented with the correct PIL information from the end of Jan 2024.

Advice for patients
This issue is about missing information on the Patient Information Leaflets (PILs) and Summary of Product Characteristics (SmPC). The medicine itself is not affected and therefore patients do not need to take any specific action relating to the product. If you have any concerns, talk to your doctor. If you **are pregnant (or planning to have a baby), suffering from depression or other psychological illnesses, please speak to a doctor** before continuing to take this medication. A copy of the correct Patient Information Leaflet containing the latest safety information for Clobazam Atnahs 5mg/5ml and 10mg/5ml Oral Suspension can be found in the following link:

- https://www.medicines.org.uk/emc/files/pil.7618.pdf

Patients who experience adverse reactions or have any questions about the medication should seek medical attention. Any suspected adverse reactions should also be reported via the MHRA Yellow Card scheme.

Further Information
For more information, or medical information queries, please contact: +44 (0) 1268 943 700 and for stock control queries, please contact: +44 (0) 1268 943 700.

Recipients of this Medicines Notification should bring it to the attention of relevant contacts by copy of this notice. NHS regional teams are asked to forward this to community pharmacists and dispensing general practitioners for information.

Yours faithfully
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Appendix 1: Safety information missing from the SmPC for the batches listed in this notification – full copies are available below:

- SmPC Clobazam Atnahs 5mg/5ml Oral Suspension: https://www.medicines.org.uk/emc/product/721/smpc
- SmPC Clobazam Atnahs 10mg/5ml Oral Suspension: https://www.medicines.org.uk/emc/product/7618/smpc

Summary of Product Characteristics (SmPC) changes

Current SmPC	**Updated SmPC**
4.2 Posology and method of administration Posology If low doses are required, the 5 mg/5ml product is a more suitable presentation. If high doses are required, the 10 mg/ 5 ml strength product is a more suitable presentation. Treatment of anxiety Adults: The usual anxiolytic dose for adults is 20-30 mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in the treatment of adult in-patients with severe anxiety. Adults: The usual anxiolytic dose for adults is 20-30 mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in	**4.2 Posology and method of administration** Posology If low doses are required, the 5 mg/5ml product is a more suitable presentation. If high doses are required, the 10 mg/ 5 ml strength product is a more suitable presentation. ***Treatment of anxiety*** Treatment should be as short as possible. The patient must be re- assessed after a period not exceeding 4 weeks and regularly thereafter in order to evaluate the need for continued treatment, especially where the patient is free of symptoms. Generally the overall duration of treatment (i.e. including tapering-off process) must not exceed 8 to 12 weeks. In certain cases extension beyond the maximum treatment period may be necessary; if so it should not take place without re-evaluation of the patient's status with special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependance. *Adults:* The usual anxiolytic dose for adults is 20-30 mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in the treatment of adult in-patients with severe anxiety. Adults: The usual anxiolytic dose for adults is 20-30 mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in

the treatment of adult in-patients with severe anxiety. The lowest dose that can control symptoms should be used. After improvement of the symptoms, the dose may be reduced. It should not be used for longer than 4 weeks. Long term chronic use as an anxiolytic is not recommended. […]	the treatment of adult in-patients with severe anxiety. The lowest dose that can control symptoms should be used. After improvement of the symptoms, the dose may be reduced. It should not be used for longer than 4 weeks. Due regard must be paid to the possibility of interference with alertness and reaction time. Long term chronic use as an anxiolytic is not recommended. […]
The patient must be re-assessed after a period not exceeding 4 weeks and regularly thereafter in order to evaluate the need for continued treatment. A break in therapy may be beneficial if drug exhaustion develops, recommencing therapy at a low dose. At the end of treatment (including in poor-responding patients), since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended to gradually decrease the dosage.	The patient must be re-assessed after a period not exceeding 4 weeks and regularly thereafter in order to evaluate the need for continued treatment. A break in therapy may be beneficial if drug exhaustion develops, recommencing therapy at a low dose. At the end of treatment (including in poor-responding patients), since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended to gradually decrease the dosage. Patients with impairment of renal or hepatic function: Increased responsiveness and higher susceptibility to adverse effects may be present in these patients and require low initial doses and gradual dose increments under careful observation. The maximum dose should not be exceeded. The patient should be checked regularly at the start of the treatment in order to decrease if necessary, the dose or frequency of administration to prevent overdose due to accumulation.
Method of administration For oral use only. […]	Method of administration For oral use only. […]
4.3 Contraindications **[…]** Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months to 2 years old, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication.	**4.3 Contraindications** **[…]** Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months to 2 years old, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication. As there is no age-appropriate formulation to enable safe and accurate dosing, no dosage

[…]	recommendations can be made in children under 6 years of age (see section 4.2. **[…]**
4.4 Special warnings and precautions for use <u>Amnesia</u> Amnesia may occur with benzodiazepines. In case of loss or bereavement psychological adjustment may be inhibited by benzodiazepines. **[…]**	**4.4 Special warnings and precautions for use** <u>Amnesia</u> 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 also Undesirable effects). **[…]**
<u>Dependence</u> Use of benzodiazepines - including clobazam - may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse. Therefore, the duration of treatment should be as short as possible (see section 4.2 Posology). Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (or rebound phenomena). These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur; derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Rebound phenomena are characterised by a recurrence in enhanced form of the symptoms which originally led to clobazam treatment. This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (for example, clobazam) to one with a short duration of action	<u>Dependence</u> Use of benzodiazepines - including clobazam - may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse. Therefore, the duration of treatment should be as short as possible (see section 4.2 Posology). Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (or rebound phenomena). These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur; derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Respiratory Depression Respiratory function should be monitored in patients with chronic or acute severe respiratory insufficiency and a dose reduction of clobazam may be necessary).	Respiratory Depression A lower dose is also recommended for patients with chronic or acute severe respiratory insufficiency due to the risk of respiratory depression (respiratory functions must be monitored and a dose reduction of clobazam may be necessary). Clobazam is contraindicated in patients with severe respiratory insufficiency (please refer to section 4.3 Contraindications).
Renal and hepatic impairment In patients with impairment of renal or hepatic function, responsiveness to clobazam and susceptibility to adverse effects are increased, and a dose reduction may be necessary. In long-term treatment renal and hepatic function must be checked regularly.	Renal and hepatic impairment In patients with impairment of renal or hepatic function, responsiveness to clobazam and susceptibility to adverse effects are increased, and a dose reduction may be necessary. In long-term treatment renal and hepatic function must be checked regularly. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.
Tolerance in epilepsy In the treatment of epilepsy with benzodiazepines - including clobazam - consideration must be given to the possibility of a decrease in anticonvulsant efficacy (development of tolerance) in the course of treatment	Tolerance in epilepsy Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks. In the treatment of epilepsy with benzodiazepines - including clobazam - consideration must be given to the possibility of a decrease in anticonvulsant efficacy (development of tolerance) in the course of treatment

Alcohol It is recommended that patients abstain from drinking alcohol during treatment with clobazam (increased risk of sedation and other adverse effects) (please refer to section (4.5).	Alcohol It is recommended that patients abstain from drinking alcohol during treatment with clobazam (increased risk of sedation and other adverse effects) (please refer to section (4.5). Benzodiazepines including clobazam, should be used with extreme caution in patients with a history of alcohol or drug abuse. Concomitant use of opioids and benzodiazepines Concomitant use of clobazam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of benzodiazepines such as clobazam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe clobazam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2). The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5). In the treatment of epilepsy with benzodiazepines - including clobazam - consideration must be given to the possibility of a decrease in anticonvulsant efficacy (development of tolerance) in the course of treatment. Concomitant use of cannabidiol The concomitant use of clobazam with cannabidiol-containing medicinal and non-medicinal products may result in increased exposure to N- desmethylclobazam, leading to increased incidence of somnolence and sedation. Dosage adjustment of clobazam may be necessary. Non-medicinal products containing cannabidiol must not be taken in combination with clobazam as they contain unknown quantities of cannabidiol and are of variable quality (see sections 4.5 and 5.2).
Excipient warnings in the formulation	Excipient warnings in the formulation

Clobazam Oral Suspension contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. The medicine also contains sodium methyl and propyl parahydroxybenzoates which may cause allergic reactions. The signs may include a rash, swallowing or breathing problems and swelling of the lips, face, throat or tongue. Sodium - contains 3.05 mg/ml. This should be taken into account by patients on a low sodium diet. **[…]**	Clobazam Oral Suspension contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. The medicine also contains sodium methyl and propyl parahydroxybenzoates which may cause allergic reactions. The signs may include a rash, swallowing or breathing problems and swelling of the lips, face, throat or tongue. Sodium - contains 3.05 mg/ml. This should be taken into account by patients on a low sodium diet. Risks from concomitant use of opioids and benzodiazepines Concomitant use of Clobazam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Clobazam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Clobazam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2). The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5). Duration of treatment The duration of treatment should be as short as possible (see Posology). Extension beyond these periods should not take place without revaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications that, in the case of benzodiazepines with a short duration of action,

	withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used (for example Frisium) it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop. Psychiatric and 'paradoxical' reactions Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the drug should be discontinued. They are more likely to occur in children and the elderly. Benzodiazepines are not recommended for the primary treatment of psychotic illness. Specific patient groups Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months and 3 years, other than in exceptional cases for anticonvulsants treatment where there is a compelling indication. The duration of treatment must be kept to a minimum. **[…]**
[…]	**4.5 Interaction with other medicinal products and other forms of interaction** Opioids The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Clobazam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).
Anticonvulsants Addition of clobazam to established anticonvulsant medication (e.g, phenytoin, valproic acid) may cause a change in plasma levels of these drugs. If used as an adjuvant in epilepsy the dosage of	Anticonvulsants Addition of clobazam to established anticonvulsant medication (e.g, phenytoin, valproic acid) may cause a change in plasma levels of these drugs. If used as an adjuvant in epilepsy the dosage of

clobazam should be determined by monitoring the EEG and the plasma levels of the other drugs checked. Phenytoin and carbamazepine may cause an increase in the metabolic conversion of clobazam to the active metabolite N- desmethyl clobazam.	clobazam should be determined by monitoring the EEG and the plasma levels of the other drugs checked. Phenytoin and carbamazepine may cause an increase in the metabolic conversion of clobazam to the active metabolite N- desmethyl clobazam which may result in adverse reactions. clobazam and its active metabolite Ndesmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels is recommended, prior to initiation of stiripentol, and then once new steady-state concentration has been reached, i.e. after 2 weeks approximately. Cannabidiol When cannabidiol and clobazam are co-administered, bi-directional PK interactions occur. Based on a healthy volunteer study, elevated levels (3- to 4-fold) of N-desmethylclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition. Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation. Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with cannabidiol.
4.6 Fertility, pregnancy and lactation Pregnancy There are limited amount of data from the use of clobazam in pregnant women. In the post-marketing safety database, limited data on exposed pregnancies are available with clobazam. Some of those cases reported fatal or neonatal disorders. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In animal studies, no congenital malformations have been found in mice, rats and rabbits. Administration of clobazam before or during childbirth can result in the occurrence of respiratory	**4.6 Fertility, pregnancy and lactation** Pregnancy There are limited amount of data from the use of clobazam in pregnant women. Nevertheless, a large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of major malformations following exposure to benzodiazepines during the first trimester of pregnancy, although incidences of cleft lip and palate were reported in certain case-control studies. Clobazam is not recommended during pregnancy and in women of childbearing potential not using contraception. Clobazam crosses the placenta. Animal studies have demonstrated reproductive toxicity (see section 5.3). Women of childbearing potential should be informed of the

depression (including respiratory distress and apnea), which may be associated with other disorders such as sedation signs, hypothermia, hypotonia, and feeding difficulties in the new-born (signs and symptoms of the so-called “floppy infant syndrome”). In the later stages of pregnancy, it must only be used if there are compelling indications. Moreover, infants born to mothers who have taken benzodiazepines over longer periods during the later stages of pregnancy may have developed physical dependence and may be at risk for developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the new born in the postnatal period is recommended. Woman of childbearing potential If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become pregnant or suspects that she is pregnant. **[…]**	risks and benefits of the use of clobazam during pregnancy. Women of childbearing potential should be informed to contact her physician regarding discontinuation of the product if they are pregnant or intend to become pregnant. If clobazam treatment is continued, it should be used at the lowest effective dose. Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy. If clobazam is administered during the late phase of pregnancy or during childbirth, effects on the neonate, such as respiratory depression (including respiratory distress and apnea), sedation signs, hypothermia, hypotonia, and feeding difficulties in the newborn (so-called "floppy infant syndrome") are to be expected. In the post-marketing safety database, limited data on exposed pregnancies are available with clobazam. Some of those cases reported fatal or neonatal disorders. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In animal studies, no congenital malformations have been found in mice, rats and rabbits. Administration of clobazam before or during childbirth can result in the occurrence of respiratory depression (including respiratory distress and apnea), which may be associated with other disorders such as sedation signs, hypothermia, hypotonia, and feeding difficulties in the new-born (signs and symptoms of the so-called “floppy infant syndrome”). In the later stages of pregnancy, it must only be used if there are compelling indications. Moreover, infants born to mothers who have taken benzodiazepines over longer periods during the later stages of pregnancy may have developed physical dependence and may be at risk for developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the new born in the postnatal period is recommended. **[…]**
<u>Fertility</u>	<u>Fertility</u>

No effects on fertility were observed in animals (see section 5.3).	There is insufficient information to assess effects of clobazam on fertility in humans (see section 5.3).
4.8 Undesirable effects Clobazam may cause sedation, leading to fatigue and sleepiness, especially at the beginning of treatment and when higher doses are used. Slowing of reaction time, drowsiness, numbed emotions, confusion, headaches, dizziness, muscle weakness, ataxia or a fine tremor of the fingers may occur. Slowed or indistinct speech (disorders of articulation), unsteadiness of gait and other motor functions or loss of libido may occur. Such reactions occur particularly with high doses or in long- term treatment, and are reversible. After prolonged use of benzodiazepines, impairment of consciousness, sometimes combined with respiratory disorders, may occur in very rare cases, particularly in elderly patients: these effects sometimes persist for some length of time. These disorders have not been seen so far under clobazam treatment. Anterograde amnesia may occur, especially at higher dose levels. Amnesia effects may be associated with inappropriate behaviour. <u>Psychiatric disorders</u> Especially in the elderly and in children, paradoxical reactions, may occur such as restlessness, irritability, difficulty in falling asleep or sleeping through, acute agitation states, anxiety, aggressiveness, delusion, fits of rage, nightmares, hallucinations, psychotic reactions, suicidal tendencies or frequent muscle spasms. In the event of such reactions, treatment with clobazam must be discontinued. Pre-existing depression may be unmasked during benzodiazepine use. Tolerance and physical and/or psychic dependence may develop, especially during prolonged use. Discontinuation of the therapy may result in withdrawal or rebound phenomena (see Warnings and Precautions). Abuse of benzodiazepines has been reported.	**4.8 Undesirable effects** The following CIOMS frequency rating is used, when applicable: Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10);uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data). *Metabolism and nutrition disorders* Common: **decreased appetite.** *Psychiatric disorders* Common: **irritability, aggression, restlessness, depression (pre-existing depression may be unmasked), drug tolerance** (especially during prolonged use), **agitation.** Uncommon: **abnormal behaviour, confusional state, anxiety, delusion, nightmare, loss of libido** (particularly with high doses or in long-term treatment and is reversible). Not known: **dependence** (especially during prolonged use), **initial insomnia, anger, hallucination, psychotic disorder, poor quality sleep, suicidal ideation.** *Nervous system disorders* Very common: **somnolence**, especially at the beginning of treatment and when higher doses are used Common: **sedation, dizziness, disturbance in attention, slow speech/dysarthria/ speech disorder** (particularly with high doses or in long-term treatment, and are reversible), **headache, tremor, ataxia.** Uncommon: **emotional poverty, amnesia (may be associated with abnormal behaviour), memory impairment, anterograde amnesia** (in (in the normal dose range, but especially at higher dose levels) Not known: **cognitive disorder, altered state of consciousness** (particularly in elderly patients, may be combined with respiratory disorders), **nystagmus** (particularly with high doses or in long-term treatment), **gait disturbance** (particularly with high doses or in longterm treatment and is reversible).

When used as an adjuvant in the treatment of epilepsy, this preparation may in rare cases cause restlessness and muscle weakness. As with other benzodiazepines, the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use. Eye disorders Visual disorders (diplopia, nystagmus). Such reactions occur particularly with high doses or in long-term treatment, and are reversible. Respiratory, thoracic and mediastinal disorders Clobazam may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (i.e., in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate. Gastrointestinal disorders Dry mouth, constipation, decreased appetite, nausea. Skin and subcutaneous tissue disorders Cutaneous reactions, such as rash or urticarial may develop in very rare cases. Stevens-Johnson syndrome, Toxic Epidermal Necrolysis. Metabolism and nutrition disorders Weight gain may occur particularly with high doses or in long-term treatment. This reaction is reversible. General disorders Fall	*Eye Disorders* Uncommon: **diplopia** (particularly with high doses or in long-term treatment and is reversible) *Respiratory, thoracic and mediastinal disorders* Not known: **respiratory depression respiratory failure (particularly in patients with preexisting compromised respiratory function** e.g. in patients with bronchial asthma or brain damage) (see Sections 4.3 Contraindications and 4.4 Warnings and Precautions) *Gastrointestinal disorders* Common: **dry mouth, nausea, constipation.** *Skin and subcutaneous tissue disorders* Uncommon: rash. Not known: **urticaria; Steven-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome).** *Musculoskeletal and connective tissue disorders* Not known: **muscle spasms, muscle weakness.** *General disorders and administration site conditions* Very common: **fatigue**, especially at the beginning of treatment and when higher doses are used. Not known: **slow response to stimuli, hypothermia.** *Investigations* Uncommon: **weight increased** (particularly with high doses or in long-term treatment) *Injury poisoning and procedural complications.*
4.9 Overdose Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. As with other	**4.9 Overdose** Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. As with other

benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). In the management of overdose it is recommended that the possible involvement of multiple agents be taken into consideration. Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious, or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Secondary elimination of clobazam (by forced diuresis or haemodialysis) is ineffective. Consideration should be given to the use of flumazenil as a benzodiazepine antagonist.	benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants The risk of a fatal outcome is increased in cases of combined poisoning with other CNS depressants (including alcohol). In the management of overdose with any medicial product, it is recommended that the possible involvement of multiple agents be taken into consideration. Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious, or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Secondary elimination of clobazam (by forced diuresis or haemodialysis) is ineffective. Consideration should be given to the use of flumazenil as a benzodiazepine antagonist.

Appendix 2: Safety information missing from the PIL for the batches listed in this notification – a full copy is available below:

- PIL Clobazam Atnahs 5mg/5ml &10mg/5ml Oral Suspension: https://www.medicines.org.uk/emc/files/pil.7618.pdf

Patient Information Leaflet (PIL) changes

Current PIL	Updated PIL
• **What you need to know before you take Clobazam Oral Suspension** **Do not take Clobazam Oral Suspension** **[…]** • If you have breathing problems. • If you stop breathing for short periods during sleep (called 'sleep apnoea syndrome'). • If the patient is 6 months -2 years old, except if the doctor decides this is necessary. • Do not take if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Clobazam Oral Suspension. **[…]** **Warnings and Precautions** **[…]** • If you have kidney problems. • If you have ever become dependent upon another drug or alcohol. Alcohol should not be taken during treatment with clobazam as there is an increased risk of experiencing side effects. • If you are over 65. This is due to	**What you need to know before you take Clobazam Oral Suspension** **Do not take Clobazam Oral Suspension** **[…]** • If you have breathing problems. • You suffer from depression, as this may lead to suicidal thoughts. • If you stop breathing for short periods during sleep (called 'sleep apnoea syndrome'). • If the patient is 6 months -2 years old, except if the doctor decides this is necessary. Do not take if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Clobazam Oral Suspension. Use of Clobazam may lead to a physical addiction. Stopping Clobazam suddenly may lead to side effects. Dependence on Clobazam may occur. Extended use of Clobazam, will lessen the effect it has on your symptoms. **[…]** **Warnings and Precautions** **[…]** • If you have kidney problems. • If you have ever become dependent upon another drug or alcohol. Alcohol should not be taken during treatment with clobazam as there is an increased risk of experiencing side effects. • You have a behavioural disorder

the increased sensitivity to adverse reactions in the elderly such as drowsiness, dizziness and muscle weakness. There is also an increased risk of fall that may result in serious injury. • You have difficulty digesting medicines. Some patient's liver may not metabolise (break down) medicines adequately. In these patients the medicine may remain in the body for a longer period of time. This may result in side effects. If you are known to poorly metabolise certain medicines, please speak to your doctor. If you are not sure if any on the above apply to you, talk to your doctor or pharmacist before taking Clobazam Oral Suspension. **[…]**	• You have breathing difficulties. • If you are over 65. This is due to the increased sensitivity to adverse reactions in the elderly such as drowsiness, dizziness and muscle weakness. There is also an increased risk of fall that may result in serious injury. • You have difficulty digesting medicines. Some patient's liver may not metabolise (break down) medicines adequately. In these patients the medicine may remain in the body for a longer period of time. This may result in side effects. If you are known to poorly metabolise certain medicines, please speak to your doctor. **[…]** **Skin Reactions** There have been very rare reports of potentially life-threatening skin rashes (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis) with the use of Clobazam. Symptoms of which may include: flu-like symptoms followed by a painful red or purplish rash that spreads and blisters. If you develop any of the above you must stop taking this medicine and inform your doctor straight away (see Section 4). **[…]**
Clobazam Oral Suspension with food, drink and alcohol Do not drink alcohol while you are taking Clobazam Oral Suspension. This is because there is increased risk of sleepiness and other side effects.	**Clobazam Oral Suspension with food, drink and alcohol** Do not drink alcohol while you are taking Clobazam Oral Suspension. This is because there is increased risk of sleepiness and other side effects. Clobazam may be taken with or without food. **[…]**
[…] **Pregnancy and breast-feeding**	**Pregnancy and breast-feeding** Do not take Clobazam Oral Suspension **[…]** • If this medicine is taken

Do not take Clobazam Oral Suspension **[…]** • If this medicine is taken regularly in late pregnancy, your baby may get withdrawal symptoms. In this case the newborn should be closely monitored during the postnatal period.	regularly in late pregnancy, your baby may get withdrawal symptoms such as agitation or shaking. In this case the newborn should be closely monitored during the postnatal period.
	4. Possible side effects – Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also, flu-like symptoms and fever. This may be something called 'Stevens Johnson Syndrome' which is a severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also, a feeling of being generally unwell, fever, chills and aching muscles. This is something called 'Toxic epidermal necrolysis' – Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis' (TEN). Both Stevens Johnson Syndrome and TEN can be fatal. If you get any of the above side effects, your doctor may decide that your treatment needs to be stopped. These side-effects are more likely to happen in elderly people and children. Prolonged use of Clobazam may lead to a dependence on the drug. Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days, or if you notice any side effects not listed in this leaflet.

	Very Common: • Feeling sleepy or tired (especially at the start of treatment) Common: • Headache • Loss of appetite, feeling sick • Feeling dizzy or confused • Dry mouth, constipation • Feeling aggressive • Shaking fingers • Difficulty in concentrating, staying awake or alert • Slurred or slow speech • Depression Uncommon: • Loss of memory, confusion, or trouble remembering things • Unusual or out of character behaviour • Feeling anxious • Skin rash • Weight gain • Double vision • Loss of sexual drive Not known: • Breathing problems • Hives • Muscle spasms or involuntary movement • Muscle weakness • Reacting to things more slowly than usual

	• Problems walking or other movement problems • Rapid uncontrollable movement of the eyes • Abnormally low body temperature (hypothermia) • Feeling angry If you take this medicine for a long time, you are more likely to get the following side effects: anxiety, confusion, depression, loss of appetite and difficulty sleeping. Use of Clobazam may lead to a physical addiction. Stopping Clobazam suddenly may lead to side effects. Dependence on Clobazam may occur. Talk to your doctor if you feel you have developed a dependence on Clobazam Oral Suspension. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, pharmacist or nurse.