

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC)  
No1901/2006, as amended**

**Clobazam (Frisium)  
UK/W/018/pdWS/001**

<b>Rapporteur:</b>	<b>UK</b>
<b>Start of the procedure (Day 0):</b>	<b>31 December 2009</b>
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<b>Finalisation procedure (day 120):</b>	<b>16 December 2010</b>

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Frisium
INN (or common name) of the active substance(s):	clobazam
MAH:	Sanofi-aventis
Currently approved Indication(s)	Add-on thereapy for epilepsy;anxiety
Pharmaco-therapeutic group (ATC Code):	Anti-convulsant/anxiolytic ATC code N05BA09
Pharmaceutical form(s) and strength(s):	Tablets 10 mg,20 mg tablets; 5 mg capsules
Rapporteur:	UK

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# **I. EXECUTIVE SUMMARY AND RECOMMENDATION**

## **I.1 Introduction**

This is an assessment of data for clobazam, as part of the Article 45 EU work-sharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force (26 Jan 2007). The UK is Rapporteur for this product; the initial assessment report (day 70) is due to be circulated to concerned Member States on 11 March 2010.

On 17 November 2009 the MAH submitted a largely bibliographic application (that included one company sponsored, completed paediatric study) for clobazam, in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. In addition, a critical expert overview has been provided. The submitted studies are for the use of clobazam for the treatment of anxiety and epilepsy in children. The MAH stated that the submitted paediatric studies do not influence the benefit risk for clobazam and that there is no consequential regulatory action.

Clobazam is an anxiolytic of the benzodiazepine (BDZ) group with anti-epileptic properties. In the UK, 10mg tablets are the only licensed formulation. It is authorised for the following indications in children aged 3 years and above:

- Acute or chronic anxiety states;
- Adjunctive therapy in patients with epilepsy who are not adequately stabilized with their anticonvulsant therapy.

Clobazam is also used off-label as monotherapy under specialist supervision for catamenial (menstruation) seizures and cluster seizures.

### **Clinical data submitted**

The submission was largely bibliographic. With regard to anxiety, most of the studies had been undertaken in the 1970s; all were uncontrolled and were written in French, with no translation to English. With regard to epilepsy, only one clinical study report was submitted: a double blind randomised controlled comparison of clobazam with other anti-epileptic drugs, as monotherapy. Most of the other data were with regard to its use as an adjunct to other therapies, for which it is already authorised in children aged 3-15 years old.

### **Preliminary Conclusions**

The submitted studies provide useful data regarding the use of clobazam in epilepsy, in particular where seizure control may be difficult to obtain, such as in Lennox-Gastaut syndrome and refractory epilepsy. Regarding the company sponsored trial, the primary endpoint was questionable. In addition, clobazam is generally only used as monotherapy under specialist supervision for catamenial (menstruation) seizures and cluster seizures; and these patients were not included in the study.

With respect to the use of clobazam in anxiety, the submitted data provide little evidence of efficacy, although it appears to sometimes be used as an adjunct to behavioural methods mainly in adolescents. It is also of note that a recent Cochrane Database Systematic Review. (2009; Ipser JC, Stein DJ, Hawkrigde S, Hoppe L) of pharmacotherapy for anxiety disorders in children and adolescents found no quantitative data regarding the use of benzodiazepines.

From the submitted safety data, no new safety concerns have arisen. Sedative effects are the most frequently observed adverse reactions. Nevertheless, as with other benzodiazepines, there is a risk of tolerance, dependence, and withdrawal syndrome with prolonged use. The SmPC already includes precautionary

information with regard to the avoidance of withdrawal syndrome and dependence (in line with The EU SmPC guideline for Benzodiazepines as Anxiolytics or Hypnotics-1995).

### **In summary:**

- Currently, with regard to the indication for add-on therapy for epilepsy in children aged 3-15 years, the assessor considers that the submitted data confirm the risk/benefit of the product. However, the UK SmPC includes minimal information with regard to dosage used for epilepsy; it may therefore be helpful to prescribers to harmonise this with the information in the company core data sheet (CCDS). In addition, the 10mg tablet formulation is not suitable for administration in children aged less than 6 years old and those who cannot swallow.
- With regard to the currently authorised indication for anxiety in children aged 3-15 years: The submitted data provide very limited evidence of efficacy. In addition, the authors of the Cochrane Systematic Review concluded that ‘given the lack of quantitative data, the routine use of benzodiazepines cannot be recommended, especially given concerns of dependency and treatment - related emergent adverse events associated with this class of drugs’. The assessor therefore considers that the available data do not support the use of the drug in children and adolescents, given the known safety profile of the drug. However, the drug is currently authorised for this indication in the UK in children; in addition, it is not known whether the licensed status is similar elsewhere in Europe and whether or not it is used to treat anxiety in other Member States. Whilst the purpose of the Article 45 Procedure is not to delete existing indications, the assessor considers that in this situation, it may be justifiable. The assessor considers that given the paucity of evidence of efficacy and the safety concerns, the MA holder should therefore be asked to provide justification for this indication and also to provide further information regarding the SmPCs elsewhere in the EU.
- In addition, the assessor considers that as 5mg capsules are available elsewhere in Europe, these should be made available to the UK and other Member States. The company should also be encouraged to develop an age appropriate formulation, as this drug is commonly given as an extemporaneous liquid formulation.

### **Recommendations following MS’ comments:**

Comments were received from Ireland, France and Germany. Ireland and Germany fully endorsed the Rapporteur’s recommendations. France had some comments regarding the dosage for epilepsy.

### **FINAL RECOMMENDATIONS FOLLOWING THE MAH RESPONSE (see p 27 for full details).**

**The outstanding issues regarding this Article 45 procedure have been resolved.**

**However, on review of the dosage information in section 4.2 of SmPC, the Rapporteur has an additional comment regarding the dosage information in section 4.2 , dosage (see p 27 for further detail). The Rapporteur therefore recommends that section 4.2 should be further amended to reflect this.**

**In conclusion, with the exception of up-dating the product information, no further regulatory action is required.**

**The Rapporteur recommends that the SmPC and PIL should be modified. The following SmPC changes are recommended (in bold, italics):**

## Section 4.2 Posology and route of administration

### Treatment of anxiety

The usual anxiolytic dose for adults and ~~adolescents over 15 years of age~~ 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. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re-evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. Patients who have taken Frisium for a long time may require a longer period during which doses are reduced.

### Treatment of epilepsy in association with one or more other anticonvulsants

#### Adults

In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily. ~~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.~~

**Elderly:** Doses of 10-20 mg daily in anxiety may be used in the elderly, who are more sensitive to the effects of psychoactive agents. Treatment requires low initial doses and gradual dose increments under careful observation.

#### *Paediatric patients aged 6 years and above ~~and those who are able to swallow:~~*

When prescribed for children, ~~aged three years of age, dosage should not exceed half the recommended adult dose.~~ Treatment requires low initial doses and gradual dose increments under careful observation. ***It is recommended that normally treatment should be started at 5 mg daily. A maintenance dose of 0.3 to 1 mg/kg body weight daily is usually sufficient.***

~~There is insufficient experience of the use of Frisium in children under three years of age to enable any dosage recommendation to be made.~~

***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.***

Tablets should to be swallowed without chewing with sufficient amount of liquid (1/2 glass).

***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.***

## II. INTRODUCTION

This is an assessment of data for clobazam, as part of the Article 45 EU work-sharing procedure for assessment of paediatric studies completed before the Paediatric Regulation entered into force (26 Jan 2007). The UK is Rapporteur for this product; the initial assessment report (day 70) is due to be circulated to concerned Member States on 11 March 2010.

On 17 November 2009 the MAH submitted a largely bibliographic application (that included one company sponsored, completed paediatric study for clobazam), in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. In addition, a critical expert overview has been provided. The submitted studies are for the use of clobazam for the treatment of anxiety and epilepsy in children.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for clobazam and that there is no consequential regulatory action.

## III. REGULATORY ASPECTS

### III.1 Regulatory History

Clobazam is an anxiolytic of the benzodiazepine (BDZ) group with anti-epileptic properties. The Marketing Authorisation was first granted in Australia and its International Birth date is on 06-Feb-1970. In the UK, 10mg tablets are the only licensed formulation. However, it is available elsewhere as 5 mg capsules and (10 and 20 mg) tablets. For the treatment of young children and those who cannot swallow, such as severely disabled children, extemporaneous solutions of clobazam are commonly used.

In the UK, clobazam is authorised for the following indications in children aged 3 years and above:

- Acute or chronic anxiety states;
- Adjunctive therapy in patients with epilepsy who are not adequately stabilized with their anticonvulsant therapy.

In the European Union, Sanofi-aventis has clobazam licences in Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, the Netherlands, Poland, Portugal, Slovakia, Spain and the United Kingdom. In the above mentioned countries, clobazam has paediatric indications and /or posology, except in Italy and in the Netherlands.

### III.2 Product Information

Clobazam has approved paediatric indications for anxiety and adjunctive therapy in epilepsy. The UK SmPC includes the following posology in section 4.2:

#### Treatment of anxiety

The usual anxiolytic dose for adults and adolescents over 15 years of age 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. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re-evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. Patients who have taken Frisium for a long time may require a longer period during which doses are reduced.

### **Treatment of epilepsy in association with one or more other anticonvulsants**

In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily. 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.

**Elderly:** Doses of 10-20 mg daily in anxiety may be used in the elderly, who are more sensitive to the effects of psychoactive agents. Treatment requires low initial doses and gradual dose increments under careful observation.

**Children:** When prescribed for children over three years of age, dosage should not exceed half the recommended adult dose. Treatment requires low initial doses and gradual dose increments under careful observation. There is insufficient experience of the use of Frisium in children under three years of age to enable any dosage recommendation to be made.

Tablets should to be swallowed without chewing with sufficient amount of liquid (1/2 glass).

### **The company core data sheet (CCDS) states the following:**

- **Treatment of anxiety states:**

Adults and in adolescents over 15 years of age: initial dose usually 20 mg daily. If necessary, the daily dose may be increased. Generally, it is recommended that a total daily dose of 30 mg is not exceeded.

Children from 3 to 15 years of age: increased responsiveness and higher susceptibility to adverse effects may be present in children and require low initial doses and gradual dose increment under careful observation/ A daily dose of 5 to 10 mg is frequently sufficient.

- **Treatment of epilepsy in combination with one or more other anticonvulsants:**

Adults and in adolescents over 15 years of age: it is recommended that administration be started at small doses (5 to 15 mg daily), if necessary, increasing the dose gradually to maximum daily dose of about 80 mg.

Children from 3 to 15 years age: it is recommended that normally treatment be started at 5 mg daily. A maintenance dose of 0.3 to 1 mg/kg body weight daily is usually sufficient.

## IV. SCIENTIFIC DISCUSSION

### IV.1 Introduction

#### Epilepsy

Epilepsy encompasses a family of disorders with multiple causes and manifestations that are characterised by episodic uncontrolled synchronous electrical discharges of neurones in the brain. These seizures present as changes in motor function (tonic or clonic convulsions, myoclonus) or consciousness (absences or aura).

The overall incidence of epilepsy in developed societies has been found to be around 50 cases per 100,000 persons per year. Although epilepsy is found in all age groups, it is the principal chronic neurological disorder in children where it may have irreversible consequences on cognitive and intellectual development. While the clinical goal of therapy is complete elimination of seizures, the relative frequency of refractory epilepsy varies from study to study but typically comprises approximately a third of newly treated patients.

The International League Against Epilepsy proposed two classifications of epilepsy being the Clinical and Electroencephalographic Classification of Epileptic Seizures, first published in 1981 and the International Classification of Epilepsies and Epileptic Syndromes, first published in 1989. Both classification systems have since been revised periodically. The seizure classification dichotomises epilepsies into generalised seizures and partial or focal seizures. The syndrome classification classifies epilepsy by aetiology into idiopathic, symptomatic and cryptogenic epilepsies. Although most patients have only one type of seizure, others can experience two or more types. The classification system of the International League Against Epilepsy is now used as the basis for recruitment of patients with epilepsy into clinical trials and as the basis for antiepileptic treatment recommendations.

The National Institute for Health and Clinical Excellence (NICE) advocates the clinical guidelines issued in 2004 by the British Collaborating Centre for Primary Care, for the management of epilepsy. Concerning children, these guidelines can be summarized as follows:

- Patients should be treated with a single antiepileptic drug (AED) wherever possible.
- If an AED has failed because of adverse effects or continued seizures, a second drug should be started, which may be an alternative first-line or second-line drug.
- Combination therapy (adjunctive or “add-on” therapy) should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom.
- The newer AEDs gabapentin, lamotrigine, oxcarbazepine, tiagabine, and topiramate are recommended for the management of epilepsy in children who have not benefited from treatment with the older AEDs such as carbamazepine or sodium valproate, or for whom the older AEDs are unsuitable.
- Vigabatrin is recommended as a first-line therapy for the management of infantile spasms.
- Benzodiazepines are used in the management of epilepsy, but their long term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Particular care should be taken when withdrawing benzodiazepines and barbiturates (may take up to 6 months or longer) because of the possibility of drug-related withdrawal symptoms and/or seizure recurrence.
- Clobazam, along with clonazepam, is one of the benzodiazepines most often used as an oral antiepileptic. Clobazam is active against partial and generalized seizures in epilepsy of widely differing aetiology in patients of all ages, and it is mainly used as an adjunctive therapy in the treatment of uncontrolled or refractory epilepsy in adults and children. However, it is also used off-label as monotherapy under specialist supervision for catamenial (menstruation) seizures and cluster seizures

## Anxiety disorder in children

Paediatric anxiety disorders are an important public health problem, affecting 6 to 18% of children and adolescents. Epidemiological studies estimate that more than 10% of children have anxiety resulting in impairment. The anxiety disorders often have important implications on a child or adolescent's school or home functioning with repercussions on the child's development. Childhood anxiety also increases child's risk for psychiatric disorders such as depression and anxiety in later life, as well as the risk of suicide attempts and psychiatric hospitalization.

Anxiety symptoms are a key characteristic of numerous psychiatric disorders. At least 13 separate anxiety-related disorders can be diagnosed in youth according to criteria in the Diagnostic and Statistical Manual (Text Revision - DSM-IV-TRTM- 2000): separation anxiety disorder (SAD), specific phobia (SpP), social phobia (SoP), selective mutism (SM), panic disorder (PD), agoraphobia (AG), hypochondriasis (HC), generalized anxiety disorder (GAD), unspecified somatisation (US), adjustment disorder with anxious mood (AD), acute stress disorder (ASD), posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD) (12). Epidemiological data suggest that childhood anxiety disorders, if left untreated, can later lead to chronic anxiety, depression and substance abuse. Comorbidity among childhood anxiety disorders approaches 40% and many children with anxiety suffer from other psychiatric conditions such as oppositional defiant disorder, major depression, attention deficit/hyperactivity disorder, or substance abuse.

For paediatric anxiety disorders, there are only limited efficacy data exist to guide the selection of treatment strategies. Standards of practice for clinical treatment of paediatric anxiety disorders are variable and often rely on extrapolation from data in adults.

There are no EU guidelines regarding the treatment of anxiety in children. However, in 2007, the American Academy of Child and Adolescent Psychiatry (AACAP) issued recommendations for the assessment and treatment of children and adolescents with anxiety disorders, which are summarised below:

- The psychiatric assessment should consider differential diagnosis of other physical conditions and psychiatric disorders that may mimic anxiety symptoms.
- Treatment planning should consider a multimodal treatment approach
- Psychotherapy should be considered as part of the treatment of children and adolescents with anxiety disorders.
- Serotonin Re-uptake inhibitors (SSRIs) should be considered for the treatment of adolescents with anxiety disorders.
- Medications other than SSRIs may be considered for the treatment of adolescents with anxiety disorders.

Except for the treatment of seizures, the literature on the use of BZD in children and adolescents is scarce. The pharmacological treatment for children and adolescents, including BZD, was reviewed in 1998 by Birmaher et al, who stated that to achieve a prompt relief of symptoms, the BZD may be used temporarily in anxiety disorders in combination with cognitive-behavioural therapy or with SSRIs. BZD having a shorter half-life show more rapid onset of relief, but, on the other hand, they may induce more intense withdrawal side effects. It is also of note that a recent Cochrane Database Systematic Review. (2009; Ipser JC, Stein DJ, Hawkrigde S, Hoppe L;66) of pharmacotherapy for anxiety disorders in children and adolescents found no quantitative data (i.e. randomised controlled trials) regarding the use of benzodiazepines. In addition, the authors concluded that 'given the lack of quantitative data, the routine use of benzodiazepines cannot be recommended, especially given concerns of dependency and treatment -related emergent adverse events associated with this class of drugs'.

## **IV.2 Pharmaceutical aspects**

Clobazam tablets were mainly used in the studies.

## **IV.3 Non-clinical aspects**

The clinical expert stated that a pharmaco-toxicological expert report on clobazam had been written in June 1995; no studies were specifically performed in juvenile animals. Since then, no further studies have been performed by sanofi-aventis. In addition, a review of literature based on Medline database was made and the nonclinical data found were analysed. Two studies confirmed the anticonvulsant effect of clobazam in immature rats. In conclusion, the clinical expert considered that a review of literature does not provide any nonclinical information relevant for the paediatric assessment in the context of this EU work-sharing procedure.

## **IV.4 Clinical aspects**

### **IV.4.1 Submitted clinical studies**

The submission was largely bibliographic. With regard to anxiety, most of the studies were old, all were uncontrolled and were written in French, with no translation to English.

Only one clinical study report was submitted with regard to the treatment of epilepsy: Comparison of clobazam with other anti-epileptic drugs, as a monotherapy; Tibbles et al; HR376/CDN/301/EP.

A literature search for clinical data on clobazam was made through the medical databases, MEDLINE and EMBASE, with the following key words: “clobazam”, “epilepsy” and “anxiety” and the following limits:

- For the search through MEDLINE: key words included in the title/abstract; type of article: “clinical trial”, “randomised controlled trial”, “meta-analysis” and “review”; ages: “all child: 0-18 years.”
- For the search through EMBASE: age groups “child: 0 to 12 years” and “adolescent: 13 to 17 years”.

All clinical studies assessing the efficacy of clobazam in children (0-17 years) or in a population including children, in the treatment of epilepsy or symptoms related to anxiety, have been selected in both databases. Two reviews in epilepsy (Michael 2008) and another one in behavioural and anxiety disorders (Koeppen 1979), gathered clinical data whatever the age of the patients and without separate analysis of data in children; the studies included in these reviews are described below. Thus, 31 studies in epilepsy and 9 in anxiety or symptoms related to anxiety, identified through MEDLINE or EMBASE, were considered relevant.

### **IV.4.2 Assessment of submitted studies.**

#### **IV.4.2.1 Pharmacokinetics**

**Monitoring of Concentrations of Clobazam and Norclobazam in Serum and Saliva of Children with Epilepsy. Bardy AH, Seppälä T, Salokorpi T et al (17).**

This was a non-comparative study in 90 children with epilepsy resistant to conventional drugs that studied the efficacy and pharmacokinetics of clobazam. The concentrations of clobazam and its active metabolite norclobazam were measured in 251 serum and 57 saliva samples. The group of seizure-free patients had the lowest clobazam and norclobazam concentrations; tolerance was associated with the highest concentrations. Adverse effects were associated with high concentrations of norclobazam; tolerance was associated with the highest concentrations. Adverse effects were associated with high concentrations of norclobazam. The concentrations of clobazam and norclobazam in saliva correlated with concentrations in serum. The authors concluded that monitoring of serum and salivary concentrations of clobazam and norclobazam is of limited value only, and no therapeutic target range for clobazam could be given.

**Assessor's comment:**

This study provides useful information regarding the pharmacokinetics of clobazam in children. However, no change in the product information is required.

#### **IV.4.2.2 Clinical studies in epilepsy**

##### **Randomised clinical trials**

The efficacy of clobazam (CLB) in the treatment of epilepsy in children was assessed in four controlled studies, of which one was placebo-controlled, one was a dose-ranging study, and the two others were comparison with an anti-epileptic drug (AED) or another benzodiazepine.

CLB was an adjunctive therapy for refractory epilepsy, in three of these four studies. It was used as a monotherapy in one study, either in newly diagnosed epilepsy (half the patients) or after failure of previous AED (second half of patients), for which CLB was assessed in subsets with separate randomisations.

##### **IV.4.2.2.1 Studies comparing clobazam with other anti-epileptic drugs as a monotherapy.**

###### **Comparison of clobazam with other anti-epileptic drugs, as a monotherapy; Tibbles et al; HR376/CDN/301/EP (18).**

The purpose of this randomised and double-blind study (which was sponsored by the MAH); was to compare the effectiveness of monotherapy CLB to carbamazepine (CBZ) and phenytoin (PHT) in children with epilepsy. The 235 children included were 2-16 years old, with epilepsy of the following seizure types: partial (43%), secondary generalized (46%), or primary generalized tonic clonic (11%). About half the patients were naïve of any antiepileptic drug (AED) (n=115; 48.9%) and were randomly assigned to receive CLB or CBZ. The other included patients were previously treated with another AED treatment, and stopped it because of poor seizure control or adverse events. The patients previously treated with CBZ were randomized to receive CLB versus PHT (n=76; 32.3%), and those previously treated with another AED were given CLB or CBZ (n=44; 18.7%). Altogether, in all study arms, 119 received CLB, 79 CBZ, and 37 PHT. The study medication was introduced over 1-3 weeks aiming for a dose of CLB 0.5 mg/kg/day, CBZ 10 mg/kg/day, and PHT 5 mg/kg/day.

##### **Efficacy Evaluation**

Intention to treat analysis using survival curves assessed the primary endpoint, which was the length of retention on the initial medication during the year after randomization.

**Results: Efficacy:** In the drug-naïve group, 54% and 65% of patients continued to receive the original medication, CLB and CBZ respectively, for a year. In the group with patients previously treated with CBZ, the one-year retention rate was 49% (CLB) and 40% (PHT), and in the last group it was 71% (CLB) and 63% (CBZ). There was no statistical difference in retention rate between CLB and CBZ, and between CLB and PHT. Overall, 104 (44%) patients discontinued the study medication before 12 months of treatment for the following reasons: poor seizure control (14.9%), side effect (9.4%), both reasons (11.5%), and another reason (8.5%). Tolerance (seizure increase after initial response) was assessed in a group of 116 patients qualified for this endpoint, and noted in 7.5% of patients receiving CLB, 4.2% of those receiving CBZ, and 6.7% of those receiving PHT.

The rate of seizure free patients was 23% for those treated with CLB, 25% with CBZ and 11% with PHT. No difference was observed in drug-naïve patients between clobazam and carbamazepine, and in previously treated patients between clobazam and carbamazepine, and between clobazam and phenytoin.

**Safety:** Overall, there was no difference in the occurrence of serious adverse events (SAEs) between CLB and standard therapy groups, as 10.1% (n=12/119) experienced a total of 28 SAEs in the CLB group versus 12.1% (n=14/116) in the standard therapy group. However, more patients were withdrawn from the study due to adverse events in the standard therapy group than in the CLB group: 26.7% vs 15.1% (n=31 vs n=18). In addition, Adverse events (AEs) leading to study discontinuation were more frequently from gastrointestinal and nervous origin, in the standard therapy group as compared to the CLB. The number of patients with personality disorders, sleep disorders and somnolence were about the same for each study drug.

The most frequently reported SAEs were of nervous origin (8 patients, 6.7%), convulsion being the most frequently reported PT (6 patients, 5.0%). Tolerance, defined as seizure increase after initial response, was noted in 7.5% of the children receiving CLB, 4.2% of those receiving carbamazepine, and 6.7% of those receiving phenytoin. A complementary analysis was performed by Bawden et al in a subset of 41 patients and showed that the cognitive and behavioural effects of clobazam appeared to be similar to those of both other treatments.

**Assessor's comments:**

The primary endpoint, which was the length of retention on the initial medication during the year after randomization between the therapies, seems more appropriate for a secondary endpoint. The CHMP Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders (CPMP/EWP/566/98) recommends that the assessment of efficacy should be primarily based on seizure frequency. Nevertheless, clobazam appears to have been as efficacious as phenytoin and carbamazepine; in addition, it was well tolerated.

Generally, clobazam is not used as monotherapy in epilepsy other than for catamenial (menstruation) seizures and cluster seizures; these patients were not specifically included in this trial.

The assessor therefore concludes that although useful information is provided, no changes to the SmPC are required.

**Comparison of clobazam with another benzodiazepine-Yamatogi Y et al. 1997 (26).**

This single blind clinical study of CLB was performed in severe epilepsy, in comparison with clonazepam (CZP). The sixty-six patients included, aged 1-17 years, were mainly suffering from Lennox Gastaut syndrome (50%), and also from West syndrome (11%), myoclonic-astatic epilepsy (5%), other generalised epilepsy (29%), and severe myoclonic epilepsy (6%). The mean age of seizure onset was about one year in each group. Two third of patients had daily seizures.

The dosage of each study medication was gradually increased from 0.23 mg/kg/day (CLB) and 0.025 mg/kg/day (CZP) at week 2, to 0.56 mg/kg/day (CLB) and 0.069 mg/kg/day (CZP) at week 12.

**Results:** More than a 50% seizure reduction was reported to have been attained in 61.8% of patients treated with CLB, which is significantly ( $p = 0.001$ ) higher than the 21.9% achieved with CZP. The respective improvement rates (over 50% seizure reduction) with CLB and CZP were 58.8% and 31.3% in Lennox-Gastaut syndrome ( $p = 0.166$ ), and 66.7% and 7.1% in its variant with significant difference ( $p = 0.002$ ). More than half the patients taking CLB showed efficacy in all seizure types excepting myoclonic seizure. There were also more seizure free patients with CLB (20.6%) than with CZP (0%). In global improvement rates, considering effects on clinical seizures, EEG and behaviour, CLB (55.9%) was significantly ( $p=0.006$ ) better than CZP (21.9%). In this study, CLB appeared significantly more effective than CZP.

**Assessor's comments:**

This published report provides useful information regarding the use of clobazam in severe epilepsy such as Lennox-Gastaut syndrome. However, no change in the product information is required.

#### IV.4.2.2.2 Studies involving clobazam as an add-on therapy

##### **Efficacy of clobazam as an add-on therapy in a placebo-controlled study**

**Keene DL et al. 1990.**

Twenty-one patients aged 2 to 19 years (mean: 11 years) were included in this double-blind, randomised, placebo-controlled cross-over study. Thirteen patients had generalised onset seizures and eight had partial onset seizures. Following an initial one-month baseline period, patients were assigned to a sequence of placebo-clobazam or clobazam-placebo. Treatment periods were of three months with a one-month wash-out period. The initial dosage of 0.5 mg/kg/day clobazam was increased to 1 mg/kg/day if no response was achieved; in addition, the dosage could be decreased by 0.25 mg/kg/day if patients developed excessive drowsiness. A drug success was stated to have occurred if the patient had a 50% or more reduction in seizure frequency when on the drug in comparison to the pre-trial and placebo phases of the trial.

**Results: Efficacy:** Eleven patients (52%) had a significant reduction (50% or greater) in their seizure frequency without significant side effects while taking clobazam, while no patients had a significant reduction in their seizure frequency when in the placebo phase. The success rate was higher in patients with partial epilepsy ( $p<0.05$ ). Two patients had to withdraw during the clobazam phase because of severe behavioural changes which did not respond to lowering the drug dosage.

All eleven patients who had shown a successful outcome during the clobazam phase of the drug entered the long term phase of the study. After 2 years on the drug, only 2 experienced an increase in seizure frequency.

**Safety:** 21 patients (mean age: 11 years; range: (2 - 19)) who received CLB as an add-on therapy for refractory epilepsy, were withdrawn of the study because of severe behavioural changes. These changes in behaviour did not respond to lowering the drug dosage (the dosage of CLB could be decreased by 0.25 mg/kg/day, in case of the occurrence of excessive drowsiness). No long term side effects were seen in the 11 children entered in the long term phase of the study, while treated with CLB for 2 years.

##### **Dose-ranging study with clobazam as an adjunctive therapy; Conry JA et al. 2009.**

This randomized, double-blind, dose-ranging study evaluated the safety and efficacy of clobazam (CLB) as adjunctive therapy for drop seizures in patients with Lennox-Gastaut syndrome (LGS). Sixty-eight patients with LGS aged 2-26 years were administered CLB (low dose target =0.25 mg/kg/day; high dose target = 1.0 mg/kg/day). The study consisted of 4-week baseline, 3-week titration, and 4-week maintenance periods, followed by a 3-week taper or continuation in an open-label study. Seizure frequency was recorded in a diary by the parent/caregiver throughout

the study.

**Results: Efficacy:** Weekly drop seizure rates were significantly reduced from baseline in both the high-dose and low-dose groups. A significantly greater proportion of patients in the high-dose group than in the low-dose group experienced reduction in drop seizures (see the table below). Non-drop seizures were also reduced in a dose-dependent manner. In both investigator and parent/caregiver global evaluations, patients in the high-dose group showed significantly greater improvements in overall symptoms compared to low-dose CLB. CLB was not discontinued because of serious adverse event. In conclusion, high-dose CLB was more effective than low-dose CLB. Other seizure types were also reduced.

**Safety:** The incidence of treatment-emergent AEs was similar between the low-dose and the high dose group (84% and 86%, respectively) as was the incidence of mild, moderate and severe AEs. A total of 9 patients were withdrawn of the study due to AEs: 3 (9.4%) in the low-dose group and 6 (16.7%) in the high-dose group. Five SAEs were reported in 4 patients during the study; none resulted in discontinuation of CLB and all resolved during the study.

#### **Assessor's comments**

The above studies provide useful information with regard to the use of clobazam as add-on therapy in epilepsy, for which it is already indicated. However, the assessor considers that no change in the product information is required.

#### **IV.4.2.2.3 Non-comparative studies**

Eleven non-comparative studies were submitted, including 672 children. These studies were prospective (n=7) or retrospective (n=4). Nine of them described the use of clobazam as an add-on therapy to AEDs. In most cases, the decision to initiate combination therapy was made after failure observed with several consecutive monotherapies with AEDs. Seizures for which the patients were included were mainly described as refractory or resistant to conventional AEDs.

Clobazam was administered at the initial daily dose of about 0.25-0.35 mg/kg/day and was then progressively increased until seizures were controlled or toxicity developed. The final dose ranged from 0.5 to 2 mg/kg/day. Clobazam was discontinued when the maximum tolerated dose was reached without seizure improvement or due to adverse event. The primary endpoints were the number of seizure free patients and the rate of patients with a seizure reduction higher than 50%, 75% or 90%, with a follow-up duration ranging from 3 months to 2 years.

**Results:** Given the variety of patients' characteristics and of types of epilepsy, the results were rather homogeneous through the 11 studies, with a seizure free rate of 9-25% (10 studies; and another one at 41%), a  $\geq 90\%$  seizure reduction of 31% (one study),  $\geq 75\%$  seizure reduction of 11-41% (4 studies), and  $\geq 50\%$  seizure reduction of 24-46% (5 studies). Safety data issued from some of these studies showed side effects such as drowsiness, somnolence and dizziness, commonly observed with CLB. Overall, these side effects did not lead to discontinuation of the drug.

#### **IV.4.2.2.4 Studies including children and adults**

Children were a part of the population recruited in ten other studies, in which the mean age of patients ranged from 21 to 44 years. Clobazam was mainly used in refractory or drug-resistant epilepsy, and it was globally evaluated for both adults and children.

The overall results showed a rate of free-seizure patients ranged from 7% to 30%. One of those studies was a 7-year Canadian experience on clobazam in refractory epilepsy, analysing 877 patients of whom 49% were children, who received clobazam at the average dose of 0.87 mg/kg/day; 40% of patients obtained a seizure reduction  $\geq 50\%$ .

Regarding the other studies, different treatments including clobazam were observed in two retrospective studies (47,48); results in subset populations treated with clobazam were in line with those of the studies focused on clobazam. In three different studies on stiripentol (49, 50,51), an antiepileptic drug, clobazam was an add-on therapy in all study arms and could not be assessed separately from the study medication. In a pilot study on clobazam (52) with some patients included in a comparative analysis and others in an open one, only preliminary results in a few patients are available.

**Assessor's comments**

The above studies (uncontrolled and those including adults and children), provide useful information, particularly with regard to the tolerability of clobazam. However, the assessor considers that no change in the product information is required.

#### **IV.4.2.3 Clinical studies in anxiety disorders**

The efficacy of clobazam in the management of anxiety disorders was assessed in 9 non-comparative studies including 526 children. All of these submitted studies were published in French. According to the clinical expert report, these studies covered various symptoms of anxiety, including those induced by a physical disease of more or less severe prognosis, or by change in environment such as hospital, school and family event, and those related to mental retardation. A wide variety of symptoms could be observed: anguish, behavioural disorders (instability, agitation and aggressiveness) sleep disorders, psychosomatic symptoms (gastrointestinal symptoms, headache, lipothymia).

One study was focused on infants children aged 2-15 years were included in 7 studies and patients aged from 8 months to 19 years (2 patients under 2 and three patients above 15 years) were included in one study . The dosage of clobazam was  $\leq 0.5$  mg/kg/day in infants, and from 5 mg/day to 15 mg/day in children aged  $\geq 2$  years in most studies. It was increased to 20-30 mg/day in adolescents in two studies.

The different symptoms were assessed separately in 8 of the 9 studies by means of 3-5 point verbal scales; all the patients had a global investigator assessment. Whatever the pathology for which the patients were included in the studies, clobazam seemed to have a beneficial effect in the majority of in- and out-patients. The overall positive effect observed ranged from 43 to 90%.

**Assessor's comments:**

Non-comparative studies only provided very limited information with regard to efficacy and safety, in particular as these were published in French without a translation to English, meaning that the assessor was unable to assess them.

#### **IV.4.3 Safety**

##### **Introduction**

In order to provide an overview of the safety profile of clobazam in the paediatric population, the Sanofi-aventis International Pharmacovigilance database was searched for solicited serious cases, and unsolicited medically-confirmed and medically-unconfirmed cases entered up to 31 May 2009, reported in patients treated with CLB and aged less than 18 years - or categorized in the age group child or adolescent. Children below 3 years in a context of drug exposure during pregnancy were excluded from the analysis. Serious adverse events (SAEs) for solicited cases and the adverse drug reactions (ADRs) for unsolicited cases were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0. The listedness for ADRs from unsolicited cases was assessed according to the Company Core Safety Data Sheet (CSDS) dated 27 October 2001. In addition, a search of the scientific literature was performed using MEDLINE, EMBASE,

## **Review of solicited cases from sanofi-aventis pharmacovigilance database**

### **Overview of all identified cases**

A total of 100 SAEs were reported in 45 children exposed to clobazam in clinical studies: 12 children being included in a Sanofi-aventis sponsored study and 33 in unsponsored studies. Regarding the unsponsored studies, information on the study design and total number of patients included and/or exposed to CLB was sometimes missing. Further details regarding the safety from the submitted studies are detailed above in section 4.4.2.

### **Other unsponsored studies**

A total of 72 SAEs were reported in 33 children exposed to CLB in unsponsored studies.

The most frequently reported SAEs were of nervous origin (15 patients), the most frequent PTs were “psychomotor hyperactivity”, “abnormal behaviour”, “aggression”, “insomnia” and “self-injurious behaviour” (7 patients).

### **Overview of all identified cases**

A total of 356 cases, including 243 medically-confirmed cases and 113 medically-unconfirmed cases were retrieved from the Sanofi-aventis pharmacovigilance database. Among these 356 cases, 196 were non serious, 160 were serious. Fifty one (51) occurred in patients aged 0-3 years, 74 cases in patients aged 3 – 6 years, 125 cases in patients aged 7-12 years, 82 cases in patients aged 13 – 17 years and 24 cases in children with not specified age.

#### **IV.4.3.1 Patients aged from 3 to 17 years**

A total of 417 adverse reactions were reported in the 203 medically-confirmed cases. These included 6 cases of an overdose. In addition, 6 cases of fatalities associated with CLB were reported; none of these cases was thought to be due to CLB.

The ADRs most frequently reported to the System Organ Classes (SOCs) were nervous system disorders (N=104), then general disorders, administration site conditions (N=47), skin and subcutaneous tissue disorders (N=38). The most frequently reported adverse reactions were somnolence, ataxia, rash and adverse events linked to the indication (epilepsy, convulsion). These reactions are listed in the CSDS. A cumulative review on pancytopenia and leukopaenia had been performed whatever the age of the patients, in the last PSUR and no signal was identified. No signal was identified among 8 cases coded with drug interaction. No important differences were observed between the 3 age groups 3 – 6 years, 7- 12 years and 13 -17 years.

### **Dependence/withdrawal syndrome**

Among the 203 medically-confirmed cases, a withdrawal syndrome was reported in 2 cases and no case of dependence or rebound was reported.

#### **IV.4.3.2 Patients aged from 0 to 3 years**

A total of 84 adverse reactions were reported in the 40 medically-confirmed cases. The ADRs most frequently reported were general disorders, administration site conditions (N=19) and nervous system disorders (N=17). The most frequently reported adverse reactions were somnolence and irritability. No dependence, withdrawal syndrome or rebound effect were reported.

## Scientific literature

One study of interaction between clobazam and conventional antiepileptics (65) was found in the literature search. Serum concentrations of clobazam, N-desmethyloclobazam and of concomitant antiepileptic drugs were monitored and prospectively collected in children with intractable seizures who received clobazam as adjunctive therapy. Whereas the clearances of most conventional antiepileptics were not affected by co-therapy with clobazam, the apparent clearances of valproic acid and primidone are significantly reduced in the presence of clobazam. Serum concentrations of clobazam increased with dosage and age, and decreased with phenobarbital cotherapy. Serum concentrations of N-desmethyloclobazam significantly correlated with clobazam serum levels, age, or clobazam dosage and were significantly increased by co-therapy with phenytoin or carbamazepine. The only clinically significant interaction observed in this study was between clobazam and valproic acid, resulting in significantly increased valproic acid levels.

The interactions between clobazam and valproic acid, or carbamazepine, or phenytoin are listed in the CSDS. Moreover in section 4.4 of the SmPC, it is mentioned that if clobazam is administered simultaneously with anticonvulsant in the treatment of epilepsy, the dosage must be adjusted under regular medical supervision, as there may be interactions with the patient's basic anticonvulsant medication.

### Assessor's comments:

From the submitted data, no differences in the safety profile in children and adolescents compared to that in adult population were identified. The safety profile of clobazam is similar to that of benzodiazepines. The most frequent observed adverse effect was somnolence; others included behaviour disorder, dependence, withdrawal syndrome, tolerance, paradoxical reactions and respiratory depression. The SmPC already includes precautionary information with regard to the avoidance of withdrawal syndrome and dependence; (in line with The EU SmPC guideline for Benzodiazepines as Anxiolytics or Hypnotics-1995). In addition, there is warning regarding the use of clobazam in combination with other anticonvulsants. The assessor therefore considers that no change in the product information is required with regard to safety issues in the paediatric population.

## V. RAPPORTEUR'S OVERALL CONCLUSIONS

### V.1 Discussion

The submitted studies provide useful data regarding the use of clobazam in epilepsy, in particular where seizure control may be difficult to obtain, such as in Lennox-Gastaut syndrome and refractory epilepsy. Most of the submitted data were with regard to its use as an adjunct to other therapies, for which it is already authorised in children aged 3-15 years old. In addition, one company sponsored study that compared clobazam monotherapy with clobazam with phenytoin and carbamazepine was submitted. However, clobazam is generally only used as monotherapy under specialist supervision for catamenial (menstruation) seizures and cluster seizures and these patients were not included in the study.

Regarding the use of clobazam in anxiety, the submitted data provide little evidence of efficacy, although it appears to sometimes be used as an adjunct to behavioural methods mainly in older children and adolescents. It is also of note that a recent Cochrane Database Systematic Review. (2009; Ipser JC, Stein DJ, Hawkrigde S, Hoppe L) of pharmacotherapy for anxiety disorders in children and adolescents found no quantitative data regarding the use of benzodiazepines.

From the submitted safety data, no new safety concerns have arisen. Sedative effects are the most frequently observed adverse reactions. Nevertheless, as with other benzodiazepines, there is a risk of tolerance, dependence, and withdrawal syndrome with prolonged use. The SmPC already includes precautionary information with regard to the avoidance of withdrawal syndrome and dependence (in line with The EU SmPC guideline for Benzodiazepines as Anxiolytics or Hypnotics-1995). In addition, clinical and biological

close monitoring should be performed in case of combination with anticonvulsants since pharmacokinetic interactions have been shown.

## V.2 Overall Conclusions

- Currently, with regard to the indication for add-on therapy for epilepsy in children aged 3- 15 years, the assessor considers that the submitted data confirm the risk/benefit of the product. However, the UK SmPC includes minimal information with regard to dosage used for epilepsy; it may therefore be helpful to prescribers to harmonise this with the information in the CCDS. In addition, the 10mg tablet formulation is not suitable for administration in children aged less than 6 years old and those who cannot swallow.

- With regard to the currently authorised indication for anxiety in children aged 3-15 years:

The submitted data provide very limited evidence of efficacy. In addition, the authors of the Cochrane Systematic Review concluded that ‘given the lack of quantitative data, the routine use of benzodiazepines cannot be recommended, especially given concerns of dependency and treatment - related emergent adverse events associated with this class of drugs’. The assessor therefore considers that the available data do not support the use of the drug in children and adolescents, given the known safety profile of the drug. However, the drug is currently authorised for this indication in the UK in children; in addition, it is not known whether the licensed status is similar elsewhere in Europe and whether or not it is used to treat anxiety in other Member States. Whilst the purpose of the article 45 Procedure is not to delete existing indications, the assessor considers that in this situation, it may be justifiable. The assessor considers that given the paucity of evidence of efficacy and the safety concerns, the MA holder should therefore be asked to provide justification for this indication and also to provide further information regarding the SmPCs elsewhere in the EU.

- In addition, the assessor considers that as 5mg capsules are available elsewhere in Europe, these should be made available to the UK and other Member States. The company should also be encouraged to develop an age appropriate formulation, as this drug is commonly given as an extemporaneous liquid formulation.

## VI. RAPPORTEUR’S PRELIMINARY RECOMMENDATIONS

**The Rapporteur therefore recommends the following:**

**VI.1 The SmPC and PIL should be modified. The following SmPC changes are recommended (in bold,italics):**

### 4.1 Therapeutic indications

#### *Adults*

Frisium is a 1,5-benzodiazepine indicated for the short-term relief (2-4 weeks) only of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short term psychosomatic, organic or psychotic illness. The use of Frisium to treat short-term “mild” anxiety is inappropriate and unsuitable. Before treatment of anxiety states associated with emotional instability, it must first be determined whether the patient suffers from a depressive disorder requiring adjunctive or different treatment. Indeed, in patients with anxiety associated with depression, Frisium must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepine (such as Frisium) alone, can precipitate suicide in such patients. In patients with

schizophrenic or other psychotic illnesses, use of benzodiazepines is recommended only for adjunctive, i.e. not for primary treatment.

Frisium may be used as adjunctive therapy in epilepsy.

### ***Paediatric population***

***Frisium is indicated for the treatment of epilepsy in association with one or more other anticonvulsants, in children aged 6 years and above and those aged 3 years and above who can swallow tablets.***

## **Section 4.2 Posology and route of administration**

### Treatment of anxiety

The usual anxiolytic dose for adults ~~and adolescents over 15 years of age~~ 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. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re-evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. Patients who have taken Frisium for a long time may require a longer period during which doses are reduced.

### Treatment of epilepsy in association with one or more other anticonvulsants

In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily. 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.

**Elderly:** Doses of 10-20 mg daily in anxiety may be used in the elderly, who are more sensitive to the effects of psychoactive agents. Treatment requires low initial doses and gradual dose increments under careful observation.

### ***Paediatric population***

When prescribed for children over three years of age, dosage should not exceed half the recommended adult dose. Treatment requires low initial doses and gradual dose increments under careful observation. ***It is recommended that normally treatment should be started at 5 mg daily. A maintenance dose of 0.3 to 1 mg/kg body weight daily is usually sufficient.***

There is insufficient experience of the use of Frisium in children under three years of age and ***no age appropriate formulation*** to enable any dosage recommendation to be made.

Tablets should to be swallowed without chewing with sufficient amount of liquid (1/2 glass).

- VI.2 The MAH should provide information regarding section 4.2 of the SmPC regarding the indication for anxiety in children aged 3 years and above throughout the EU.**
- VI.3 The MAH should be asked to provide further justification for the indication for anxiety in children aged 3 years and above.**
- VI.4 The MAH should make the 5mg capsules widely available in Europe, these should be made available to the UK and other Member States.**
- VI.5 The company should also be encouraged to develop an age appropriate formulation, as this drug is commonly given as an extemporaneous liquid formulation.**

## **VII. DAY 85 COMMENTS FROM MEMBER STATES**

Comments were received from Ireland, France and Germany. Ireland and Germany fully endorsed the Rapporteur's recommendations.

The following comments were received from France:

In France, clobazam (URBANYL) is registered in 3 different formulations: 5 mg capsules, 10 mg tablets and 20 mg tablets. The MAH is the same than in UK (Sanofi-Aventis)

The indications in France for clobazam are the followings:

- Adults:
  - symptomatic treatment of severe or disabling anxiety symptoms
  - prevention and treatment of delirium tremens and of other symptoms of alcohol withdrawal in adults
  
- Adults and children above 6 years of age: adjunctive therapy in patients with epilepsy in the following clinical pictures: clonic, tonic or tonico-clonic convulsions, absences (epileptic vertigo), myoclonus, atonic seizures, infantile spasms and Lennox-Gastaut syndrome.

Our comments are presented below:

### **General comments:**

Due to the need of harmonisation for paediatric information in SPC, the MAH should provide further information in order to compare current SPC in all member states.

The MAH should be asked to comment on discrepancies (in particular in posology, limit of age and duration of treatment) existing across Europe in SPC of clobazam medicinal products

### **Use in anxiety symptoms:**

We share the opinion of Rapporteur that the available data do not support the use of the drug in children and adolescents, given the known safety profile of the drug. Even not directly concerned at a national level, we support the proposal to ask the MAH providing supportive data on this UK indication.

Regarding the changes of UK SPC as proposed by Rapporteur, and in order to harmonize information across Europe, we support the Restriction to adult patients as proposed by Rapporteur (See Section 4.2), since similar information is already stated in French SPC of Urbanyl.

### **Use as add-on therapy in epilepsy for children aged 3-15 years:**

Regarding the changes as proposed by Rapporteur, we have the following comments:

Due to probable discrepancies existing all across Europe, it would be preferable to consider at this moment “minimal information” to be stated in SPC, than changes to be made. Indeed, current information in French SPC is already detailed and is describing a similar use.

- In France, the tablet and capsule formulations are not suitable for administration in children aged less than 6 years old (food choking risk). In the absence of adequate formulation, we are not prepared to support a use in children below 6 years of age.
- Of course, we fully support the opinion of the Rapporteur that the MAH should be encouraged to develop an age appropriate formulation.
- We do not support the proposed dose in epilepsy in children, which is different than the one proposed in French SPC (1 mg/kg body weight daily). Indeed, the proposed changes (or “minimal information”, See above) do not seem to be based on clinical data submitted during the present procedure and should then be justified, including the proposed up-titration.

## **VIII. REQUEST FOR FURTHER INFORMATION**

The Rapporteur acknowledges the comments made by France.

**The MAH is asked to provide further information and comments regarding the following questions:**

**VIII.1 The Rapporteur recommends the following SmPC and PIL modifications. The following SmPC changes are recommended (in bold, italics):**

### **Section 4.2 Posology and route of administration**

#### Treatment of anxiety

The usual anxiolytic dose for adults and ~~adolescents over 15 years of age~~ 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. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re-evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. Patients who have taken Frisium for a long time may require a longer period during which doses are reduced.

#### Treatment of epilepsy in association with one or more other anticonvulsants

In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily. 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.

**Elderly:** Doses of 10-20 mg daily in anxiety may be used in the elderly, who are more sensitive to the effects of psychoactive agents. Treatment requires low initial doses and gradual dose increments under careful observation.

***Paediatric patients aged 6 years and above and those who are able to swallow:***

When prescribed for children over ~~three~~ 6 years of age, dosage should not exceed half the recommended adult dose. Treatment requires low initial doses and gradual dose increments under careful observation. ***It is recommended that normally treatment should be started at 5 mg daily. A maintenance dose of 0.3 to 1 mg/kg body weight daily is usually sufficient.***

~~There is insufficient experience of the use of Frisium in children under three years of age to enable any dosage recommendation to be made.~~

***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.***

Tablets should to be swallowed without chewing with sufficient amount of liquid (1/2 glass).

**VIII.2 The MAH should provide information regarding section 4.2 of the SmPC regarding the indication for anxiety in children aged 3 years and above throughout the EU.**

**VIII.3 The MAH should be asked to provide further justification for the indication for anxiety in children aged 3 years and above.**

**VIII.4 Further to the comments form France, the MAH should provide further justification for the dosage in the CCDS for epilepsy.**

**VIII.5 The MAH should make the 5mg capsules that are available in France, widely available in Europe.**

**VIII.6 The company should also be encouraged to develop an age appropriate formulation, as this drug is commonly given as an extemporaneous liquid formulation.**

**A response is requested by 12<sup>th</sup> June.**

## **IX REQUEST FOR SUPPLEMENTARY INFORMATION AND MA HOLDER'S RESPONSE.**

### **IX.1 Regarding the Rapporteur recommended changes to the following SmPC and PIL**

#### **Sanofi-aventis response:**

The MAH agrees with the Rapporteur's proposal.

#### ***Assessor's Comments:***

The Applicant has raised no objections to the recommended modifications of the SmPC, which include the deletion of the indication for anxiety in children aged 3 yrs and above.

***ISSUE RESOLVED.***

### **IX.2 The MAH should provide information regarding section 4.2 of the SmPC regarding the indication for anxiety in children aged 3 years and above throughout the EU Sanofi-aventis response:**

The information is provided in Annex 2- p4 (Response to Agency Request - Clobazam paediatric assessment document). Clobazam is indicated for anxiety in 10 Member States.

#### ***Assessor's Comments:***

Clobazam is indicated for anxiety in children aged 3 years and above in 10 Member States. The Applicant and CMS have raised no objections to the deletion of the indication for anxiety in children aged 3 yrs and above.

***ISSUE RESOLVED.***

### **IX.3 The MAH should be asked to provide further justification for the indication for anxiety in children aged 3 years and above.**

#### **Sanofi-aventis response:**

Sanofi-aventis has no further justification for the anxiety indication in children aged 3 years and above.

#### ***Assessor's Comments:***

The Applicant has not provided further justification or raised no objections to the deletion of the indication for anxiety in children aged 3 yrs and above.

***ISSUE RESOLVED.***

**IX.4 Further to the comments from France, the MAH should provide further justification for the dosage in the CCDS for epilepsy.**

**Sanofi-aventis response:**

In the studies mentioned in the clinical overview, clobazam in paediatric epilepsy was typically administered at the initial daily dose of about 0.25-0.35 mg/kg/day and was then progressively increased until seizures were controlled or toxicity developed. The final dose ranged from 0.5 to 2 mg/kg/day. Clobazam was discontinued when the maximum tolerated dose was reached without seizure improvement or due to adverse event. Two non-comparative studies need to be specifically mentioned here:

A retrospective study of clobazam in children between 1 and 17 years with epileptic encephalopathy (Silva et al., 2006: reference #27 of Critical Expert Overview-6Oct09-CES1215) found patients to be treated at doses between 5 and 60 mg. Patients were found to be treated with at least one other anti-epileptic drug. Treatment with clobazam led to improvement (between slight improvement and seizure-freeness) in 54.5% of patients. Given the refractory character of the conditions under evaluation, the success rate was judged to be quite impressive. Adverse effects were found to be mild and tolerated by the patients and the use of clobazam at this dose range in paediatric patients found to be safe.

A prospective study by Jan and Shaabat (2000: reference #29 of Critical Expert Overview- 6Oct09-CES1215) investigated clobazam for the treatment of intractable childhood epilepsy in 31 children 2 months to 15 years (mean: 4.6 years) for 3 to 12 months. Clobazam was introduced with a starting dose of 0.25 mg/kg body weight, then doubled every 5-7 days until the minimum effective dose was reached, with a maximal dosage of 2.0 mg/kg body weight. Clobazam was mostly used as add-on therapy. 11 patients (35.5%) became seizure-free and 14 (45%) had >50% seizure reduction. Adverse effects were reported in 7 patients (22.5%): excessive sedation, vomiting, irritability, behavioural change, and ataxia. In 4 patients these adverse effects resolved spontaneously or with dose reduction.

The MAH concludes that the recommended paediatric starting dose of 5 mg and the recommended usual maintenance dose of 0.3 to 1.0 mg/kg body weight are justified in terms of safety and efficacy based on the data presented.

***Assessor's Comments:***

The Applicant has provided further justification for the dosage in the CCDS for epilepsy. Given that this is an old drug, with established usage, the assessor considers that adequate justification has been provided.

***ISSUE RESOLVED.***

**IX.5 The MAH should make the 5mg capsules that are available in France, widely available in Europe.**

**Sanofi-aventis response:**

Currently the 5mg capsules are available in France. Sanofi-aventis will consider the potential availability of 5mg capsules widely in Europe. In the meantime, Sanofi-aventis stresses that the European Pharmacopoeia (Ph. Eur.) test on the subdivision of scored tablets is performed for clobazam 10mg tablets and the result shows that the tablets are divided into equal halves.

**Assessor's Comments:**

The Applicant states that the availability of the 5mg capsules throughout Europe will be considered. However, regarding the justification provided for splitting of tablets, the Rapporteur stresses that this is not a recommended method of providing an accurate dosage.

**ISSUE RESOLVED.**

**IX.6 The company should also be encouraged to develop an age appropriate formulation, as this drug is commonly given as an extemporaneous liquid formulation.**

**Sanofi-aventis response:**

Further to this request, Sanofi-aventis will consider the potential industrial development of an age appropriate formulation and will keep the Competent Authorities informed of the outcome.

**Assessor's Comments:**

The Applicant states that the development of an age appropriate formulation be considered.

**ISSUE RESOLVED.**

**X RAPPORTEUR'S FINAL CONCLUSIONS AND RECOMMENDATIONS.**

The outstanding issues regarding this Article 45 procedure have been resolved.

However, on review of the dosage information in section 4.2 of SmPC. the Rapporteur has an additional comment: regarding the following statement:

*'When prescribed for children over ~~three~~ 6 years of age, dosage should not exceed half the recommended adult dose',*

Although this is in line with the dosage recommendations in the BNFc, (which is the dosage recommendation based on established clinical practice in the UK), this dosage would be too low for children aged 12 years and above, in whom the adult dosage is recommended. The Rapporteur therefore recommends that section 4.2 should be further amended to reflect this. The Rapporteur has consulted with the MAH (response received 29<sup>th</sup> October 2010), who has informed us that the statement is present in the UK, Hungary, Greece and Ireland SmPC, and not in the other 12 EU SmPCs.

In their response, the MA holder is still resistant with regards to the removal of dosage instructions in children aged 3-5 years old, as they consider that not allowing treatment under 6 years old will deprive epileptic children of a useful drug in a severe disease for which suitable treatment are difficult to adjust.

However, the Rapporteur concurs with France, that whilst there is no age appropriate formulation available to ensure accurate dosing, licensed usage in this age group cannot be supported.

The MA holder has also proposed moving some of the text in section 4.2 for further clarity; the Rapporteur endorses the changes. However, as this work –sharing procedure relates only to children, the Rapporteur considers that revision of the section that relates to anxiety in the elderly should be done as a separate variation.

In conclusion, with the exception of up-dating the product information, no further regulatory action is required.

## **X.1 RAPPORTEUR'S FINAL RECOMMENDATIONS TO UPDATE PRODUCT INFORMATION.**

**The MA holder is requested to submit a licence variation with modifications to the SmPC and PIL. The following SmPC changes (in bold, italics) are recommended:**

### **Section 4.2 Posology and route of administration**

#### Treatment of anxiety

The usual anxiolytic dose for adults and ~~adolescents over 15 years of age~~ 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. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re-evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. Patients who have taken Frisium for a long time may require a longer period during which doses are reduced.

#### Treatment of epilepsy in association with one or more other anticonvulsants

##### **Adults**

In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily. ~~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.~~

**Elderly:** Doses of 10-20 mg daily in anxiety may be used in the elderly, who are more sensitive to the effects of psychoactive agents. Treatment requires low initial doses and gradual dose increments under careful observation.

***Paediatric patients aged 6 years and above ~~and those who are able to swallow:~~***

When prescribed for children, aged ~~three~~ years of age, dosage should not exceed half the recommended ~~adult dose~~. Treatment requires low initial doses and gradual dose increments under careful observation. ***It is recommended that normally treatment should be started at 5 mg daily. A maintenance dose of 0.3 to 1 mg/kg body weight daily is usually sufficient.***

~~There is insufficient experience of the use of Frisium in children under three years of age to enable any dosage recommendation to be made.~~

***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.***

Tablets should to be swallowed without chewing with sufficient amount of liquid (1/2 glass).

***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.***

# ANNEX 1

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