IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Clobazam Thame 5mg/5ml Oral Suspension
Clobazam
PA22697/006/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Competent Authorities of Ireland and the UK considered that the applications for Clobazam Thame 5mg/5ml Oral Suspension and Clobazam Thame 10mg/5ml Oral Suspension (PL 39307/0026-0027; UK/H/5718/001-002/DC) could be approved. These are prescription-only medicines (POMs).

Clobazam 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 clobazam 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, clobazam must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepine (such as clobazam) 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.

Clobazam may be used as adjunctive therapy in epilepsy.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS).

The application for Clobazam Thame 5mg/5ml Oral Suspension was made under Article 10(3) of Directive 2001/83/EC, as amended, as a so-called hybrid application. The application for Clobazam Thame 10mg/5ml Oral Suspension was made under Article 10(1) of Directive 2001/83/EC, as amended, as a so-called generic application.

The reference medicinal product for these applications is Frisium 10mg tablet (PL 04425/0214), authorised to Aventis Pharma Limited (trading as Sanofi-aventis or Sanofi) following a change of ownership on 15 January 2002. Prior to this the reference product was authorised to Hoechst Marion Roussel Ltd (Marketing Authorisation number: PL 13402/0030) following a change of ownership on 31 December 1997. Prior to this the reference product was authorised to Hoechst UK Ltd (Marketing Authorisation number: PL 00086/0202) on 7 May 1997. As this reference product has been authorised in the EEA for at least 10 years the legal basis of these applications is acceptable.

Clobazam is a 1, 5-benzodiazepine. In single doses up to 20mg or in divided doses up to 30mg, clobazam does not affect psychomotor function, skilled performance, memory or higher mental functions.

No new non-clinical data were submitted, which is acceptable given that the applications are for generic medicinal products of an originator product that have been in clinical use for over 10 years.

The applicant has submitted a report of a bioequivalence study. Assurance has been provided that the study has been conducted according to the principles of Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

The lack of an Environmental Risk Assessment (ERA) with these applications for a generic product and hybrid is acceptable.

The UK and Ireland considered that the applications could be approved on day 205 of the procedure, on 4 December 2015. After a subsequent national phase, Marketing Authorisations were granted to Syri Limited (trading as Thame Laboratories) in the UK on 21 December 2015.

II. QUALITY ASPECTS

II.1 Introduction

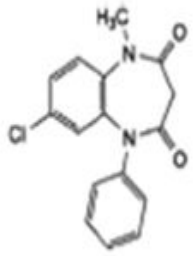
These medicinal products are white to off-white viscous suspensions containing 5mg/5ml or 10mg/5ml clobazam and the excipients methyl parahydroxybenzoate (E218), citric acid monohydrate (E330), sodium citrate (E331), sucralose (E955), xanthan gum (E415) and purified water.

The suspensions are stored in amber glass bottles with a HDPE-EPE wadded, tamper evident, child resistant screw on white plastic polypropylene cap. A 5ml polypropylene oral syringe with 0.1ml graduation mark and an adaptor for the syringe are included in the pack. Where higher doses are to be administered, dosing cups should be considered.

Pack sizes of 100ml and 150ml have been authorised, although not all pack sizes may be marketed.

II.2 Drug substance – clobazam

INN: Clobazam
Chemical name: 7-Chloro-1-methyl-5-phenyl-1,5-dihydro-*3H*-1,5-benzodiazepine-2,4-dione
Structure:



CAS number: 22316-47-8
Molecular formula: $C_{16}H_{13}ClN_2O_2$
Molecular weight: 300.7

All aspects of the manufacture and control of clobazam are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 MEDICINAL PRODUCTS

Pharmaceutical Development

The aim of the pharmaceutical development of Clobazam Thame 5mg/5ml Oral Suspension and Clobazam Thame 10mg/5ml Oral Suspension was to develop, respectively, hybrid and generic versions of the innovator product, Frisium 10mg tablet.

All the excipients comply with their respective pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. None of the excipients contain materials of animal or human origin.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the medicinal products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with commercial scale batches and has shown satisfactory results.

Control of Finished Products

The finished product specifications are acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Products
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months is applied to the products when stored in unopened bottles. Clobazam Thame 5mg/5ml Oral Suspension should be discarded within 30 days after first opening and Clobazam Thame 10mg/5ml Oral Suspension should be discarded within 60 days after first opening.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Clobazam Thame 5mg/5ml Oral Suspension and Clobazam Thame 10mg/5ml Oral Suspension.
II.5 Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

III. NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of clobazam are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.
III.2 Pharmacology
Not applicable, see Section III.1 Introduction, above.
III.3 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.
III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.
III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the products are intended for generic substitution with products that are already marketed, no increase in environmental exposure to clobazam is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.
III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Clobazam Thame 5mg/5ml Oral Suspension and Clobazam Thame 10mg/5ml Oral Suspension.

IV. CLINICAL ASPECTS

IV.1 Introduction
The applicant has submitted details of a bioequivalence study in support of these applications. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
An open label, balanced, pivotal, laboratory blind, randomised, two-period, two-treatment, two-sequence, single dose, two-way crossover, bioequivalence study was conducted comparing Clobazam Thame 10mg/5ml Oral Suspension with Frisium 10mg Tablets in healthy, adult, male and female subjects under fasting conditions.

Blood samples were collected from each subject in each period at pre-dose and at intervals up to up to 144 hours following drug administration. The plasma samples from the subjects were analysed for clobazam using a validated method.

The drug administrations were separated by a wash-out period of 23 days.

Samples from 22 subjects were considered in the pharmacokinetic analysis and the results are presented below:

Table of Geometric Means and 90% Confidence Interval for Clobazam (N=22)

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for	
	Test (A)	Reference(B)	A/B	Lower Limit	Upper Limit
AUC_{0-t}	6916.50	6981.23	99.0727	94.7342	103.6100
C_{max}	249.29	228.56	109.0723	100.1865	118.7462

**Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.*

The 90% confidence intervals for AUC and C_{max} were within the acceptance range of 80.00 to 125.00 %. Bioequivalence between 10mg/5ml oral suspension and Frisium 10mg tablet has been adequately demonstrated.

As the 5mg/5ml and 10mg/5ml strength products meet the criteria specified in the guideline on investigation of bioequivalence, the extrapolation of results and conclusions from the bioequivalence study on the 10mg/5ml to the 5mg/5ml strength is justified. Therefore, bioequivalence has been shown between Clobazam Thame 5mg/5ml Oral Suspension and Clobazam Thame 10mg/5ml Oral Suspension and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data are required for these applications and none have been submitted.

IV.4 Clinical efficacy

No new clinical efficacy data are required for these applications and none have been submitted.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data are presented for these applications and none are required. No new or unexpected safety issues arose during the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Clobazam Thame 5mg/5ml Oral Suspension and Clobazam Thame 10mg/5ml Oral Suspension. Routine pharmacovigilance activities and risk minimisation measures should be adequate for this product, which contains a widely used active substance with a well-established safety profile.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.4, 4.5 and appropriate advice is provided to the prescriber to minimise these risks.	
Overdose	The risks associated with the overdose of the drug product are described in the SPC Section 4.9 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in combination with alcohol and other CNS depressants	The risks associated with use of the drug product in combination with alcohol and other CNS depressants are described in the SPC Sections 4.4, 4.5, 5.2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Dependence	The risk of dependence associated with the use of the drug product are described in the SPC Sections 4.3, 4.4, 4.5 and 4.8, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients with pre-existing muscle weakness or spinal or cerebellar ataxia	The risks associated with use of the drug product in patients with pre-existing muscle weakness or spinal or cerebellar ataxia are described in the SPC Sections 4.4, 4.8 and appropriate advice is provided to the prescriber to minimise these risks.	None
Respiratory depression	The risk of respiratory depression associated with use of the drug product are described in the SPC Sections 4.3, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimise this risk.	None
Enhanced sensitivity to adverse reactions and increased risk of falls in the elderly	The risk of enhanced sensitivity to adverse reactions and increased risk of falls associated with use of the drug product in elderly is described in the SPC Sections 4.2, 4.4, 4.8 and	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	minimise these risks.	
Amnesia	The risk of amnesia associated with use of the drug product in patients is described in the SPC Sections 4.4, 4.8, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients with depression and personality disorders	The risks associated with use of the drug product in patients with depression and personality disorders are described in the SPC Sections 4.4, 4.5, 4.8 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use during breast-feeding	The risks associated with use of the drug product during breast-feeding are described in the SPC Sections 4.3, 4.6 and appropriate advice is provided to the prescriber to minimise these risks.	None
Effects on ability to drive and use machines	The risks associated with use of the drug product on ability to drive and use machines are described in the SPC Sections 4.5, 4.7, 4.8 and appropriate advice is provided to the prescriber to minimise these risks.	None
Alteration in antiepileptic efficacy due to clobazam tolerance or simultaneous use of other drugs	The risks associated with alteration in antiepileptic efficacy due to clobazam tolerance or simultaneous use of other drugs are described in the SPC Sections 4.4, 4.5 and appropriate advice is provided to the prescriber to minimise these risks.	None
Simultaneous use of drugs that alter the levels of clobazam and/or its active metabolite	The risks associated with simultaneous use of drugs that alter the levels of clobazam and/or its active metabolite are described in the SPC Sections	None

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Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.4, 4.5 and appropriate advice is provided to the prescriber to minimise these risks.	
Overdose	The risks associated with the overdose of the drug product are described in the SPC Section 4.9 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in combination with alcohol and other CNS depressants	The risks associated with use of the drug product in combination with alcohol and other CNS depressants are described in the SPC Sections 4.4, 4.5, 5.2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Dependence	The risk of dependence associated with the use of the drug product are described in the SPC Sections 4.3, 4.4, 4.5 and 4.8, and appropriate advice is provided to the prescriber to minimise this risk.	None
Use in patients with pre-existing muscle weakness or spinal or cerebellar ataxia	The risks associated with use of the drug product in patients with pre-existing muscle weakness or spinal or cerebellar ataxia are described in the SPC Sections 4.4, 4.8 and appropriate advice is provided to the prescriber to minimise these risks.	None
Respiratory depression	The risk of respiratory depression associated with use of the drug product are described in the SPC Sections 4.3, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimise this risk.	None
Enhanced sensitivity to adverse reactions and increased risk of falls in the elderly	The risk of enhanced sensitivity to adverse reactions and increased risk of falls associated with use of the drug product in elderly is described in the SPC Sections 4.2, 4.4, 4.8 and	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	appropriate advice is provided to the prescriber to minimise this risk.	
Use in patients with rare hereditary problems of fructose intolerance	The risks associated with the use of the drug product in patients with rare hereditary problems of fructose intolerance are described in the SPC Section 4.4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Serious skin reactions, including SJS and TEN	The risks of serious skin reactions, including SJS and TEN associated with use of the drug product are described in the SPC Sections 4.4, 4.8 and appropriate advice is provided to the prescriber to minimise these risks.	None
Important potential risks		
Medication errors	The appropriate advice to avoid risk of medication error is present under SPC Section 4.2, 6.5 and PIL Section 3 and is available to the prescriber and user.	None
Abuse potential/ diversion	The risk of abuse potential/ diversion associated with use of the drug product are described in the SPC Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimise this risk.	None
Off-label use	SPC Section 4.1, 4.2, 4.3 mentions clobazam approved use for the treatment of severe anxiety over a short time, epilepsy over longer time and adjunctive therapy for mental illness such as schizophrenia. No dosage recommendations can be made in children less than 6 years of age. Clobazam must not be used in children between the ages of 6 months	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and 3 years, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication.	
Use in pregnancy and adverse effects in the neonate	The risks associated with use of the drug product in pregnancy and adverse effects in the neonate are described in the SPC Sections 4.3, 4.6 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients on a controlled sodium diet	The risks associated with the use of the drug product in patients on a controlled sodium diet are described in the SPC Section 4.4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Paradoxical reactions	The risk of paradoxical reactions associated with the use of the drug product is described in the SPC Section 4.8 and appropriate advice is provided to the prescriber to minimise this risk.	None
Missing information		
Use in children less than 6 years of age	SPC Section 4.2 and 4.3 suggests no dosage recommendations can be made in children less than 6 years of age. It is also stated that the drug product be only used in exceptional cases for anticonvulsant treatment where there is a compelling indication.	None

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Clobazam Thame 5mg/5ml Oral Suspension and Clobazam Thame 10mg/5ml Oral Suspension.

IV USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSIONS

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with clobazam is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

VI. REVISION DATE

07.02.2025