Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Temazepam 10mg/5ml Oral Solution

(temazepam)

UK Licence Number: PL 39307/0080

Syri Limited t/a Thame Laboratories

LAY SUMMARY

Temazepam 10mg/5ml Oral Solution
(temazepam 10mg/5ml)

This is a summary of the Public Assessment Report (PAR) for Temazepam 10mg/5ml Oral Solution (PL 39307/0080). It explains how Temazepam 10mg/5ml Oral Solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Temazepam 10mg/5ml Oral Solution.

For practical information about using Temazepam 10mg/5ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Temazepam 10mg/5ml Oral Solution and what it it used for?
Temazepam 10mg/5ml Oral Solution is a medicine with 'well-established use'. This means that the medicinal use of the active substance, temazepam, is well established in the European Union for at least 10 years, with recognised efficacy for the proposed indications and an acceptable level of safety.

This medicine is used to aid sleeping and reset sleep patterns when a patient has been having difficulty sleeping. It is also a medicine that could be taken before a medical procedure.

How do Temazepam 10mg/5ml Oral Solution work?
Temazepam 10mg/5ml Oral Solution contains the active substance temazepam. Temazepam belongs to a group of medicines called benzodiazepines. Temazepam works by affecting the way certain natural brain chemicals (neurotransmitters) transmit messages. This has a calming effect which helps a person to sleep.

How are Temazepam 10mg/5ml Oral Solution used?
The pharmaceutical form of Temazepam 10mg/5ml Oral Solution is an oral solution and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

Adults
For sleeping problems:

- the usual dose is 5ml to 20ml each day before going to bed
- this should only be taken for up to 4 weeks at a time
- your doctor may advise you to take this only when necessary.

As a pre-medication:

- the usual dose is 10ml to 20ml, half to 1 hour before your surgery or test
- make sure that you have someone to take you home after the procedure.

Please read Section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Temazepam 10mg/5ml Oral Solution have been shown in studies?
As temazepam is a well-known substance, and its use in the licenced indications is well established, the applicant presented data from the scientific literature. The literature provided, confirmed the efficacy and safety of the use of temazepam in the licensed indications.

What are the possible side effects of Temazepam 10mg/5ml Oral Solution?
Like all medicines, Temazepam 10mg/5ml Oral Solution can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Temazepam 10mg/5ml Oral Solution, see Section 4 of the package leaflet available on the MHRA website.

Also, for the full list of restrictions, see the package leaflet.

Why were Temazepam 10mg/5ml Oral Solution approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of Temazepam 10mg/5ml Oral Solution outweigh the identified risks and recommended that the product be approved for use.

What measures are being taken to ensure the safe and effective use of Temazepam 10mg/5ml Oral Solution?
A risk management plan (RMP) has been developed to ensure that Temazepam 10mg/5ml Oral Solution are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Temazepam 10mg/5ml Oral Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Temazepam 10mg/5ml Oral Solution
The Marketing Authorisation for Temazepam 10mg/5ml Oral Solution was granted in the UK on 20 October 2017.

The full PAR for Temazepam 10mg/5ml Oral Solution follows this summary.

For more information about use of Temazepam 10mg/5ml Oral Solution, please refer to the package leaflet.

This summary was last updated in December 2017.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Syri Limited a Marketing Authorisation for the medicinal product Temazepam 10mg/5ml Oral Solution (PL 39307/0080) on 20 October 2017. The product is a prescription-only medicine (POM) indicated for the short-term treatment of sleep disturbances, considered severe or disabling or where insomnia is subjecting the individual to extreme distress. This product is especially useful in those patients for whom particularly rapid onset of hypnotic action is required and for whom the persistence of hypnotic effect after rising would be undesirable.

Temazepam is particularly suitable for patients with transient sleep disorders in whom re-establishment of normal sleep patterns is expected following the resolution of precipitating factors.

It is also indicated for pre-medication for minor surgical and investigative procedures, especially in the case of outpatients.

Benzodiazepines bind to specific receptors on GABA-mediated chloride ion channels, activating the GABA receptor and subsequently cause membrane chloride channels to open. This increases the influx of negative chloride ions through the cell membrane, prevents depolarization of the neuron and excitability of the target cell, and thus inhibits neurotransmission. It is by this mechanism that temazepam produces central nervous system sedation, anxiolysis and muscle relaxation.

The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Temazepam 10mg/5ml Oral Solution has been developed taking into account the pharmaceutical properties of a currently marketed generic temazepam oral solution, Temazepam 10 mg/5 mL Oral Solution (PL 00427/0089) granted a marketing authorisation to Rosemont Pharmaceuticals Ltd on 26 September 1995 and Temazepam Elixir (PL 03433/0054), a temazepam solution formulation that was previously licensed as a full application, but cancelled in December 2002 to which Temazepam 10 mg/5 mL Oral Solution (PL 00427/0089) cross-refers.

Bibliographic data on temazepam has been submitted to support this application. No new non-clinical or clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active ingredient of well-established use. Bridging of the data presented in the bibliography to the product formulation was adequate.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for its manufacture and assembly.

II QUALITY ASPECTS

II.1 Introduction

Each 5 ml of Temazepam 10mg/5ml Oral Solution contains 10mg of temazepam. Other ingredients consist of the pharmaceutical excipients ethanol, propylene glycol (E1520), trometamol, citric acid monohydrate, non-crystallising liquid sorbitol (E420), purified water, peppermint oil, Patent Blue V (E131), caramel (E150) and glycerol (E422).

The finished product is packed into Type III (Ph. Eur) amber glass bottles with tamper evident, child-resistant plastic caps with polypropylene inners, polyethylene outers, and expanded polyethylene (EPE) liners. The bottle is supplied with a 10ml oral syringe with 0.5 ml graduations. The pack size is 300 ml.

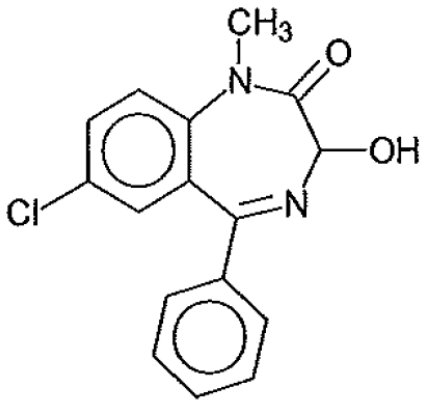
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substances

Temazepam

INN:	Temazepam
Chemical name:	7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Structure:



Molecular formula:	$C_{16}H_{13}ClN_2O_2$
Molecular weight:	300.74
Appearance:	White or almost white, crystalline powder.
Solubility:	Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol (96 per cent).

Temazepam is the subject of an Active Substance Master File (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification.

Batch analyses data that comply with the proposed specification are provided.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, oral solution containing 10mg of temazepam per 5ml of solution.

A satisfactory account of the pharmaceutical development has been provided.

Comparative dissolution between the Temazepam 10mg/5ml Oral Solution and the Temazepam 10 mg/5 mL Oral Solution (Rosemont Pharmaceuticals Ltd) was presented, showing rapid and complete dissolution demonstrated across physiological pH (>90% in 10 min) suggesting *in vivo* solubility is not likely to be an issue.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of the colouring agents Patent Blue V and caramel, which are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

No materials of animal origin are used in the manufacture of the medicinal product.

No genetically modified organisms (GMO) have been used in the manufacture of the medicinal product.

Manufacture of the product

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

Finished Product Specification

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

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 21 months with the storage recommendations ‘Do not store above 25°C’ and ‘Keep the container in the outer carton in order to protect from light’. The in-use shelf life is 90 days after first opening.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this product from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of temazepam are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report 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

Temazepam is an active metabolite of diazepam, belonging to the benzodiazepine class of sedative anti-anxiety drugs. The actions of the benzodiazepines, including temazepam, result from their capacity to enhance GABA-mediated synaptic inhibition. At therapeutic concentrations, benzodiazepines act on GABA receptors and increase the frequency, but not duration, of openings at GABA-activated chloride channels. At higher concentrations, diazepam and other benzodiazepines can reduce sustained, high-frequency firing of neurons. Augmentation of interneuronal GABAnergic inhibitory pathways in the brain and pre-synaptic GABAnergic inhibition in spinal cord may underlie the anticonvulsant and muscle relaxant properties of the benzodiazepines.

The ED_{50} (mg/kg) of temazepam after intravenous and oral administration in rats

Route of administration	Pharmacological activity	ED_{50} (mg/kg)
Oral	Muscle relaxation (Rota rod)	8.7 (2.4-14.6)
	Protection against PTZ clonic convulsion	6.7 (5.1-8.7)
	Anti-conflict	7.9 (1.6-38.6)
Intravenous	Muscle relaxation (Rota rod)	0.56 (0.41-0.83)
	Protection against PTZ clonic convulsion	0.41 (0.33 -0.52)

III.3 Pharmacokinetics

There are extensive clinical pharmacokinetic data with temazepam which supersedes the non-clinical pharmacokinetic data.

III.4 Toxicology

The following information is drawn from the scientific literature, i.e. not derived from new non-clinical study data submitted by the applicant.

Single-dose toxicity

In standard single-dose toxicity studies the median lethal dose (LD_{50}) for the oral route was about 800 to 1900mg/kg in mice and 2000 to 8000mg/kg in rats. By the intraperitoneal route the LD_{50} was about 500 to 1000mg/kg in mice and about 600mg/kg in rats. In dogs, the oral LD_{50} was 3620mg/kg. Thus, like other benzodiazepine drugs, temazepam has a relatively low order of acute toxicity.

Acute LD_{50} (mg/kg) of temazepam

SPECIES	ROUTES	SEX	LD50 mg/kg
Mouse	Oral	M & F	1963 (1813-2126)
		M	980 (860-1117)
Mouse	i.p.	M & F	1050 (967-1140)
		M	485 (411- 572)
Rat	Oral	M & F	1823 (1639-2027)
		M	2800 (2059-3808)
Rat	i.p.	M & F	617 (551- 690)
		M	670 (626- 717)
Rabbit	Oral	M & F	≥2400
Dog	Oral	M & F	≥1600

Repeat-dose toxicity

Rats

In subacute toxicity experiments, lasting from 6 to 13 weeks in rats (9-250 mg/kg/day p.o.), changes in hepatic function were seen at the doses over 100 mg/kg/day. Chronic toxicity studies of 6 to 12 months duration were performed in rats (10-160 mg/kg/day p.o.), with the major finding a liver weight increase at high doses and minimal hepatic lipidosis at mid and high doses. In longer term toxicity studies (up to 2 years in rats receiving temazepam 10 to 250mg/kg/day orally), somnolence or sedation, decreased bodyweight gain, enlarged livers and kidneys, and some haematological changes (decreased haematocrit, haemoglobin and erythrocytes, and a shift to the left in differential leucocyte counts) were seen with 'higher' doses in some animals, but no important effects were noted at doses below 20mg/kg/day.

Dogs

In subacute studies lasting from 6 to 13 weeks in dogs (80-200 mg/kg/day p.o.) treatment-related symptoms included decreased locomotion, sedation, abdominal distension and weight loss. Sporadic hyperexcitability was seen in some animals. In longer term toxicity studies (up to 1 year in dogs receiving 10 to 200mg/kg/day), somnolence or sedation, decreased bodyweight gain, enlarged livers and kidneys, and some haematological changes (decreased haematocrit, haemoglobin and erythrocytes, and a shift to the left in differential leucocyte counts) were seen with 'higher' doses in some animals, but no important effects were noted at doses 5-120 mg/kg/day p.o. Dogs at the higher doses employed exhibited slight lethargy.

Genotoxicity/Carcinogenicity

The frequency of DNA single-strand breaks and/or alkali-labile sites was checked in the liver of rats orally administered a single dose (1 mmol/kg) or 15 successive daily doses (0.2 mmol/kg) of temazepam. Rats given a single dose were killed 14 hours after administration, and animals given 15 successive daily doses were killed 14 hours after the last dose. Treatment with temazepam as a single oral dose of 1 mmol/kg and multiple doses of 0.2 mmol/kg for up to 15 days did not show any DNA strand breakage. The doses tested in rats were from 100 to more than 5000 times higher than doses usually administered to humans. The clastogenicity of 12 benzodiazepines, including temazepam, was investigated following a single intraperitoneal injection (0.85 mg/kg) administered to male mice. Bone marrow metaphases were analysed 12-72 hours after the treatment. No mutagenic effects of the benzodiazepines could be observed. In addition, no significant increase over the control level was obtained.

In an 18-month mouse carcinogenicity study, no evidence was found of compound-induced carcinogenicity.

Reproductive and developmental toxicity

Male and female rats were given temazepam in doses up to 90mg/kg/day for several weeks before mating. There was a small increase in pup mortality and a lower mean pup weight compared with

untreated animals, especially with 'higher' doses. In studies for dysmorphogenic effects, some changes in rib formation occurred in rats and rabbits receiving doses of 240mg/kg or higher and 40mg/kg or higher, respectively, but no such changes were seen with lower doses.

The effect of temazepam on perinatal mortality has been reported in 13 healthy mature pregnant New Zealand white rabbits (3.6 to 5.3 kg). Temazepam (10mg/kg), when orally administered with diphenhydramine (15 mg/kg), caused an increase in perinatal mortality. Eighty-one percent of the foetuses were either stillborn or died shortly after birth. Treatment with temazepam or diphenhydramine alone did not increase the mortality rates significantly. It was concluded that both drugs may be acting synergistically to cause mortality.

The effects of temazepam on reproduction and the offspring has been assessed in rats and rabbits. Two segment II type studies in rats provided evidence of the possible increased incidence of foetal resorptions, at doses of 30-120 mg/kg. In perinatal and postnatal studies it was observed that temazepam at doses of 60 and 120 mg/kg/day caused increasing nursling mortality in rats. There were minimal untoward effects on the newborn survival rate. Two segment II type studies in rabbits produced no evidence of potential teratologic effects.

Studies on impurities
The proposed specifications are in accordance with the requirements of the ICH Q3B(R2) guideline.

Residual solvents
The proposed limits are acceptable.

Excipients
Only relevant excipients are discussed in this report, those with established safety are not.

Propylene Glycol
The content of propylene glycol is compliant with the limits stated in the Commission for Human Medicinal Products (CHMP) document EMA/CHMP/334655/2013 dated 20 November 2014.

Patent Blue V
No acceptable daily intake (ADI) has been allocated for Patent Blue V by a committee of the World Health Organisation, named the Joint Expert Committee on Food Additives (WHO JECFA, Patent Blue V, 1982). Patent Blue V (E131) is a tri-arylmethane dye permitted for use as a food additive in the EU and has been previously evaluated by JECFA in 1970 and 1975 and the EU Scientific Committee on Food (EU SCF) in 1983; JECFA established a Temporary Acceptable Daily Intake (ADI) of 0-1 mg/kg bw/day in 1970, but withdrew it in 1975. The EU SCF established an ADI of 0-15 mg/kg bw/day. The panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that became available since then and the data available following a public call for data. The EU Panel on Food Additives and Nutrient Sources has re-evaluated the safety of Patent Blue V (E131) in 2013. The panel concluded that the present dataset provides a rationale for a re-definition of the ADI. Using the no-observed-adverse-effect-level (NOAEL) of 500 mg per kg of body weight per day (500mg/kg bw/day) derived from a chronic toxicity study in mice and applying an uncertainty factor of 100 to this NOAEL, the panel establishes an ADI of 5 mg/kg bw/day.

The panel noted that at the maximum permitted levels of use of Patent Blue V (E131), exposure estimates for high consumers are above the ADI of 5 mg/kg bw/day in toddlers and children. At the maximum reported use levels of Patent Blue V (E131), exposure estimates are below the ADI of 5 mg/kg bw/day for all groups of the population (EFSA Journal 2013;11(3):2818). The content of Patent Blue V in the proposed product is well within the proposed European ADI.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since this medicine is intended for substitution with other temazepam products that are currently marketed, no increase in environmental exposure to temazepam is expected when this product is introduced to the market. An environmental risk assessment is, therefore, not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

This is a national application for a Marketing Authorisation for Temazepam 10mg/5ml Oral Solution. The legal basis of this application is well-established use according to Article 10a of Directive 2001/83/EC, as amended, supported by bibliographic literature.

The applicant's clinical expert report has been written by an appropriately qualified person and is satisfactory.

The clinical use and safety of temazepam is well-established in the EU with over 39 years of clinical experience.

IV.2 Pharmacokinetics

The Guideline on Investigation of Bioequivalence "CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) specifies the following, in relation to oral solutions:

"If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However, if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc), absorption (e.g. surfactants or excipients that may affect transport proteins), *in vivo* solubility (e.g. co-solvents) or *in vivo* stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data."

The proposed product should not be considered as an aqueous solution, since the bulk of the vehicle is made up from non-aqueous (co-)solvents; therefore, it would not automatically qualify for a biowaiver. The currently approved Temazepam 10 mg/5 mL Oral Solution (PL 00427/0089) is qualitatively identical, although there are some differences in the amounts of some of the excipients. The current application has been submitted under Article 10a of Directive 2001/83/EC, a well-established use application. However, for approval as an Article 10a product, a link to the formulations discussed in the supporting literature should be established.

Appropriate investigative work and discussion to bridge the proposed formulation to those reported in the literature, in support of the Article 10a application, was presented.

The applicant has performed and reported some comparative dissolution studies on their product and Temazepam 10 mg/5 mL Oral Solution (PL 00427/0089), in aqueous media, across the physiological pH range. Rapid and complete dissolution (>90%) was confirmed for both products within 10 minutes in all media; there is no indication that *in vivo* solubility would be an issue.

Co-solvents and excipients with potential to affect gastrointestinal motility

With reference to the guideline on bioequivalence, the impact that excipients in the proposed formulation, such as co-solvents and excipients with potential to affect gastrointestinal motility (e.g. glycerol, sorbitol), could have on bioavailability of the active substance should be considered and discussed, in relation to already authorised products, including justification for why any differences in formulations do not necessitate formal demonstration of bioequivalence.

The applicant was made aware that, if the literature did not provide sufficient evidence in support of the established use/bioavailability of their precise formulation, then further confirmatory bioequivalence studies against the currently marketed product may be necessary.

Glycerin is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, parenteral, and topical preparations. When used as an excipient or food additive, glycerin is not usually associated with any adverse effects and is generally regarded as a non-toxic and non-irritant material. Exogenously administered oral glycerol is rapidly emptied from the stomach, absorbed by the intestine, integrated into the body, and distributed among the body fluid pools. Time to attain peak plasma concentration for glycerol is 60 to 90 minutes. The elimination half-life of glycerol in man is about 30-45 minutes. Therefore, faster absorption and elimination of glycerol leads to the reduction in the amount of glycerol available to exert local actions in the gastrointestinal (GI) tract.

The applicant has conducted a literature search to evaluate the effects of glycerol in GI tract and the evidence is summarised below:

In a study, glycerol was given at 30ml doses (95%) in orange juice three times daily after food to ten men and four women for 50 days. No alteration in blood picture occurred. No abnormal urinary constituents were found and bowel movement remained undisturbed.

In the literature it was found that glycerol elicits gastric distress in isolated cases when the dosage was greater than 1.0g/kg glycerol solution and vast majority of subjects did not experience problems.

Similarly, in another study evaluated the effect of glycerol administered as a food to 60 patients. In treated patients, no toxic effect or gastrointestinal disorders were observed.

In another study, the effects of glycerol ingestion on hydration and subsequent cycle ergometer submaximal load exercise were examined in well-conditioned subjects. In total 11 subjects were treated with 1.2gm/kg glycerol in 26 ml/kg solution. Glycerol was well tolerated in the treated subjects and no complains of gastrointestinal symptoms with glycerol was reported. However, in the literature it was reported that gastrointestinal symptoms were observed following ingestion of high concentrations (50%) of glycerol.

In a review article, of the various studies in which glycerol were used for the therapeutic purpose of various clinical conditions. The review of the various studies concludes that the glycerol ingestion at doses up to 1.5 g/kg and for glycerol solutions up to 850 g/L, there is no evidence for gastrointestinal distress during rest conditions, even when followed by added fluid ingestion. When glycerol ingestion is followed (<45 minutes later) by exercise, there is an increased likelihood of symptoms of gastrointestinal distress and headache. One study reported that an oral dose of glycerol 1.0 g/kg bodyweight every 6 hours is considered to be well tolerated. Similarly, one study concluded that the ingestion of 1.0 g/kg bodyweight dose of glycerol every 6 hours for 72 hours shows no symptoms of gastrointestinal distress, while another studies concluded that the ingestion of glycerol 1.0 to 1.5 g/kg bodyweight in periods of less than 30 minutes, the volunteers did not experience nausea.

In addition to above studies, glycerol at doses of 0.25-2.0 g/kg decreases intracranial pressure in numerous disease states, including Reye's syndrome, stroke, encephalitis, meningitis, pseudotumor cerebri, central nervous system tumor, and space-occupying lesions.

It is also effective in lowering intraocular pressure in glaucoma and shrinking the brain during neurosurgical procedures. The notable adverse effects of glycerol in man for the treatment of above conditions include intravascular hemolysis, hemoglobinuria, renal damage, hyperglycemia and hyperosmolality.

The maximum amount of Glycerol ingested as a part of Temazepam solution, is below the threshold frequency reported in the literature (i.e. 1gm/kg). Additionally, the therapeutic dose of glycerol is also significantly higher as compared to the amount of glycerol consumed by the adults using Temazepam 10mg/5ml Oral Solution. Therefore, it can be concluded that the amount present in the Temazepam 10mg/5ml Oral Solution will not affect the GI motility or did not produce any adverse effect on GI tract in target population. In support of effect on GI motility applicant has conducted the literature search for the effect of glycerol on bioavailability of drug product. The results of the animal and human studies are summarised below:

A pharmacokinetic study of sodium salicylate in oily and aqueous vehicle in rabbits in which glycerine was used as aqueous vehicle. The results of the study show that there was no statistically significant different between solutions with and without glycerin in any of pharmacokinetic parameters like peak concentration (*c*max), peak time (*t*max), area under the curve (AUC), elimination rate constant (*k*), absorption rate constant (*k*a), drug clearance (clt) and the volume of distribution (*v*d).

In addition, glycerine did not affect the gastric emptying rate in rabbit compared to the oily solution of salicylate in rabbit and therefore doses not affect the bioavailability of the drug.

A study was conducted to evaluate the comparative bioavailability of Temazepam Elixir and capsule formulation in healthy volunteers. There was no significant difference in the extent of drug absorption from the two formulations as determined by the area under the plasma concentration vs time curve and the peak plasma concentration. The lack of any significant difference in area under the curve data and in peak plasma concentration data would suggest no difference in the extent of drug absorption between capsule and elixir. However, the highly significant difference in concentration 20 min post-dosing would suggest that the dissolution of the capsule shell is critical in terms of drug absorption. The higher levels achieved 20 min after elixir administration suggests that a more rapid onset of activity is possible with this formulation. The fact that there is no significant difference in the extent of drug absorption from the two formulations as determined by the area under the plasma concentration vs time curve and the peak plasma concentration the capsule and soft gelatine capsule it is considered that the capsules and elixir are bioequivalent. The elixir formulation selected is consisting of glycerol, ethanol and sorbitol as the main components of the vehicle.

From the above data, it was concluded that the glycerol did not affect the bioavailability of the drug product in human and animal and elixir formulation of temazepam shows comparable bioavailability to the soft capsule in healthy volunteers. Therefore, from the above data it was concluded that the amount of glycerol present in the proposed Thame formulation did not affect the GI motility at the proposed concentration and neither affect the bioavailability of the Temazepam.

The rationale that this amount of glycerine in Temazepam 10mg/5ml Oral Solution is unlikely to affect bioavailability is accepted

Reported elimination half-life values for Temazepam after night time administration in young volunteers vary from 5.3 - 11.5 hours. There is, however, an approximately 30% increase in the half-life of

Temazepam when taken in the morning. The mean elimination half-life values in young volunteers after morning administration vary from 8.3 - 13.6 hours. In the elderly the half-life may be longer with a mean value of about 15 hours. The half-life in elderly women may be longer than in elderly men.

IV.3 Pharmacodynamics

Benzodiazepines bind to specific receptors on GABAmediated chloride ion channels, activating the GABA receptor and subsequently causing membrane chloride channels to open. This increases the influx of negative chloride ions through the cell membrane, preventing depolarisation of the neuron and excitability of the target cell, and thus inhibits neurotransmission. It is by this mechanism that temazepam produces central nervous system sedation, anxiolysis and muscle relaxation.

IV.4 Clinical efficacy

11 studies investigated the clinical efficacy of tempazepam in insomnia whilst 7 studies investigated the efficacy of temazepam as a pre-medication, all clinical trials suggest that temazepam is an efficacious hypnotic agent with the advantage of a good safety profile.

The proposed indication and dosage regimen are the same as that of currently approved products within the EU.

IV.5 Clinical safety

The safety of temazepam for its proposed indications has been well documented in several placebo-controlled and comparison trials. Post-marketing surveillance data for over 10,000 patients has shown temazepam (20 mg) to be generally well tolerated. The adverse reactions consisted mainly of morning nausea, gastro-intestinal disturbances, headache, drowsiness, vivid dreaming and hangover effects.

Insufficient data are available on temazepam to assess its safety during pregnancy and lactation. Since benzodiazepines are found in breast milk, temazepam should not be administered to breast feeding mothers. If the product is prescribed to a woman of child bearing age, she should be warned to contact her physician about stopping the product if she intends to become, or suspects that she is, pregnant. Reports of reproductive system abnormalities are limited with the use of temazepam and other benzodiazepines.

Temazepam can impair cognitive function and thus affect a patient’s ability to drive safely. Overdose of benzodiazepines commonly cause drowsiness, ataxia, dysarthria, mental confusion and nystagmus. The use of activated charcoal or flumazenil is considered for the management of overdose.

The bibliographic review by the clinical expert validates the well-established safety of temazepam.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) 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 Temazepam 10mg/5ml Oral Solution.

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

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	• Hypersensitivity to the active substance or to any of the excipients • Long term use, dependence, tolerance and withdrawal symptoms • Hangover effects • Suicide risk • Psychiatric and paradoxical reactions • Use in patients with severe respiratory insufficiency, liver problems and kidney problems • Use in patients with myasthenia gravis • Use in patients with psychiatric disorder. • Use in patients with sleep apnoea syndrome • Use in patients with narrow angle glaucoma • Drug interactions (with CNS depressants, antiepileptic, antihypertensive, anti-viral, medicines used to treat Parkinson's disease and schizophrenia, compounds that affect hepatic enzymes (particularly cytochrome P450), drug used in alcoholism, anti asthmatics and muscle relaxants). • Overdose
Important potential risks	• Effect on ability to drive and use machines • Use in pregnancy and lactation
Missing information	• Use in children less than 18 years of age

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

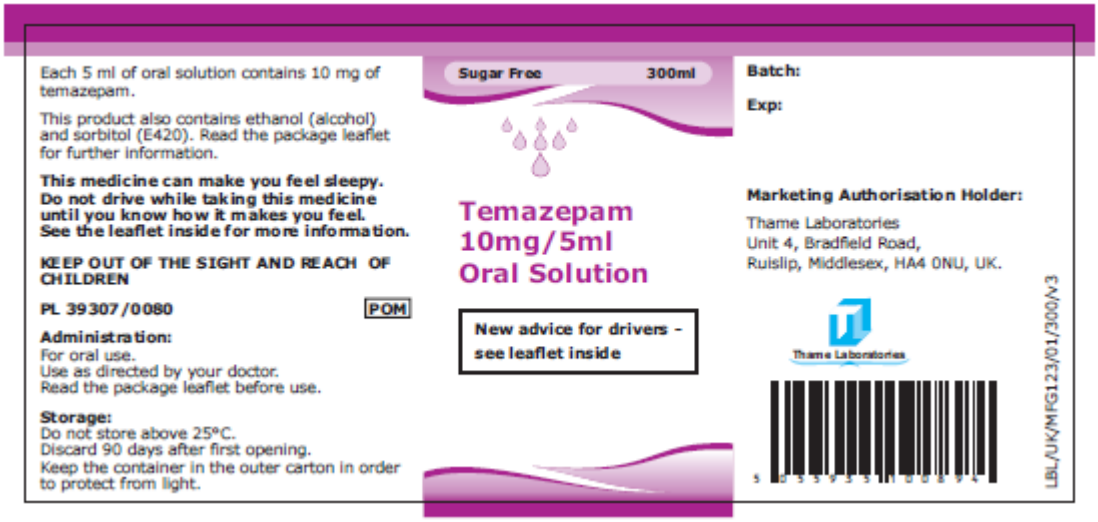
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable.Extensive clinical experience with temazepam is considered to have demonstrated the well-established use and the therapeutic value of the compounds. The benefit-risk assessment is, therefore, considered to be positive.

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

The approved labelling for Temazepam 10mg/5ml Oral Solution is presented below:


Each 5 ml of oral solution contains 10 mg of temazepam.
This product also contains ethanol (alcohol) and sorbitol (E420). Read the package leaflet for further information.
This medicine can make you feel sleepy. Do not drive while taking this medicine until you know how it makes you feel. See the leaflet inside for more information.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
PL 39307/0080
POM
Administration:
For oral use.
Use as directed by your doctor.
Read the package leaflet before use.
Storage:
Do not store above 25°C.
Discard 90 days after first opening.
Keep the container in the outer carton in order to protect from light.
Sugar Free
300ml
Temazepam 10mg/5ml Oral Solution
New advice for drivers - see leaflet inside
Batch:
Exp:
Marketing Authorisation Holder:
Thame Laboratories
Unit 4, Bradfield Road,
Ruislip, Middlesex, HA4 0NU, UK.
Thame Laboratories
LBL/UK/MFG123/01/300/v3

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)