Public Assessment Report

UKPAR

Temazepam 10mg/5ml Oral Solution

(temazepam)

UK Licence Number: PL 44710/0034

Kinedexe UK Limited
LAY SUMMARY
Temazepam 10mg/5ml Oral Solution
(temazepam)

This is a summary of the Public Assessment Report (PAR) for Temazepam 10mg/5ml Oral Solution (PL 44710/0034). 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 ease of reading, this medicinal product will be referred to as Temazepam Oral Solution in this Lay Summary.

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

What is Temazepam Oral solution and what is it used for?
Temazepam 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 help sleeping and reset sleep patterns when a patient has been having difficulty sleeping. It is also a medicine that could be taken before an operation or a medical test.

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

How is Temazepam Oral Solution used?
The pharmaceutical form of Temazepam 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.

This medicine contains 10 mg of temazepam in each 5 ml.

Temazepam can be habit-forming. Long-term use of this medicine is NOT recommended.

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
- a doctor may advise patients to take this only when necessary.

Before surgery or a test:
- the usual dose is 10ml to 20ml, half to one hour before a surgery or test
- Patients must ensure that they have someone to take them home after the procedure.
Older people and people with disease of the blood vessels
The usual dose is 2.5 ml to 7.5 ml each day before going to bed.

Children
For sleeping problems:
• This medicine should NOT be used to help children sleep.

Before surgery or a test:
• The usual dose is 0.5 ml per kilogram of body weight before surgery or a test.
• A doctor will work out the correct dose for a child.

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 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 licenced indications.

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

For the full list of all side effects reported with Temazepam 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 was Temazepam Oral Solution approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of Temazepam 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 Oral Solution?
A risk management plan (RMP) has been developed to ensure that Temazepam 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 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 Oral Solution
A Marketing Authorisation for Temazepam Oral Solution (PL 43659/0023) was granted in the UK on 29 January 2019.

Following a change of ownership procedure this license was granted to Kinedexe UK Limited (PL 44710/0034) on 21 March 2019.

The full PAR for Temazepam Oral Solution follows this summary.

This summary was last updated in March 2019.
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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 Primegen Limited a Marketing Authorisation for the medicinal product Temazepam 10mg/5ml Oral Solution (PL 43659/0023) on 29 January 2019.

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.

Temazepam has a similar pharmacological action to Oxazepam and Diazepam, which is central nervous system sedation, anxiolysis and muscle relaxation. Animal studies show anticonvulsant activity. These effects are likely to be due to potentiation of gamma-aminobutyric acid (GABA) although other neurotransmitters may also be affected. Evidence suggests a close molecular association between the sites and action for GABA and the benzodiazepines.

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.

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 type at all sites responsible for the manufacturing and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application, and these are satisfactory.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Temazepam 10mg/5ml Oral Solution outweigh the risks and a Marketing Authorisation was granted.

The license for Temazepam 10mg/5ml Oral Solution was originally authorised to Primegen Limited (PL 43659/0023) on 29 January 2019. Following a change of ownership procedure this license was granted to Kinedexe UK Limited (PL 44710/0034) on 21 March 2019.
II QUALITY ASPECTS

II.1 Introduction
Each 5 ml of Temazepam 10mg/5ml Oral Solution contains 10mg of temazepam, as active substance. Other ingredients consist of the pharmaceutical excipients ethanol, propylene glycol (E1520), peppermint oil, burnt sugar (caramel (E150), trometamol, citric acid monohydrate (E330), patent blue sodium salt (E131), glycerol (E422) and purified water.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of the colouring agents patent blue sodium salt and caramel (E150) which are controlled to suitable in-house specifications and peppermint oil, ethanol and glycerol which comply with the British Pharmacopoeia monograph. 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.

This product does not contain or consist of genetically modified organisms (GMO).

The finished product is packed into a 300 ml amber glass bottle with high density polyethylene (HDPE)/low density polyethylene (LDPE) child resistant closure with a tamper evident band. The bottle is supplied with a 15ml dosing cup.

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:

![Temazepam Structure](image)

Molecular formula: $C_{16}H_{13}ClN_{2}O_{2}$
Molecular weight: 300.7 g/mol
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 a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, temazepam, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.
II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe and efficacious oral solution containing 10mg of temazepam per 5ml of solution.

A satisfactory account of the pharmaceutical development has been provided.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Process validation has been completed for 2 commercial scale batches, and the applicant has committed to carry out process validation on a third batch.

Finished Product Specification
The proposed finished product specification is acceptable. The 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 18 months for unopened bottle with the storage conditions ‘Do not store above 25°C’ and ‘Keep the bottle tightly closed’. Once the bottle is opened the medicine should be used within one month.

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
Gamma-aminobutyric acid (GABA) is an amino acid that exerts a fast, inhibitory neurotransmission in the central nervous system. GABA_A receptors are of a huge diversity and are functionally linked to benzodiazepine receptors, GABA_A receptors are pentameric membrane proteins that operate as GABA-gated Cl– channels. They are assembled from several families of subunits, of which at least 19 occur in the CNS. However, the vast majority of receptors appear to be associations of two α-subunits, two β-subunits, and a single γ-subunit, which comprise a central ion channel. The majority of them contain a benzodiazepine-binding site located at the interface of the γ2-subunit and the respective α-subunit (α1, α2, α3, or α5). Sedative and anterograde amnesic effects of benzodiazepines were mainly attributed to α1-containing GABA_A receptor subtypes, anxiolytic action to the α2-containing receptors, anticonvulsant
activity partially, but not fully, to the α₁-containing receptors, and muscle relaxant effect largely to the α₂-containing receptors.

As a consequence of the enhancement of GABA’s inhibitory activity caused by benzodiazepines, the brain’s output of excitatory neurotransmitters is reduced. Such excitatory neurotransmitters are necessary for normal alertness, memory, muscle tone and co-ordination, emotional responses, endocrine gland secretions, heart rate and blood pressure control and a host of other functions, all of which may be impaired by benzodiazepines. Other benzodiazepine receptors, not linked to GABA, are present in the kidney, colon, blood cells and adrenal cortex and these may also be affected by some benzodiazepines. These direct and indirect actions are responsible for the well-known adverse effects of dosage with benzodiazepines.

The activity of the benzodiazepines can be largely explained by the GABA_A receptor activation model. The GABA_A receptor has been described as a pentameric polypeptide that forms a macromolecular complex, gating hyperpolarising inward chloride currents. Apart from the sites binding endogenous GABA, high affinity binding sites have been demonstrated for the benzodiazepines. Binding of the benzodiazepines to the GABA-benzodiazepine receptor complex modulates the opening of the Cl-channel, enhancing the rate of Cl- influx. The sedative and hypnotic properties of the benzodiazepines are thought to result from their action on the thalamocortical neuronal network, but other sites also seem to be involved in antianxiety and ‘anticonvulsant benzodiazepine action.

GABA is a major neurotransmitter in the suprachiasmatic nuclei (SCN), and recent data suggest that benzodiazepines might influence the circadian rhythmicity and sleep-wake cycle by acting directly on the SCN neurons. The alteration of the endogenous rhythmicity in the SCN by benzodiazepines is presumably a result of the facilitation of the inhibitions produced by endogenous GABA. A study was performed to investigate the effects of muscimol on benzodiazepine receptor binding related to the hypnotic activity of nine benzodiazepines (including temazepam). There was no correlation between the basal receptor binding affinities of the drugs tested and their hypnotic potencies, whereas the benzodiazepine receptor agonists whose receptor bindings are strongly modulated by muscimol possess potent hypnotic activity. These results indicate that benzodiazepine receptors that couple to GABA receptors are involved in the hypnotic activity of the benzodiazepines.

A study investigated the effect of muscimol on the inhibition of ^3^H-flunitrazepam binding by benzodiazepines and CL 218,872, their hypnotic potencies, and sleep time induced by the HD50 (median hypnotic dose) of the agents in mice. The rank order of the percent increase in the inhibitory potency induced by muscimol was flurazepam (77.6%) > clobazam > chlordiazepoxide > diazepam > temazepam > CL 218,872 > clonazepam > oxazepam > nitrazepam (13.6%). Five benzodiazepines (diazepam, flurazepam, temazepam, clobazam, and chlordiazepoxide) showed hypnotic activity (HD50: 207 ± 16.9, 173.2 ± 3.6, 228.7 ± 13.4, 336.0 ± 29.6, and 164.6 ± 7.2 mg/kg, ip, respectively). In an inclined screen test in mice, temazepam was relatively highly active (similar to diazepam and nitrazepam), but it was slightly less effective than diazepam or nitrazepam in inducing sedation and muscle relaxation in cats. Tests of anticonvulsant activity in mice showed it to be of similar potency to diazepam. In other animal screening tests, orally administered temazepam was slightly less potent than diazepam in reducing aggressive behaviour in monkeys and in depressing conditioned avoidance behaviour in rats.

In a study in dogs designed to measure changes in coronary and systemic haemodynamics resulting from conditioned anxiety (aversion stimulus), temazepam (1 mg/kg orally) prevented the anxiety-induced increases in heart rate, cardiac output and left ventricular work seen in untreated animals. Temazepam administered to rats 10 mg/kg i.p. depressed the striatal contents of met-enkephalin and leu-enkephalin by 60% and 35% respectively. The changes were most pronounced 30 minutes after the treatment. In the hypothalamus, temazepam produced a short-lasting elevation of met-enkephalin content (225% of the control value). The pattern of changes produced by temazepam resembles that as of
diazepam. This suggests that enkephalins participate in the pharmacological effects of benzodiazepine ataractics on the CNS.

Diazepam and its metabolites (1.8 and 3.0 mg/kg) and clorazepate (2.6 and 4.3 mg/kg) were given to monkeys by i.p. injection. Hydroxylation of diazepam (temazepam and oxazepam) led to a loss of, or a considerable reduction in, behavioural activity, whereas activity was preserved, though modified, by demethylation (nordiazepam). It was not possible to establish change in behaviour at specific time intervals after clorazepate, but combined performance data revealed an effect. The maximum mean plasma concentrations of diazepam, temazepam, oxazepam and clorazepate were observed at 0.5 h, and the maximum mean plasma concentration of nordiazepam was observed at 1 h. It is suggested that differences in the effects of closely related benzodiazepines may not be due solely to their plasma pharmacokinetic properties but may arise from differences in their intrinsic activity.

Adult male Wistar rats were administered temazepam (0.5, 1, and 3 mg/kg IV) with plasma concentrations of corticotropin (ACTH) and vasopressin (AVP) measured. Temazepam blunted the stressor exposure-induced secretion of ACTH in a dose-dependent manner. Concurrently, and also in a dose-dependent manner temazepam enhanced the intra-PVN release of AVP, known to originate from magnocellular neurons of the hypothalamic neurohypophyseal system. Furthermore, temazepam did not affect the in vitro secretion of ACTH from the adenohypophyseal cells. Results suggest that temazepam modulates the central nervous regulation of the HPA axis by altering intra-PVN AVP release. An increasingly released AVP of magnocellular origin seems to provide a negative tonus on ACTH secretion most probably via inhibiting the release of ACTH secretagogues from the median eminence into hypophyseal portal blood.

Male Sprague-Dawley rats, weighing 175 - 200 g were determined to be dependent on pentobarbital following 12 days of continuous, i.p. infusion of pentobarbital using an escalating drug infusion schedule. On day 13 (substitution phase) the pentobarbital was replaced with temazepam, midazolam or vehicle and the rats were infused for an additional 24 hours. This was followed on Day 14 (withdrawal phase) by a 24-hr saline infusion period. Rats were observed for changes in overt behaviour and alterations of body weight during both day 13 and Day 14. Temazepam, in doses of 32.5, 65 and 130 mg/kg/24 hr, was demonstrated to substitute for pentobarbital and provided dose-dependent suppression of overt behavioural signs indicative of withdrawal. Temazepam also suppressed the weight loss typically observed during withdrawal. Substitution of saline for temazepam resulted in an increased incidence of withdrawal signs and an approximate 10% decline in body weight. Midazolam, in doses of 60 and 120 mg/kg/24 hr, also substituted for pentobarbital and suppressed both overt behaviour and weight loss. Following saline substitution on Day 14, a mild withdrawal syndrome was evident although body weight was noted to remain near control values. From the results of study, it was concluded that both temazepam and midazolam may be substituted for pentobarbital in dependent rats and, therefore, there is an indication that these drugs may possess a liability for the production of physical dependence. Acute IV injections of temazepam were examined for the ability to impair the performance of young (3 – 4 month-old), mature (12 – 15 month-old) and old (28 – 30 month old) male Fischer 344 rats in the step-down task relative to vehicle-injected controls. The effect of temazepam on the passive-avoidance response could be characterised as a U-shaped function of age. The performance of the mature rat was not significantly impaired by an IV injection of temazepam between 18 and 320 μg/kg. Temazepam was more effective in impairing the performance of the young and old rat. The brain levels of temazepam after a single iv injection of 18 μg/kg in mature and senescent rats, and 32 μg/kg in young rats were measured over a 2-hour time period. The brain of the mature rat was exposed to less temazepam between 0 and 120 minutes than the brain of the old rat. Therefore, the increased sensitivity of the senescent rat relative to the mature rat may in part be due to changes in the pharmacokinetics of temazepam. However, the inability of temazepam (between 18 and 320 μg/kg) to impair the performance of mature rats in the passive-avoidance task suggests that pharmacodynamic changes may be involved in the decreased sensitivity of mature rats relative to young and senescent rats.
Temazepam was administered chronically by the intraperitoneal route in rats, the stimulating action and tolerance to the anxiolytic effects developed rapidly but was accompanied with an only slight decrease in the anticonvulsant effect.

Adverse consequences were reported in rats when temazepam was co-administered with buprenorphine. The behaviour of mice treated with magnesium and benzodiazepine/GABA<sub>δ</sub> receptor ligands, in the elevated plus maze was examined. The anxiolytic-like effect of magnesium (20 mg/kg) was antagonised by flumazenil (10 mg/kg) while combined treatment with the non-effective doses of magnesium (10 mg/kg) and benzodiazepines (diazepam (0.5 mg/kg) or chlordiazepoxide (2 mg/kg)) produced synergistic interaction (increased time in open arms and number of open arm entries) in this test. The data indicate that benzodiazepine receptors are involved in the anxiolytic-like effects of magnesium. Interactions between benzodiazepines like diazepam and oxazepam, and the narcotic analgesics, morphine and methadone, were evaluated on locomotor activity and in the tail-flick and hot-plate tests for analgesia in the mouse. The dose-related stimulation of locomotor activity by morphine was reduced by diazepam and oxazepam at doses which alone had no effect on locomotor activity. However, only oxazepam reduced the dose-related stimulation of locomotor activity by methadone. The observed decreases produced by diazepam and oxazepam were comparable in magnitude to those produced by naloxone. Stimulation of locomotor activity by d-amphetamine was not affected by either diazepam or oxazepam. Dose-response curves for locomotor activity were also determined with morphine and methadone administered intraventricularly. As before, diazepam and naloxone given i.p. decreased the stimulation of locomotor activity produced by morphine, but only naloxone affected methadone-stimulated locomotor activity. Neither diazepam, oxazepam nor naloxone reduced the brain or plasma levels of 3H-morphine or 3H-methadone. These results demonstrate that prominent interactions occur between members of the benzodiazepine and narcotic analgesic classes; these interactions are dependent upon both the specific combination of drugs administered and upon the test procedure.

Interaction of ethanol with benzodiazepines in rats can lead to enhanced therapeutic anxiolytic, sedative and hypnotic effects but can also augment unwanted effects such as drowsiness, confusion, amnesia and impaired coordination.

A study was performed, using in-vivo microdialysis, to assess the effects of the benzodiazepines (oxazepam or temazepam) on the selective serotonin (5-HT) reuptake inhibitors (SSRIs) (paroxetine)-induced 5-HT increase in the hippocampus of freely moving guinea-pigs. It was found that the acute systemic administration of paroxetine increased extracellular 5-HT levels. Pre-administration of oxazepam or temazepam significantly diminished the paroxetine-induced elevation of extracellular 5-HT levels (from 350% to 200% of baseline). It was concluded that benzodiazepines attenuate the ability of SSRIs to elevate hippocampal 5-HT levels. Thus, co-administration of benzodiazepines might affect the therapeutic efficacy of SSRI treatment.

β-adrenoreceptor antagonists potentiate the anti-aggressive action of benzodiazepines when given in doses which by themselves do not suppress aggression.

In rats, the withdrawal syndrome resulting from chronic administration of diazepam, chlordiazepoxide, clonazepam and temazepam was characterised by audiogenic seizures, hypermotility and weight loss. Administration of the non-selective NO synthase inhibitors N-nitroL-arginine (L-NOARG) and N-nitro-L-arginine methyl ester hydrochloride (L-NAME) significantly attenuated the withdrawal syndrome (i.e., pentetrazole-induced seizures) in diazepam-dependent mice. L-NOARG significantly suppressed hypermotility in clonazepam-dependent rats and inhibited the decrease in body weight observed after 12 h of withdrawal in chlordiazepoxide- and clonazepam-dependent rats. Moreover, a clear propensity of L-NOARG to protect benzodiazepine-dependent rats against audiogenic seizures was observed. These findings suggest that the cGMP/NO system may participate in causing the signs of benzodiazepine withdrawal.
Interaction studies between different injectable benzodiazepines and vecuronium, a non-depolarizing neuromuscular blocking drug, were performed in the rat in vivo sciatic nerve-tibialis anterior muscle preparation. A significant antagonism of a steady state depression of the twitch height induced by vecuronium was observed during approximately 10 min after IV injection of temazepam containing organic solvent in the formulation. This antagonism is mainly due to propylene glycol, the main organic solvent for the poorly water-soluble benzodiazepines. After the initial antagonism, a potentiation of the vecuronium-induced depression occurred with some of these benzodiazepines (diazepam, desmethyldiazepam, temazepam and lormetazepam).

Duration of recumbency in short-term anaesthesia in adult horses was significantly prolonged when temazepam was administered with xylazine and ketamine. All horses remained recumbent longer when temazepam was included in the anaesthetic regimen. The increase in recumbency time may be due to the anxiolytic effects of temazepam.

III.3 Pharmacokinetics

Temazepam is well absorbed- approximately 100% in man and dog, and over 80% in mouse and rat. The enterohepatic circulation of radioactive material after administering [14C] temazepam was evaluated in rats connected in pairs by bile duct-duodenum cannulae. Mean total recovery of the administered radioactivity was 92.2%. Based on the amount remaining in the donor rat (gastrointestinal tract and faeces), 81.7% of the dose was absorbed by the donor. The total amount recovered from the recipient, 69.4% of original dose (85.1% of donor's absorbed dose), represented the amount excreted in the donor's bile. Similarly, 54.1% of the original dose (77.9% of the transferred biliary excretion from donor) was reabsorbed by the recipient, and the biliary excretion from this animal (45.9% original dose) accounted for 86% of the amount reabsorbed.

In a whole body autoradiographic study in mice, temazepam was distributed to most body tissues, especially the central nervous system. In vitro, temazepam was 76% bound to bovine serum albumin. The metabolic pathways of temazepam involve conjugation of the hydroxyl group, loss of the N-methyl, and either conjugation of the desmethyl derivative or demethylation of the O-conjugate. All four compounds may be further metabolised to unidentified metabolites.

In the mouse, the N-desmethyl metabolite and its conjugate occurred in high concentrations, and only trace concentrations of the parent drug and its conjugate were found. In the rat, free parent drug and free N-desmethyl metabolite occurred in relatively high concentrations. Their conjugates were either not present or present in trace amounts. In the dog, the highest concentration was found for the conjugate of the parent drug, followed by a relatively high concentration of the N-desmethyl metabolite and its conjugate. The parent drug occurred in very low concentrations only.

The metabolic pathway of diazepam in horses in comparison with rats. Temazepam was produced in the greatest quantities, followed by nordiazepam in both horses and rats. Production of oxazepam was low in both species. Species differences existed for p-hydroxydiazepam production: in horses, the production of p-hydroxydiazepam was low, and horses had a lower Vmax/Km compared with rats. This indicates that horses had a lower ability to metabolize diazepam as compared with rats. In rats, it was reported that CYP3A2 was involved in diazepam metabolism and was responsible for temazepam production and oxazepam produced from nordiazepam. Study results showed temazepam as the major diazepam metabolite produced from microsomal reactions in horse liver, but horses produced drastically less p-hydroxydiazepam as compared with rats. Furthermore, CYP3A was a major contributor from the CYP subfamily of temazepam production.

Excretion patterns of temazepam show considerable interspecies variation. In man 80% of the dose was excreted in the urine and 12% in the faeces, whereas in the rat 15% was excreted in the urine and 78% in the faeces. The mouse and dog seemed to be between these extremes, with 37% in the urine and 50-60% in the faeces. In the rat, where most of the excreted drug was found in the faeces, the excretion was
mainly biliary and not related to unabsorbed drug. Total recovery was 90% or higher in all four species. In the rat, where biliary excretion was measured, the sum of biliary plus urinary excretion was used for estimating the adsorption. In the mouse, dog and man indirect methods were used. The excretion of temazepam and its N-desmethyl metabolite, oxazepam, and their respective O-conjugates was examined following a single intravenous dose of [14C] temazepam to two groups of bile fistula rats, with and without bile replenishment to the animals via duodenal cannulae. Elimination of the radioactive dose was rapid during 0 - 8 hr, with a half-life of ~1 hr. Approximately 85 - 90% of the administered radioactivity was recovered in the bile: ~1% as free temazepam, 3% as oxazepam, and ~10% as their O-conjugates. Results of this study confirmed the biliary route as the major excretion pathway of temazepam in the rat.

Diazepam was administered at a dose of 10 mg intramuscularly to four standard-bred mares. Diazepam urinary concentrations were found to be less than 6 ng/mL. Nordiazepam was found to be mainly in its glucuronide-conjugated form and was measured out to a collection time of 53-55 h. Oxazepam and temazepam were entirely conjugated, and their urinary concentrations were measured out to collection times of 121 h and 77-79 h, respectively. Diazepam and nordiazepam were measured in equine post administration serum out to collection times of 6 and 54 hours, respectively. Oxazepam and temazepam were not detected in post administration serum.

Temazepam induced a dose-dependent and reversible increase of dimethadione/trimethadione ratios in plasma of the rat, and dose-related shortening of hexobarbital-induced sleeping time in the mouse.

III.4 Toxicology

In single-dose toxicity studies, LD50 for the oral route was about 800 to 1900 mg/kg in mice and 2000 to 8000 mg/kg in rats. By the intraperitoneal route the LD50 was about 500 to 1000 mg/kg in mice and about 600 mg/kg in rats. In dogs the oral LD50 was 3620 mg/kg. Thus, like other benzodiazepine drugs, temazepam has a relatively low order of acute toxicity. No deviations from normal were recorded in a number of physiological, biochemical and haematological parameters in the dog, rat and monkey, following treatment with doses of 40 - 100 mg/kg/day, for periods of up to 6 months.

In studies up to 2 years in rats receiving temazepam 10 to 250 mg/kg/day orally; up to 1 year in dogs receiving 10 to 200 mg/kg/day somnolence or sedation, decreased bodyweight gain, enlarged livers and kidneys and some haematological changes (decreased hematocrit, 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 20 mg/kg/day.

In a perinatal-postnatal study in rats, 60 mg/kg/day orally resulted in increasing nursing mortality. Teratology studies in rats demonstrated increased foetal resorptions at doses of 30 and 120 mg/kg in one study and increased occurrence of rudimentary ribs, which are considered skeletal variants, in a second study at doses of 240 mg/kg or higher. In rabbits, occasional abnormalities such as exencephaly and fusion or asymmetry of ribs were reported without dose relationship. Although these abnormalities were not found in the concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg or higher, there was an increased incidence of the 13th rib variant when compared to the incidence in concurrent and historical controls.

Male and female rats were given temazepam up to 90 mg/kg/day for several weeks before mating, a small increase in pup mortality was reported 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 240 mg/kg or higher and 40 mg/kg or higher, respectively.
Temazepam contains no structural alerts for mutagenicity, and all of the elements of its chemical structure are replicated in oxazepam and temazepam. Consequently, read across has been used in relation to genotoxicity. Oxazepam was not mutagenic in any strains of *S. typhimurium*, nor did it induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These *in vitro* tests were performed with and without S9 metabolic activation. An *in vivo* peripheral blood micronucleus test performed on B6C3F mice was also negative. Diazepam was negative for bacterial mutagenicity and for *in vitro* chromosomal aberrations and sister chromatid exchange. In rats administered one dose of 1 mmol/kg or 15 doses 0.2 mmol/kg temazepam orally there were no statistically significant changes of viscometric parameters indicative of liver DNA fragmentation. Doses tested in rats were 100 to more than 5000 times higher than human doses. In a 78-week study in mice there was no significant increase in the incidence of benign hepatocellular adenomas observed for male or female mice. In a 104-week study in rats there were no significant increase in the incidence of tumours was observed in male or female rats. No liver adenoma was reported.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

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

Bioequivalence

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 also provided clinical overview with comparison of the formulations used in the studies underlying quoted publications and interchangeability of the proposed product with the existing temazepam products.
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 provided the breakdown of compositions of the existing oral solutions and the proposed products. The only important difference appears to be presence of sorbitol in the marketed products. The company argues that the differences due absence of sorbitol would not affect the safety and efficacy to any significant extent. The clinical studies underlying the publications have not been conducted using the currently UK marketed temazepam oral solutions.

The body of evidence for efficacy and safety of temazepam as an active substance (in the proposed doses and for the proposed indication) comes from studies with various immediate release formulations including capsules, tablets, suspensions and solutions. The quoted publications, along with majority of what is known about temazepam indicate that the extent of absorption is of primary importance for its efficacy with all immediate release oral formulations. The rate of absorption has been reported to be of no importance or of slightly improved efficacy for the products with lower rates.

The safety of the immediate release oral formulations also does not seem to be adversely affected with either faster or slower absorption rates between the products. Since the proposed product does not contain sorbitol and the closest matching marketed temazepam products do, its absorption rate is expected to be either equal or slower than these marketed products, but it would be very unlikely any faster.

In conclusion, there are at present a variety of immediate release temazepam formulations available on the UK market which are all considered safe and efficacious. Comparing them to the proposed product, capsules and tablets are expected to have slower and the solutions containing sorbitol similar or faster rate of absorption. In that respect the proposed product would fall within the PK brackets of what is currently approved and accepted as safe and efficacious temazepam product. It would, therefore, be extremely unlikely that there are any issues with either lack of efficacy or decrease in safety of the proposed product compared to the marketed products or the products used in the studies underlying publications quoted in support of safety and efficacy.

Absorption
Orally administered temazepam is well absorbed in man. Oral administration of 15 to 45 mg temazepam in man resulted in rapid absorption with significant blood levels achieved in 30 minutes and peak levels at 2-3 hours. In a multiple dose study, steady-state was approximated after the second daily dose with no evidence of accumulation after 5 consecutive daily doses of 30 mg temazepam. Steady-state plasma levels at 2.5 hours were 382 ± 192 ng / mL.

Distribution
The mean apparent distribution volume (Vd) for temazepam vary from 1.32 to 1.53 L/kg with a free fraction of about 3% (between 1.7 and 4.2%). Temazepam easily passes through the blood-brain barrier and its free plasma concentrations in humans have been found to correlate well with concentrations in the cerebrospinal fluid. The drug is known to pass the placental barrier and has also been found in milk during lactation. In study involving healthy human subjects; after administration of a single oral dose, the Vd was estimated to be about 57 L.

In another study involving 12 young volunteers; following administration of a single oral dose of 10 mg temazepam, the Vd was reported to be 2.2 ± 1.4 (mean ± standard deviation) L / Kg.
Metabolism
Temazepam was found to have minimal (8%) first-pass metabolism. There were no active metabolites formed and the only significant metabolite present in blood was the O-conjugate. Drug levels in blood declined in a biphasic manner with a short half-life ranging from 0.4 to 0.6 hours and a terminal half-life from 3.5 to 18 hours (mean 9 hours). The inactive O-conjugate metabolite was formed with a half-life of 10 hours and excreted with a half-life of approximately 2 hours. Thus, O-conjugation is the rate limiting step in the bio disposition.

Metabolic pathways
The metabolic pathways of temazepam are illustrated in Figure 1. They involved conjugation of the hydroxyl group, loss of the N-methyl, and either conjugation of the desmethyl derivative or demethylation of the O-conjugate. All four compounds may be further metabolized to unidentified metabolites. In man, the four compounds shown account for more than 80% of the radioactivity present in blood, and close to 100% of the radioactivity present in urine. It therefore was highly unlikely that an additional major metabolite would be present in man. In man, parent drug and its conjugate occurred at high concentrations, and only traces of the N-desmethyl metabolite and its conjugate were found.

Figure 1

Elimination
Twenty-four hours after a single oral dose of temazepam, approximately 80% - 90% of the drug was recovered in urine, primarily as the O-conjugate. Total recovery from feces and urine in single- and multiple-dose studies was approximately 95%, with only 3-13% of the radioactivity detectable in feces. Less than 1% of the dose was excreted as unchanged drug or N-desmethyl temazepam.
In a study involving 12 healthy subjects; following administration of a single oral dose of 10 mg temazepam, clearance and terminal half-life were reported to be $113.7 \pm 80.5 \text{ mL/h/kg}$ and $7.7 \pm 3.0 \text{ hrs (mean \pm standard deviation)}$.

**Pharmacokinetics in Elderly**

In a double-blind randomised controlled study, old (n = 10; age range 67-77 years) and young (n = 10; age range 21-31 years) female volunteers were randomised to receive 20 mg temazepam and pharmacokinetic parameters were analysed. Rate of absorption of temazepam was significantly faster in the older subjects (mean age 72.9 years); their mean tmax was 0.3 (range 0.12 - 0.71) h, compared with 1.75 (0.90 – 3.43) h in the younger subjects. Mean T½el were 14.0 hours in the old and 11.5 hours in the young subjects (calculated from mean log plasma concentration time curves for each group). The mean plasma concentrations 11 hours after dosing were 82 μg/L in the old and 102 μg/L in the young and at 18 hours 68 μg/L in each group.

Plasma temazepam concentrations rose by about 50% and 113% respectively after first and seventh of seven regular night-time doses of temazepam 20 mg studied in 58 elderly patients.

Pharmacokinetic profile of temazepam was evaluated in older patients (both male and female) after single and multiple doses. In single dose study, 10 patients (aged 72 - 98 years) received a single oral dose of 10 mg temazepam (soft gelatin capsule) after overnight fasting following which blood samples were collected at regular intervals. In chronic dose study, which began one week after single dose study, 13 patients (aged 70 - 98 years) received one soft gelatin capsule of temazepam 10 mg on 14 consecutive nights. Blood samples were taken before the first dose (Day 1) and subsequently at the same time on Days 3, 5, 8, 12 and 15. After a single 10 mg oral dose, mean $C_{\text{max}}$ was 306 ng/ml with a median time of 0.75 hour to $C_{\text{max}}$. Temazepam was eliminated from plasma in a biexponential manner, with a distribution phase (mean $t_{1/2\alpha}=0.7$ hour) predominating for 3 hours. The drug had a mean $T_{1/2\text{el}}$ of 8.7 hour. In a chronic dose, the plasma concentrations on Days 3, 5, 8, 12 and 15 were not significantly different from each other, presented rapid attainment of steady state levels and the lack of drug accumulation. Significantly higher plasma levels were attained in females (mean 92 ng/ml) than males (mean 34 ng/ml) patients.

In another study involving 09 elderly patients; following administration of a single oral dose of 10 mg temazepam, clearance, $T_{1/2\text{el}}$ and Vd were reported to be $88.8 \pm 20.8 \text{ mL/h/kg}$, $9.2 \pm 4.1 \text{ hours}$ and $1.2 \pm 0.4 \text{ L / Kg (mean \pm standard deviation)}$.

**Pharmacokinetics in Chronic Users**

Pharmacokinetic parameters following administration of temazepam to chronic users in comparison with controls is tabulated below:

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Temazepam Patients (N = 13)</th>
<th>Temazepam Controls (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Concentration $[C_{(p=0)}]$ ng / mL</td>
<td>113 ± 134</td>
<td>0</td>
</tr>
<tr>
<td>$C_{\text{max}}$ ng / mL</td>
<td>441 ±211</td>
<td>377 ± 203</td>
</tr>
<tr>
<td>$AUC_{(0-8\text{hour})}$ ng.hr / mL</td>
<td>118 ± 58</td>
<td>86 ± 46</td>
</tr>
</tbody>
</table>
Pharmacokinetics in Patients with Hepatic Impairment
Pharmacokinetics of temazepam was evaluated in 16 healthy subjects aged 18-92 years and in 15 cirrhotic patients aged 32-79 years, to ascertain the effect of ageing and liver disease. After an overnight fasting, subjects ingested 20 mg of temazepam soft gelatin capsule. Blood samples were collected at pre-dose and up to an interval of 48.0 hours post dose. Temazepam was rapidly absorbed in all the subjects, peak levels were attained within 45 minutes and were followed by a biphasic decline. The mean T½el in the control group was 15.5 hours. There was no correlation of age neither with apparent oral clearance nor with T½el. The mean pharmacokinetic parameters of the cirrhotic group did not differ from the control group. No correlation was noted between the severity of the disease and the clearance of the drug. Based on PK profile, temazepam may prove to be a useful hypnotic-sedative for patients with liver disease.

Food Effect
No effect of food on absorption has been determined.

Pharmacokinetics in Patients with Renal Impairment
Pharmacokinetics of temazepam 30 mg were evaluated in 11 patients with end-stage renal disease (age 18-65 years). Mean Cₘₐₓ, tₘₐₓ, T½el, AUC at 12 hour and AUC at 24 hours were reported to be 223 ng/mL, 2.03 hours, 10.8 hours, 1354 ng.hr / mL and 1943 ng.hr/mL respectively. Although mean Tₘₚₜ values were in the range reported for normal subjects, the mean Cₘₐₓ in patients (223 ng / mL) was lower than values reported for normal subjects (371 to 754 ng/mL) which may be likely explained by differences in distribution and decreased protein binding.

Pharmacokinetics in Surgical Patients
Pharmacokinetics of temazepam were studied in 09 male surgical patients (age: 28-57 years) who received single 40 mg doses, 4 hours prior to minor surgical procedures. Temazepam was rapidly absorbed, with peak concentrations (1480 ng / mL) achieved within one hour post administration. Mean Vd, total clearance and terminal T½el values were 1.13 L/kg, 1.55 ml/min/kg and 8.16 hrs respectively. The rapid absorption of temazepam was observed in this study.

Pharmacokinetic Interactions
Disulfiram
Disulfiram inhibits the metabolism of benzodiazepines.

Zidovudine
No Data Available in public domain

Antiepileptic drugs
Phenytoin
No Data Available in public domain

Antibiotics
Effect of pretreatment with a 4 day course of ciprofloxacin (500 mg twice daily) on the pharmacokinetics of a single oral dose of temazepam (10 mg) was investigated in 12 healthy young and 09 elderly patients in a crossover trial. Temazepam clearance was lower in the elderly than in the young, but this difference was not statistically significant concluding that ciprofloxacin had no significant effect on temazepam pharmacokinetics in either age group.

No significant pharmacokinetic interaction is reported between erythromycin 500 mg and temazepam 20 mg as studied in healthy volunteers.

Oestrogen
The effects of low-dose oestrogen oral contraceptives on the elimination of temazepam were studied in two parallel crossover studies of 20 women. Women taking oral contraceptives steroids containing low doses of oestrogen and women matched for age, weight, and cigarette smoking received single oral doses of temazepam (30 mg). Kinetics were determined as plasma concentrations during 48 hours after dosing. Oral contraceptives decreased the AUC and the elimination rate constants of temazepam (Table 8). Thus, low-dose oestrogen oral contraceptives may accelerate the metabolism of temazepam.

<p>| Table 8: Temazepam kinetics in control subjects and users of oral contraceptives (Stoehr GP et al. 1984) |
|---------------------------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Oestrogen</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak plasma concentration (ng/ml)</td>
<td>688 ± 256</td>
<td>561 ± 193</td>
<td>ns</td>
</tr>
<tr>
<td>Time of peak concentration (h)</td>
<td>1.75 ± 1.08</td>
<td>1.55 ± 0.44</td>
<td>ns</td>
</tr>
<tr>
<td>Vd (l/kg)</td>
<td>1.06 ± 0.31</td>
<td>1.21 ± 0.49</td>
<td>ns</td>
</tr>
<tr>
<td>Kd (h⁻¹)</td>
<td>0.052 ± 0.001</td>
<td>0.087 ± 0.002</td>
<td>p &lt; 0.005</td>
</tr>
<tr>
<td>Elimination t1/2</td>
<td>13.3</td>
<td>8.0</td>
<td>-</td>
</tr>
<tr>
<td>Total AUC (ng/ml × h)</td>
<td>9600 ± 3775</td>
<td>5840 ± 3780</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>CL (ml/min/kg)</td>
<td>0.87</td>
<td>1.41</td>
<td>-</td>
</tr>
</tbody>
</table>

Itraconazole
Possible pharmacokinetic interaction between itraconazole and temazepam was evaluated in a double-blind, randomized crossover study in healthy subjects. Ten subjects received placebo or 200 mg itraconazole a day orally for 4 days. The challenge dose of 20 mg of temazepam was given on the fourth day following which blood samples were collected up to 24 hours. Both the AUC₀-2₄ and AUC₀-∞ values of temazepam were significantly higher when administered after itraconazole as compared to placebo. None of the values for Cₘₐₓ, tₘₐₓ or t½ of temazepam differed significantly between itraconazole and placebo pretreatments.

Aluminum hydroxide
Concurrent administration of aluminum hydroxide gel does not have any effect on absorption of temazepam as studied in patients with end-stage renal disease undergoing dialysis.

Cimetidine
The possible kinetic interaction of the hypnotic temazepam and the H₂-receptor antagonist cimetidine was evaluated. Nine healthy male and female volunteers received a 30-mg oral dose of temazepam on two occasions in random sequence, separated by at least 1 week. On one occasion, temazepam was given in the otherwise drug-free state; on the other, temazepam was given with concurrent administration of cimetidine, 300 mg every 6 hours. Mean pharmacokinetic parameters for temazepam in control versus cimetidine trials were: peak plasma concentration, 560 versus 498 ng/mL; time of peak concentration, 2.0 versus 2.1 h after the dose; volume of distribution, 1.30 versus 1.39 L/kg; elimination half-life, 9.9 versus 11.4 hours; total clearance, 1.59 versus 1.60 mL/min/kg; free fraction of temazepam in plasma, 4.1 versus 3.8% unbound. Cimetidine reduced the metabolic clearance of the benzodiazepines that are biotransformed by oxidative mechanisms. Temazepam, transformed by conjugation, appeared unaffected by the coadministration of cimetidine.

IV.3  Pharmacodynamics
The exact mechanism of action of benzodiazepines has not yet been elucidated; however, benzodiazepines appear to work through several mechanisms. Benzodiazepines presumably exert their effects by binding to specific receptors at several sites within the central nervous system (CNS) either by
potentiating the effects of synaptic or pre-synaptic inhibition mediated by gamma-aminobutyric acid or by directly affecting the action potential generating mechanisms. The activity of the benzodiazepines can be largely explained by the GABAa receptor activation model. The GABAa receptor has been described as a pentameric polypeptide that forms a macromolecular complex, gating hyperpolarising inward chloride currents. Apart from the sites binding endogenous GABA, high affinity binding sites have been demonstrated for the benzodiazepines. Binding of the benzodiazepines to the GABA-benzodiazepine receptor complex modulates the opening of the chloride channel, enhancing the rate of chloride influx. The sedative and hypnotic properties of the benzodiazepines are thought to result from their action on the thalamocortical neuronal network, but other sites also seem to be involved in antianxiety and anticonvulsant benzodiazepine action.

In sleep laboratory studies, the effect of temazepam 15 mg and 30 mg, was compared to placebo over a two week period. There was a linear dose-response improvement in total sleep time and sleep latency with significant drug-placebo differences occurring for total sleep time at both doses, and for sleep latency at the higher dose. Rapid eye movement (REM) sleep was essentially unchanged and slow wave sleep was decreased. Blood pressure regulation was studied in 12 healthy elderly subjects after double-blind randomised administration of placebo, 15 mg and 30 mg temazepam at 10.00 hours and 22.00 hours. Supine and standing heart rate (HR) and blood pressure (BP) were measured after daytime administration and supine measurements were obtained during sleep. Temazepam caused a fall in systolic blood pressure (SBP) and an increase in heart rate after morning administration. These changes were greater in the standing position and were dose-dependent; for standing BP and HR, after one hour of drug administration, there was a 7 mm Hg fall and 6 beats / minute increase after 15 mg temazepam and a 10 mm Hg fall and 8 beats / minute increase after 30 mg temazepam. Temazepam magnified the fall in SBP and increase in HR that occurred with standing. Temazepam enhanced the fall in SBP that occurred during sleep.

Cardiovascular orthostatic reflexes were studied at night in 12 healthy male subjects after administration of two soft gelatin capsules each containing placebo or 10 mg temazepam at 21.30 hours. The changes in heart rate, blood pressure and forearm blood flow on consecutive 5 min exposures to lower body negative pressure (suction) at 30, 40 and 50 mm Hg were measured before and then 1.5 and 9.5 hour after giving doses of 10 or 20 mg temazepam in a placebo-controlled double-blind cross-over study. Pre-suction resting values were not affected by temazepam, but 1.5 hour after giving the capsules there were significant differences in the responses to suction between the placebo and 20 mg temazepam experiments: the tachycardia after 20 mg temazepam was about one-third greater and the forearm vasoconstriction was about 50% less. The effect of the 10 mg dose was equivocal.

Effect of temazepam (20 mg) on sleep latency and body temperature was studied in 20 healthy adult volunteers when administered at 14.00 hours. From 08.00 to 20.30 hours, subjects lay down in bed, and foot and rectal (Tc) temperatures were recorded. Sleep onset latency (SOL) was measured using 20 minutes multiple sleep latency tests performed hourly from 11.00 to 20.00 hours, during which time heart rate was recorded. Temazepam significantly reduced Tc and SOL while increased heat loss. Importantly, there was a temporal relationship between minimum SOL and the maximum rate of decline in Tc for temazepam. Results conclude that both core temperature and sleep propensity exhibit comparable changes after administration of temazepam. The temporal association between changes in core temperature and sleep propensity supports the suggestion that thermoregulatory effects may mediate changes in sleepiness.

A study evaluated the effects of temazepam (20 mg) on daytime sleep, subsequent levels of nocturnal alertness / sleepiness and performance in a laboratory simulation of acute night shift. For evaluating alertness, sleepiness and performance, maintenance of wakefulness test (MWT), multiple sleep latency test (MSLT) and two pencil and paper tests: digit symbol substitution test (DSST) and deux barrages test (DBT) were used. All tests were administered four times at 2-hour intervals during the nighttime after
daytime sleep. Results showed that the ability to maintain wakefulness (MWT) and to perform some visuo-attentive tasks were substantially maintained during the night. On the other hand, sleep tendency (MSLT) linearly increased during the night. Temazepam resulted as an effective diurnal hypnotic, increasing total sleep time with no residual detrimental effects on sleepiness and performance and with an increase in the ability to stay awake.

**Pharmacodynamic Interactions**

**Alcohol**

Because alcohol is so widely used as a social drug and benzodiazepines are so widely used as therapeutic agents, the number of persons who may be using both drugs concurrently is high. Despite this frequent concurrent use, interactions of major consequence are not common. Major interactions are pharmacodynamic, involving common actions of both drugs as sedatives. Excessive sedation from a combination of both drugs is a most important consideration when driving an automobile. However, it is well known that tolerance develops quickly to the sedative effects of benzodiazepines when used in anxiolytic doses. Also, one must balance the benefit from relief of anxiety versus possible impairment of function from oversedation. Abuse of benzodiazepines is almost exclusively among subjects who also abuse alcohol, doubtless due to the fact that the two drugs show cross-dependence. The clinical practice of avoiding use of benzodiazepines (or other sedative-hypnotics) in known alcoholics is sound and should avoid many potential problems.

The frequency and quantity of alcohol consumption is a major consideration in patients who need treatment with benzodiazepines. Alcohol affects the GABA-benzodiazepine-chloride ionophore complex and has an agonist-like action. Thus, additive interactions should be expected from combining alcohol with benzodiazepines. Furthermore, alcohol has clinically meaningful anxiolytic efficacy, and many anxious patients may take advantage of that fact. Therefore, co-administration of alcohol and benzodiazepines is to be expected in an anxious patient receiving benzodiazepines who does not totally abstain from alcohol.

Concomitant use of alcohol with temazepam is not recommended as the sedative effects of temazepam are enhanced affecting the ability to drive or use machines.

A study was aimed to compare the morning-after effects of three dose levels of temazepam given with alcohol, was carried out in 18 healthy volunteers. Matched placebos were given for two days before and four days after the four nights on active drug and a standard dose of alcohol was given on all ten nights of the study. Objective measurements made on the mornings after days 2, 4, 6 and 10 were critical flicker fusion threshold (CFF), choice reaction time (CRT) and digit symbol substitution tasks (DSST). The administration of 10 or 20 mg temazepam with alcohol produced no significant change in any of these measurements. 30 mg produced no change in DSST and although there was some impairment of CRT at this dose, it was not statistically significant. The combination of 30 mg temazepam and alcohol significantly depressed CFF following four nights on these drugs.

The effects of temazepam 20 mg and temazepam 20 mg plus whisky 100 ml on sleep and performance were investigated in 5 healthy volunteers in comparison with placebo. In the sleep laboratory, after temazepam there was a trend for reduction of sleep latency, stage wake and stage 1 sleep, and for an increase in REM sleep. The addition of alcohol to the regimen reduced the sleep latency still further, and diminished REM sleep. In subjective assessments, temazepam received the highest score for quality of sleep and the temazepam/alcohol combination that for ease of falling asleep. None of the observed changes reached statistical significance. No morning hangover, as measured by effects on wakefulness, performance or affective state, was seen after the combined treatment. Its effect on blood pressure was negligible. It was concluded that the combined administration of temazepam and alcohol in the doses used here does not result in excessive additive, but in moderate pharmacological effects.

**CNS depressants**
The concurrent use of other CNS depressants such as general anaesthetics, antipsychotics, monoamine oxidase inhibitors, anxiolytics/sedatives, sedative antihistamines, antidepressants and hypnotics, lofexidine and nabilone should be avoided as it will result in an enhancement of the central depressive effect. In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychotic dependence.

Side effects may be more evident if temazepam is administered along with hydantoins or barbiturates.

Antihypertensive
No Data Available in public domain

Clozapine
Severe adverse reactions such as cardiac arrest, respiratory arrest, and sudden death when clozapine and benzodiazepines are used concomitantly. A retrospective chart review was conducted at a 240-bed New York State mental health facility. Most patients in this facility have been diagnosed with refractory schizophrenia, resulting in high rates of clozapine use. It was concluded that precautionary measures that can be used when initiating concomitant clozapine and benzodiazepines therapy include slow titration of clozapine, blood pressure monitoring, and/or nightly pulse oximeter measurements.

Disulfiram
Disulfiram enhances sedative effects of temazepam and also causes its toxicity.

As the test product of Temazepam contains 0.5g/5ml of ethanol, the amount of alcohol that would be ingested with the intended level of use of the medication, which can cause interactions with other medications (disulfiram reaction), is discussed here. Ethanol can be found as a solvent in numerous oral liquid formulations and OTC medicines such as cough and cold medicines, iron supplements as well as homeopathic preparations with the aim to improve drug solubility. Ethanol is present as an endogenous substance in the blood of man, probably produced in the intestinal tracts, at an average level of 1.5 mg/L. Disulfiram irreversibly inhibits acetaldehyde dehydrogenase. Intake of ethanol during disulfiram therapy will lead to accumulation of acetaldehyde, which is considered the main contributing factor to the disulfiram-alcohol reaction. Disulfiram-alcohol reactions often develop within 15 minutes after exposure to ethanol; symptoms usually peak within 30 minutes to 1 hour, and then gradually subside over the next few hours. Symptoms may be severe and life-threatening. The disulfiram-alcohol reaction is characterised by: Intense vasodilation of the face and neck causing flushing, increased body temperature, sweating, nausea, vomiting, pruritis, urticaria, anxiety, dizziness, headache, blurred vision, dyspnoea, palpitations and hyperventilation.

In severe cases tachycardia, hypotension, respiratory depression, chest pain, QT prolongation, ST depression, arrhythmias, coma and convulsions may occur. Rare complications include hypertension, bronchospasm and methaemoglobinaemia.

In an article by Koff et al a case was reported where Disulfiram reaction occurred in 46 year old man after ingesting approximately 1 oz. of a proprietary cough preparation (NyQuil) containing 25 % alcohol content with his usual morning dose of disulfiram (0.25 gm.). One hour later, while at work, he experienced severe Disulfiram reaction effects. Twenty-four hours after admission and treatment he became asymptomatic. Author suggested that increased awareness of the presence and relatively large quantity of alcohol in some of these preparations may aid in the prevention of disulfiram-alcohol reactions in otherwise abstinent patients. Clear and prominent labelling of the alcohol content of these products may also be helpful in avoiding untoward reactions. The minimal dose of alcohol necessary to evoke a reaction in the disulfiram treated patient is somewhat controversial, although it has been
suggested that as little as 7 ml of alcohol may cause typical reactions. Thus, in disguised forms, alcohol could represent a serious hazard for patients receiving disulfiram.

The Disulfiram reaction is generally proportional to the amounts of disulfiram and alcohol ingested. Mild effects may occur at blood alcohol concentrations of 5 to 10 mg/100 mL. At 50 mg/100 mL, effects usually are fully developed. When the concentration reaches 125 to 150 mg/100 mL, unconsciousness may occur.

Theoretical blood alcohol concentration (BAC) rise from a single dose can be estimated using a standard formula. The equation below assumes complete and instantaneous absorption of ethanol orally ingested ethanol.

\[
\text{BAC (g/L)} \approx \frac{\text{Blood ethanol (mg/100mL or mg/dL)}}{\text{Volume of distribution (L/kg)xWeight (kg)}}
\]

BAC = Blood Alcohol Concentration (g/L) is a common way of expressing ethanol (alcohol) concentrations that avoids the use of decimal points. Alternatively g/L can be used. As there are many ways of expressing BAC it is sometimes advisable to express the amount in both mg/100mL and g/L to achieve clarity.

Volume of distribution (L/kg) can be assumed to be 0.6. (EMEA “Questions and Answers on Ethanol in the context of the revision of the guideline on ‘Excipients in the label and package leaflet of medicinal products for human use” (CPMP/463/00), 2014).

The test product contains 0.5 g of ethanol per 5 ml. Taking the average weight as 60 kg, the value of BAC was calculated by using the above equation for the minimum dose that is 5 ml and the BAC would be 0.013 g/dL which is equivalent to 1.3 mg/100ml. The same is calculated for the maximum dose that is 20 ml and BAC was found to be 0.05 g/dL or 5.55 mg/100ml.

As Mild Disulfiram reaction effects may occur at blood alcohol concentrations of 5 to 10 mg/100 mL, we can interpret that the amount of ethanol that would be ingested with the intended level of use of the medication would produce blood alcohol (ethanol) concentration (BAC) within the acceptable limits. As per the current EC ‘Guideline on excipients in the label and package leaflet’, as the ethanol concentration in the oral drug is 100 mg – 3 g per dose appropriate information has to be listed in the SmPC and PIL. (EMEA “Questions and Answers on Ethanol in the context of the revision of the guideline on ‘Excipients in the label and package leaflet of medicinal products for human use” (CPMP/463/00), 2014)

Doapminergics
No Data Available in public domain

Muscle relaxants
No Data Available in public domain

Antibiotics
Effect of pretreatment with a 4 day course of ciprofloxacin (500 mg twice daily) on the pharmacodynamics of a single oral dose of temazepam (10 mg) was investigated in 12 healthy young and nine elderly patients in a crossover trial and ciprofloxacin had no significant effect on temazepam pharmacodynamics in either age group.
IV.4 Clinical efficacy

Sleep Disorders/Sleep Disturbances/Insomnia/Hypnotic effects

Temazepam was evaluated in insomniac patient population under sleep laboratory conditions as a short-term (26-night) and a long-term (54-night) treatment with doses of 15 mg and 30 mg respectively. Temazepam seemed to be both safe and effective at doses of 15 and 30 mg with up to 5 weeks of ingestion. Suppression of slow wave sleep was observed at the high doses. Rapid eye movement (REM), sleep time showed no significant changes across conditions in either study. No evidence was found for development of tolerance or rebound effects. Results concluded that temazepam is effective in prolonging and maintaining sleep at doses of 15 mg and 30 mg.

The effect of temazepam 10 mg and 20 mg on sleep was studied in healthy subjects using electroencephalography for sleep measures and analogue scales for subjective assessments of well-being and sleep quality. Effect on total sleep time was restricted to the night of ingestion. There was no change in total sleep time after temazepam (10 mg) but with 20 mg total sleep time was increased. Sleep onset latencies and awakenings were markedly reduced. Temazepam reduced the duration (min) of stage 0 and stage 1 sleep and the effect on stage 1 was seen during each two hourly interval of sleep. No effects were observed with stage 3, 3+4 and REM sleeps, except that the appearance of the first REM period was delayed with temazepam 20 mg. The subjects, as a group, reported improved sleep, but subjective assessments of well-being were not altered.

A series of randomized double-blind N-of-1 trials were conducted in general practices in the Netherlands for patients who were using temazepam regularly. Each patient received five pairs of treatments consisting of one week of temazepam (10 or 20 mg) and one week of the control intervention (placebo or 10 mg temazepam). Per pair, the sequence of treatments was randomised. Main outcome measures were: time to fall asleep and the individual main complaint. Twelve out of 15 patients completed their trial. In three patients there was no difference, in five a large difference, and in four a small difference in favour of temazepam. At follow-up, seven patients had stopped or reduced their temazepam use. The results regarding the efficacy of temazepam varied across patients. N-of-1 trials seem to be valuable in patients who are motivated to stop or reduce their temazepam use. It was demonstrated that temazepam may give patients additional confidence to discontinue regular hypnotic use.

Efficacy of nocturnal temazepam was assessed in patients with narcolepsy as measured by the Epworth Sleepiness Scale (ESS). Doses of temazepam ranged from 15 mg to 30 mg and were administered once nightly prior to bedtime for a minimum of one week. Baseline ESS and ESS at the highest tolerated temazepam dose were compared using a paired sample t-test. Out of the seven patients, six patients reported a decrease in daytime sleepiness on temazepam, with a mean change in ESS score of -5.1 points (range -10 to 1). The mean ESS score was 16.4 prior to initiation of temazepam and was 11.3 on the highest tolerated dose. Four patients who had frequent cataplexy at the time of initiation of temazepam reported a subjective improvement in frequency of cataplexy, three of whom had improvement in their subjective sleepiness. Six of the 7 patients elected to remain on the temazepam.

Equivalent efficacy of two strengths of temazepam 7.5 mg and 15 mg was evaluated in treatment of transient insomnia in a prospective, randomized, double-blind, parallel group, uncontrolled, multicenter trial. Healthy male and female subjects with previous but not current complaints of transient insomnia were enrolled. Transient insomnia was induced in the sleep laboratory by means of the ‘first night’ effect and by implementing a 2-h phase advance. One hundred and forty-one patients were enrolled of which 131 completed the study; 65 received the 7.5 mg dose and 66 received the 15 mg dose. No statistically significant differences between doses were detected for Latency to persistent sleep (LPS) or total sleep time (TST) or any other objective (PSG) measure of sleep. The 90% confidence intervals calculated for LPS and TST fell well within the predefined clinical equivalence intervals. The mean number of sleep
interruptions was also not significantly different between treatment groups. Results concluded that 7.5 mg and 15 mg doses of temazepam were equally effective for the treatment of transient insomnia.

Efficacy of 7.5 mg of temazepam was evaluated in the sleep laboratory in 8 elderly insomniacs, using a 14-night protocol (4 placebo-baseline nights, 7 drug nights and 3 placebo-withdrawal nights). With short-term administration of temazepam (nights 5 - 7), total wake time compared to baseline decreased by 45 minutes, with a sleep latency of 15.9 min and wake time after sleep onset of 84.4 mins. Night-by-night evaluation of this short-term drug period showed that temazepam, 7.5 mg, was most effective on night 7, with a total wake time of 95.1 min. With continued drug administration (nights 9-11), total wake time remained decreased by 14.0 % compared to baseline which was not so significant. Both Sleep latency and wake time after sleep onset showed a similar pattern of a continued but non-significant decrease compared to baseline. For the drug withdrawal condition (all nights of placebo-withdrawal combined), total wake time returned approximately to baseline. Separate assessment of each of the three withdrawal nights (nights 12, 13, & 14) resulted in values for total wake time which were similar to baseline on each night. Results concluded that temazepam 7.5 mg is effective in elderly subjects with short-term use.

Efficacy of temazepam 20 mg prepared as a liquid in a soft gelatin capsule was evaluated in female population who were about to seek medication for stress-induced insomnia in randomised, double-blind, controlled study. Temazepam reduced sleep latency and stage I nocturnal waking time whereas increased total sleep time. The significant reductions in shifts to sleep stages 1 and 2 and significant reduction in time spent in stages 0 + 1 suggest more restful sleep. The sleep "architecture" (including REM / NREM cycling, total SWS and REM time) was relatively undisturbed. Study confirmed that temazepam is significantly effective in improving the sleep pattern and therefore be considered by the clinician as a first-line hypnotic for short-term use in stressed patients.

Pre-medication for Minor Surgical Procedures
In a double-blind randomised study; sixty patients scheduled for day case surgery were allocated into two groups, one group received temazepam 20 mg or 30 mg orally 1 hour before surgery while the second group received a placebo with an objective to evaluate the potential of temazepam as a premedicant in day case surgery. Temazepam 10 mg capsules and placebo capsules of identical appearance were used; subjects who weighed less than 60 kg received 20 mg and those who weighed more than 60 kg received 30 mg. Subjective assessments of sedation and anxiety using 100 mm visual linear analogues, were performed by the patients immediately before premedication and before the induction of anaesthesia 1 hour later. Results of study indicated that temazepam, while producing sedation and a reduction in anxiety, did not cause any discernible adverse effects during the recovery period. Recovery from anaesthesia was not prolonged and subjective assessments of sedation were similar to the placebo group. Indeed the use of the drug was followed by a reduction in the incidence of minor induction problems such as coughing, laryngospasm and excessive salivation.

A double-blind trial of temazepam pre-medication for day surgical cases was undertaken. Sixty patients were randomly allocated to three groups receiving either 10 or 20 mg temazepam or a placebo. Before induction of anesthesia, temazepam 20 mg group scored significantly less anxiety than the other two. The pre-operative-admission score demonstrated that the anxiety level of the placebo group increased whilst patients awaited surgery, whereas that of the two temazepam groups decreased over this period. These differences were no longer apparent at 1 and 2 hours into the postoperative period. Effective anxiolysis was recorded in the groups that received temazepam 10 or 20 mg and there was no prolongation of delayed recovery times as measured by memory test cards. Results of this study demonstrated the effective use of temazepam in a day surgery unit.

A comparative efficacy, double-blind, randomized, cross-over trial was performed to compare the sedative effect of two doses (0.3 mg/kg and 0.5 mg/kg) of temazepam elixir 10 mg / 5 mL for the
behaviour management of paediatric dental patients. Twenty-two children aged 2-5 years classified as ASA Class I and II (American Society of Anesthesiologists Classification) were enrolled in the study. All treatment sessions were videotaped and rated independently by three paediatric dentists. No significant differences were demonstrated between the two doses of temazepam with regard to crying, sleep, movement or overall behaviour, irrespective of which dose had been used first. The overall behaviour ratings for the 0.5 mg / kg group ranged between ‘good’ to ‘excellent’ (19 patients) and ‘fair’ (03 patients) and for the 0.3 mg / kg group between ‘good’ to ‘excellent’ (16 patients), ‘fair’ (03 patients) and ‘abandoned’ (03 patients). Results show that a dose of 0.5 mg / kg provides satisfactory sedation for young uncooperative children undergoing dental treatment.

Relationship between plasma concentration and clinical effect of temazepam soft gelatin capsule after a dose of 40 mg was evaluated in 14 patients receiving oral premedication before minor surgery. The plasma concentrations of temazepam and its sedative, anxiolytic and amnesic effects were measured for 24 hours. Following administration, absorption was rapid and peak concentrations of 375 ng / mL reached at 49 minutes after dosing. Clinical effects were evident at 30 minutes and persisted for about 4 hours. The decline in plasma concentration was biphasic with a distribution half-life of 1.24 hours and mean T½el of 7.5 hrs. Maximum effects of temazepam on memory, sedation and anxiety occurred after 01 hour when most of the patients were asleep. The effects persisted throughout the observation period and although some recovery occurred, memory and sedation were still significantly different from normal after 4 hours. A relationship between plasma concentration and effect was observed; concentrations above 300 ng / ml produced measurable changes in tests of mental function. Higher temazepam concentrations produced drowsiness, reduced anxiety and impaired memory. Patients recovered fully from the effects of temazepam after 24 hours. Results suggested that temazepam showed a prolongation of clinical effects for more than 3.5 hours after oral temazepam 40 mg and the same dose is reliable and effective as premedication before surgery.

IV.5 Clinical safety
Overview of Clinical Safety Data
After administration of Temazepam 30 mg tablets in insomnia patients, no changes were noted during the final physical and ophthalmological examinations. No clinically or statistically significant changes in the patient’s oral temperatures, respiratory rates, systolic and diastolic blood pressures (supine and standing) or radial pulse rates (supine and standing) were observed. All pre and post-treatment clinical laboratory values were within ranges acceptable.

Safety and tolerability of two strengths of temazepam 7.5 mg and 15 mg was evaluated in patients with transient insomnia. No adverse events were reported in the 7.5 mg dose while in the 15 mg dose group, 3 subjects reported four adverse events (AEs), all of which were mild in intensity. Three of the four events appeared to be sedation-related: fatigue, sensation of heaviness and somnolence. Eye irritation was also reported. Changes from baseline in blood pressure, pulse rate, and respiratory rate were clinically insignificant and were similar for the 7.5 mg and 15 mg dose groups. Differences between treatment groups in adverse events rates and vital sign changes were not statistically significant. Results confirm that Temazepam in strengths of 7.5 mg and 15 mg is safe and well tolerated in patients with transient insomnia.

Safety of temazepam (dose range 7.5 mg to 30 mg) was evaluated in 20 older adults with chronic insomnia over the 8-week course of treatment. Incidence of adverse effects was infrequent and severity was mild in intensity and decreased over the course of treatment. The commonly reported events included residual day time sedation, diarrhoea, nausea, vomiting, excitement / agitation, headache, confusion, impaired coordination, syncope / dizziness, shortness of breath, constipation and nightmares. Results concluded that temazepam is a safe hypnotic for use by older adults over an 8-week treatment period.
Of 795 patients receiving temazepam in clinical studies, the most common adverse effects were those affecting the CNS specifically drowsiness (17%), dizziness (7%), and lethargy (5%). Confusion, euphoria, ataxia and a "relaxed feeling" were reported less frequently. A dose-related cumulative "hangover" effect occurred after repeated doses of temazepam for several nights in elderly patients.

In a large post marketing surveillance report which included more than 12,000 general practice patients treated with temazepam in doses up to 30 mg at night for 2 weeks and more than 3000 patients treated for 3 months, approximately 10% of the patients experienced adverse effects. In addition to the CNS effects, gastrointestinal complaints, sleep disturbances and headaches were also reported. Among the rarely reported side effects were weakness, lack of concentration, loss of equilibrium and falling.

No serious evidence of toxicity was reported in laboratory investigations following administration of temazepam in psychiatric patients in mean dose of 13.2 mg.

Rebound insomnia refers to the sleep disturbance that follows discontinuation of hypnotic drugs and is characterized by a worsening of sleep beyond the baseline levels and is thought to be associated with short and intermediate half-life hypnotics. Temazepam caused significant rebound insomnia after 14 nights of a 30 mg dose but not a 7.5 or 15 mg dose. After longer term use (several weeks) of temazepam, both the 15 mg and 30 mg dose in sleep laboratory studies showed a trend towards increased sleep latency, increased wake time and decreased total sleep time over baseline values upon abrupt discontinuation of therapy.

Undesirable Effects, Safety and Tolerability

Amnesia
During a study of pharmacodynamic and pharmacokinetic relationship of temazepam in 25 patients receiving spinal anesthesia, anxiety was measured before and after premedication; the two scores were correlated but the change in anxiety after premedication did not correlate with either the plasma or the cerebrospinal fluid concentrations. Amnesic effects were measured before and after premedication and decline in short-term memory ability was moderately well correlated with both the plasma and the cerebrospinal fluid levels. With temazepam, the variation in sedative and anxiolytic effects between subjects is explained not by differences in pharmacokinetics but rather by differences in the pharmacodynamic response. Because sedative and anxiolytic effects are poorly correlated, but the amnesic effect is well correlated with temazepam concentrations, different sites of action for these effects are suggested.

In a placebo-controlled study in 55 outpatients most reported adverse effects occurred with a similar frequency in placebo-treated and drug-treated groups with the exceptions of a few instances of drowsiness, lethargy, vertigo, and severe depression or nightmares, which did appear to be drug-related.

Behavioral adverse effects
In a double-blind safety and hypnotic efficacy study of temazepam in insomniac outpatients, patients reported 83 definite drug related side-effects of which 43 were attributed to temazepam and 40 to placebo. Those reported most frequently were (in order): headache, drowsiness, lethargy, dry mouth, restlessness, hangover, nervousness, nightmares, vertigo, irritability and constipation. Of these side-
effects, drowsiness, lethargy and vertigo tended to occur more frequently in the temazepam treatment group, whereas dry mouth, nervousness, and restlessness tended to occur more frequently in the placebo treatment group. The incidences of headache, hangover, dizziness, nightmares, irritability and constipation occurred with approximately the same frequency in both the temazepam and placebo groups. Severe side-effects reported were depression (temazepam 2), lethargy (temazepam 1), nightmares (temazepam 1), headache (placebo 4 and temazepam 3), irritability (temazepam 1), restlessness (temazepam 1), burning eyes (placebo 1), and “felt funny” (temazepam 1). In individual patients other reactions such as paraesthesia, tachycardia, panic.

A number of studies have demonstrated that temazepam also possesses less hangover effects when compared to either nitrazepam or triazolam.

Another benzodiazepine side effect of significant clinical importance is rebound insomnia, it has been noted frequently following an abrupt withdrawal from certain benzodiazepines used at hypnotic doses. Withdrawal from temazepam (30 mg for 4 to 5 weeks) did not result in statistically significant differences in sleep latency, total sleep and wake time over the baseline in a trial with a limited number of patients.

Table 3: summary of the side effects of temazepam (in percent incidence):

<table>
<thead>
<tr>
<th>Side effects in 10 057 patients treated with 40–60 mg of temazepam for 2 weeks and 8043 for 3 months (from [67])</th>
<th>2 weeks (%)</th>
<th>3 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hangover</td>
<td>1069 (10.9)</td>
<td>490 (6.3)</td>
</tr>
<tr>
<td>No hangover</td>
<td>8731 (89.1)</td>
<td>7239 (93.7)</td>
</tr>
<tr>
<td>All</td>
<td>9800 (100)</td>
<td>7729 (100)</td>
</tr>
<tr>
<td>Missing data</td>
<td>257</td>
<td>314</td>
</tr>
<tr>
<td>Total patients</td>
<td>10 057</td>
<td>8043</td>
</tr>
<tr>
<td>Headache</td>
<td>135 (1.3)</td>
<td>71 (0.9)</td>
</tr>
<tr>
<td>Nausea, vomiting, epigastric pain, etc.</td>
<td>114 (1.1)</td>
<td>52 (0.6)</td>
</tr>
<tr>
<td>Dizzy, giddy, unsteady, etc.</td>
<td>93 (0.9)</td>
<td>35 (0.4)</td>
</tr>
<tr>
<td>Morning drowsiness</td>
<td>74 (0.7)</td>
<td>37 (0.5)</td>
</tr>
<tr>
<td>Vivid dreams, nightmares</td>
<td>60 (0.6)</td>
<td>19 (0.2)</td>
</tr>
<tr>
<td>Morning confusion</td>
<td>45 (0.5)</td>
<td>21 (0.3)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>34 (0.3)</td>
<td>22 (0.3)</td>
</tr>
<tr>
<td>Generally unwell</td>
<td>16 (0.2)</td>
<td>6 (&lt;0.1)</td>
</tr>
<tr>
<td>Restless sleep</td>
<td>15 (0.1)</td>
<td>3</td>
</tr>
<tr>
<td>Palpitation</td>
<td>13 (0.1)</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>12 (0.1)</td>
<td>15 (0.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11 (0.1)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>Bad taste in mouth</td>
<td>11 (0.1)</td>
<td>1</td>
</tr>
<tr>
<td>Difficulty in swallowing capsule</td>
<td>10 (0.1)</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (&lt;0.1)</td>
<td>—</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Patients with adverse reactions</td>
<td>593 (5.9)</td>
<td>287 (3.6)</td>
</tr>
<tr>
<td>Patients with no adverse reactions</td>
<td>9460 (94.1)</td>
<td>7752 (96.4)</td>
</tr>
<tr>
<td>All</td>
<td>10 053 (100)</td>
<td>8039 (100)</td>
</tr>
<tr>
<td>Missing data</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total patients</td>
<td>10 057</td>
<td>8043</td>
</tr>
</tbody>
</table>

Dependence: Benzodiazepines are often used in the medical management of anxiety, insomnia, seizures and muscle spasm, benzodiazepines lead to significant complications after continuous use. These complications include tolerance, addiction, dependence and abuse.

Withdrawal
A study was aimed to assess the effect of withdrawal from the long-term use of temazepam, zopiclone or zolpidem (benzodiazepines) as hypnotics drugs on cognitive performance. Ninety-two adults (age ≥55 years) with primary insomnia and who were long-term daily users of above mentioned benzodiazepines, volunteered to participate in a 1-month medically supported withdrawal attempt from benzodiazepines use, with a subsequent 5-month follow-up. Withdrawal was based on plasma benzodiazepines measurements at baseline, at 1 month and during subsequent regular clinical appointments. Attention and psychomotor performance. Eighty-nine (97 %) participants (59 women, 30 men) were followed-up for a maximum of 6 months. During the follow-up period, changes in reaction times and errors did not differ between short-term withdrawers (no residual benzodiazepines at 1 month; N = 69), non-withdrawers (residual benzodiazepines at 1 month; N = 20) or long-term withdrawers (N = 34). It was concluded that long-term use of benzodiazepines as hypnotic drugs by older adults is related to prolonged impairment of attentional and psychomotor cognitive functioning that persists for at least 6 months after withdrawal.

31 of 36 elderly mainly confused hospitalized patients (69–98 years) taking temazepam 10 mg for more than one month completed a double blind randomised placebo controlled trial comparing abrupt versus gradual withdrawal of temazepam. Hours of sleep were recorded for all patients during a 7 day baseline period while taking temazepam 10 mg. Then the abrupt withdrawal (AW) group (n=15) received placebo for 10 nights and the gradual withdrawal (GW) group (n=16) received temazepam 5 mg for the first 4 nights, 2 mg for the next 4 nights and placebo for the last 2 nights. There was no significant difference in mean hours of nightly sleep during the baseline period between the AW group (5.9 ± 1.1 SD) and GW group (5.8 ±1.1 SD) and between the baseline and withdrawal periods in each group (withdrawal periods, AW 5.6 ± 1.2, GW 5.6 ±1.0). There was no rebound insomnia when temazepam was withdrawn either abruptly or gradually in long-term hospitalised elderly patients and may not be effective as a long-term hypnotic.

Safety in Elderly
No unwanted effects occurred after administration of Temazepam 20 mg capsules in elderly subjects with mean age 72.9 years.

Safety of temazepam 15 mg was compared with 50 mg diphenhydramine and placebo in elderly individuals with insomnia in a comparative, randomized, placebo controlled, crossover trial. Numbers of adverse events reported were similar after all treatments. Adverse effects that were reported more than once listed in table below. Adverse effects that were reported included a subject that experienced dizziness and loss of balance that resulted in falling (minor injuries sustained) after taking temazepam, a subject that stopped taking temazepam after 11 nights because of morning dizziness, and an individual that stopped taking temazepam after 13 nights because of gastrointestinal reflux. In the placebo arm, 3 subjects reported using rescue medication (their own hypnotic) because of extreme fatigue, discomfort, and/or anxiety due to lack of sleep on the placebo arm. Another individual experienced a stroke after 2 nights of temazepam; this was thought to be unrelated to study medication. All adverse effects were resolved by cessation of medication, except for the stroke and the bruising that occurred after the fall. Other adverse events reported and not mentioned in table include neck pain, stomach ache, cold symptoms, facial warmth, forgetfulness, reflux and forgetfulness. Results indicate that temazepam was safe and well tolerated in elderly patients with insomnia.

Safety of temazepam 7.5 mg was evaluated in the sleep laboratory in 8 elderly insomniacs. No major CNS and behavioral adverse effects reported such as daytime sedation, memory impairment or hyperexcitability (daytime anxiety) were reported. Reports of minor side effects were relatively infrequent and 03 subjects reported headache. In a single-dose trial in older patients with insomnia, neuropsychological testing was improved or unchanged at a low dose (15 mg) compared with baseline and placebo. However, with the standard dose (30 mg) the results of a serial learning task were impaired. In another trial enrolling a small sample of elderly patients with mild sleep apnoea, temazepam (15 to 30 mg / day) showed no worsening of the pre-existing respiratory distress index. Results of above mentioned studies suggest that temazepam is safe and well tolerated in elderly insomniacs.
**Contraindications**

Temazepam should not be used in following cases:

- Myasthenia gravis
- Known hypersensitivity to Benzodiazepines.
- Severe respiratory insufficiency.
- Sleep apnoea syndrome.
- Severe hepatic insufficiency.
- Phobic or obsessional state; chronic psychosis
- Mild anxiety states
- Acute narrow angle glaucoma
- As monotherapy in patients with depression or those with anxiety and depression (suicide may be precipitated in these patients).

The effects of temazepam on indices of circadian respiratory function, dyspnea, sleep quality, and sleepiness in patients with severe chronic obstructive pulmonary disease (COPD) and insomnia were studied. The primary objective of this study was therefore to examine whether prolonged usage of the benzodiazepine temazepam influences indices of breathing and gas exchange during sleep in patients with severe COPD who experience insomnia. Secondary objectives were to assess the effects of prolonged usage of temazepam on diurnal breathing, gas exchange, and dyspnea in patients with severe COPD and insomnia. In addition, sleep quality and diurnal sleepiness were examined in these patients.

All subjects were studied for three weeks in a double-blind, randomized, cross-over design. Subjects were randomized after the baseline measurements to use 10 mg temazepam or placebo once a day orally, both during one week, separated by a washout-period of one week. Subjects were instructed to take the study medication 30 min before they went to bed. In conclusion, in this preliminary study repeated doses of temazepam did not adversely affect nocturnal respiratory function in severe but stable normocapnic COPD patients without complications, but it did improve TST and sleep-onset latency. Furthermore, temazepam did not affect diurnal gas exchange, diurnal central respiratory centers, and subjective dyspnea. Temazepam can, not automatically be dismissed from patients with stable, normocapnic COPD who experience insomnia and consequently have a reduced quality of life, but it remains to be seen as a last resort when other, non-pharmacological remedies have failed.

**Warnings and Precautions**

Doses of 30 mg and above are more likely to cause hangover effects to persist into the following day than lower doses, particularly in patients unused to hypnotics and in the elderly. As with all compounds which have an effect on the CNS, patients should be advised not to consume alcohol whilst taking temazepam. An underlying cause for insomnia should be sought before deciding upon the use of benzodiazepines for symptomatic relief. Temazepam should be given with caution to patients with chronic pulmonary insufficiency or those with renal or hepatic dysfunction. Where Temazepam is used as a medication before surgical or investigative procedures, the patients should be accompanied home. Tolerance: Some loss of efficacy to the hypnotic effects of short acting benzodiazepines may develop after repeated use for a few weeks.

Psychiatric and 'paradoxical' reactions: reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioral effects are known to occur when using benzodiazepines. Should this occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly. Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Dependence potential and withdrawal symptoms: In general, the dependence potential of benzodiazepines is low, but this increases when high dosage is used, especially when given over long periods. This is particularly so in patients with a history of alcoholism, drug abuse or in patients with marked personality disorders. Regular monitoring of treatment in such patients is essential and routine repeat prescriptions should be avoided.
Treatment in all patients should be withdrawn gradually as symptoms such as depression, nervousness, rebound insomnia, irritability, sweating, headaches, dizziness, impaired concentration, tinnitus, loss of appetite, tremor, perceptual disturbances, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, orthostatic hypotension, photophobia, hyperacusis, muscle pain, extreme anxiety, tension, restlessness, confusion and diarrhoea have been reported following abrupt cessation of treatment with benzodiazepines in patients receiving even normal therapeutic doses for short periods of time. Abrupt withdrawal following excessive dosage may produce confusion, toxic psychosis, convulsions, derealisation, depersonalisation, tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations, epileptic seizures or a condition resembling delirium tremens. Broken sleep with vivid dreams may persist for some weeks after withdrawal. Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse. In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines. Extreme caution should be used in prescribing benzodiazepines in patients with personality disorders.

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction is advisable. In rare instances some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended. The use of temazepam may worsen hepatic encephalopathy; therefore, temazepam should be used with caution in patients with severe hepatic insufficiency and/or encephalopathy.

Pregnancy and Lactation
Insufficient data are available on temazepam to assess its safety during pregnancy and lactation.

Pregnancy.
The placental transfer of temazepam and fentanyl was studied in 37 women undergoing surgical termination of pregnancy between 12 and 17 weeks. The women received temazepam 10 mg, approximately 1 hour pre-operatively and fentanyl 2 mg/kg intravenously, at induction of anaesthesia. A single 2 ml fetal blood sample was taken from each anaesthetized subject using an ultrasound-guided trans-abdominal puncture at either 5, 10, 15 or 20 min after administration of fentanyl. A maternal blood sample was collected simultaneously and both were assayed for temazepam and fentanyl. Both drugs were detected in all fetal serum samples. In a study a drug concentration ratio was 0.38 for temazepam, which did not change between 60 and 120 min after oral administration to the mother. Overall F:M ratio for fentanyl was 1.87 for fentanyl, which increased from 1.42 at 5 min to 2.6 at 20 minutes. F:M ratio of fentanyl concentrations increased with time (r = 0.48, P < 0.003), whereas F:M ratio of temazepam concentrations did not change significantly with time, between 50 and 120 minutes after the drug was administered to the mother (r = 0.32, P = 0.06). F:M ratios changed with gestational age of the fetus for both drugs, increasing as gestational age increased in the case of temazepam (r = 0.47, P = 0.003) and decreasing in the case of fentanyl (r = 0.38, P = 0.02). These changes were explained by variation in uterine blood flow, trophoblast membrane thickness and feto-placental metabolism.

Lactation
Only very small amounts of temazepam were found in breast milk after administration of Temazepam (10 – 20 mg) as a bed time hypno-sedative to nursing mothers. Plasma levels reveal that even though bioavailability was high, the neonate would receive negligible amounts of temazepam.

Overdosage
Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria, mental confusion and nystagmus. Coma, hypotension, hypotonia and respiratory depression occasionally occur but are seldom serious if these drugs are taken alone. Coma usually lasts only a few hours but in elderly people it may be more protracted and cyclical. Benzodiazepine respiratory depressant effects are more serious in patients with
severe chronic respiratory disease. Benzodiazepines potentiate the effects of other CNS depressants, including alcohol.

Management
Efficacy of activated charcoal and gastric lavage in preventing the absorption of moclobemide, temazepam, and verapamil 30 min after drug ingestion was studied. Concomitant administration of 25 gm activated charcoal in the form of suspension 30 minutes after administration of 10 mg of temazepam decreased the AUC$_0$-$24$ and C$_{\text{max}}$ of the later by 45 % and 29 % respectively. It was concluded that the absorption of moclobemide, temazepam, and verapamil can be moderately reduced by activated charcoal given 30 minutes after drug ingestion, while gastric lavage seems to be less effective.

Effects on Ability to Drive and Use Machines
Actual driving performance in the morning has been somewhat less affected following a single night of 20 mg temazepam, than flurazepam (10 mg). Following temazepam, the weaving test (number of bollards hit) was no different from the placebo. The gap test ('passable' gaps hit in passing through), however, was affected in a manner similar to that of flurazepam, i.e. more passable gaps hit, without increases in speed, which suggests carelessness, rather than enhanced risk taking.

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:

<table>
<thead>
<tr>
<th>Safety in pregnancy</th>
<th>Insufficient data are available for safety in pregnancy is mentioned in section 4.6 of proposed SmPC. If temazepam is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia, and moderate respiratory depression, can be expected due to the pharmacological action of the product. Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors and risk groups</td>
<td>Risk factors included: Female in late phase of pregnancy or during labour Risk groups included: Neonate (new born) of female who received temazepam during the late phase of pregnancy,</td>
</tr>
</tbody>
</table>
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 compound. 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:
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)

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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</table>