

Lormetazepam 0.5 mg Tablets
Lormetazepam 1 mg Tablets

PL 17507/0131-2

UK Public Assessment Report

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Auden Mckenzie (Pharma Division) Ltd Marketing Authorisations (licences) for the medicinal products, Lormetazepam 0.5 mg and 1 mg Tablets (PL 17507/0131-2) on 09 January 2012. These are prescription-only medicines (POM).

The active ingredient, lormetazepam, belongs to a group of medicines called benzodiazepines. Lormetazepam is prescribed as a short-term therapy to help with sleeping difficulties which are significantly affecting normal daily life.

Based on the data submitted by Auden Mckenzie (Pharma Division) Ltd, Lormetazepam 0.5 mg and 1 mg Tablets were considered to be generic versions of the UK reference products, Lormetazepam Tablets 0.5 mg and 1 mg (PL 17225/0012-3, Genus Pharmaceuticals Holding Limited).

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Lormetazepam 0.5 mg and 1 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

Lormetazepam 0.5 mg Tablets
Lormetazepam 1 mg Tablets

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Auden Mckenzie (Pharma Division) Ltd Marketing Authorisations for the medicinal products, Lormetazepam 0.5 mg and 1 mg Tablets (PL 17507/0131-2) on 09 January 2012. These are prescription-only medicines (POM).

These are generic applications for Lormetazepam 0.5 mg and 1 mg Tablets, submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applications refer to the UK products, Lormetazepam Tablets 0.5 mg and 1 mg (PL 17225/0012-3), licensed to Genus Pharmaceuticals Holding Limited on 01 August 1999. The cross-referenced products were initially authorised to John Wyeth and Brother Limited (PL 00011/0068-9) on 27 July 1981; these licences underwent Change of Ownership (CoA) procedures to the current Genus Pharmaceuticals Holding Limited. The UK reference products have been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

Lormetazepam 0.5 mg and 1 mg Tablets are indicated for the short-term treatment of insomnia when it is disabling or subjecting the individual to extreme distress.

Lormetazepam is a benzodiazepine with anxiolytic, muscle relaxant, sedative and hypnotic properties. Clinical studies have shown minimal effects on REM sleep and on psychomotor performance on the day after treatment with lormetazepam. Lormetazepam is rapidly absorbed from the gastrointestinal tract and is metabolised by a simple one-step process to a pharmacologically inactive glucuronide. There are no major metabolites and little risk of accumulation. Lormetazepam has a terminal phase half-life of about 11 hours.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Lormetazepam 1 mg Tablets, to that of the reference product, Lormetazepam Tablets 1 mg (Genus Pharmaceuticals Holding Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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 manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The MHRA considers that the pharmacovigilance system described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

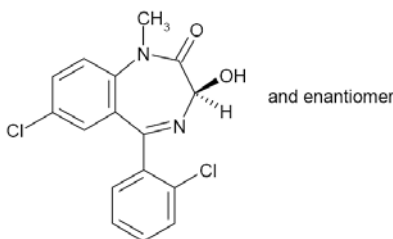
Lormetazepam

Nomenclature:

INN: Lormetazepam

Chemical name: (RS)-7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1-methyl-1,4-benzodiazepin-2-one

Structure:



Molecular formula: C₁₆H₁₂Cl₂N₂O₂

Molecular weight: 335.2 g/mol

CAS No: 848-75-9

Physical form: White crystalline powder

Solubility: Practically insoluble in water, soluble in ethanol (96%) and in methanol, freely soluble in chloroform

The active substance, lormetazepam, is the subject of a British Pharmacopoeia (BP) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer for testing the active substance.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.

MEDICINAL PRODUCT

Description and Composition

Lormetazepam 0.5 mg and 1 mg Tablets are presented as white, round, biconvex, tablets with “LMT 0.5”/“LMT 1” embossed on one side and plain on the other side. Each tablet contains 0.5 mg or 1 mg of the active ingredient, lormetazepam.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, talc and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective Ph. Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic, immediate-release, tablet formulations of lormetazepam 0.5 mg and 1 mg, bioequivalent to the reference products, Lormetazepam Tablets 0.5 mg and 1 mg (Genus Pharmaceuticals Holding Limited).

Comparative dissolution and impurity data were provided for batches of the test and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted on production scale batches and the results were satisfactory. The validation data demonstrate consistency of the manufacturing process.

Finished product specifications

Finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

Lormetazepam 0.5 mg and 1 mg Tablets are licensed for marketing in polyvinylchloride (PVC)-aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in a pack size of 30 tablets.

Satisfactory specifications and Certificates of Analysis for all packaging components have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 24 months. Storage instructions are 'Keep the blister in the outer carton in order to protect from light'. These medicinal products do not require any special temperature storage conditions.

Quality Overall Summary

A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is accepted. It supports the readability of the package leaflet. The labelling fulfils the statutory requirements for Braille.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Lormetazepam 0.5 mg and 1 mg Tablets from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10(1) of Directive 2001/83/EC, as amended, are for Lormetazepam 0.5 mg and 1 mg Tablets, products claiming to be generic versions of the UK reference products, Lormetazepam Tablets 0.5 mg and 1 mg (PL 17225/0012-3, Genus Pharmaceuticals Holding Limited).

No new non-clinical data have been supplied with these applications and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of these products from a non-clinical point of view.

CLINICAL ASSESSMENT

BACKGROUND

Lormetazepam is considered a hypnotic benzodiazepine and is indicated for moderate to severe insomnia. Lormetazepam is a short-acting benzodiazepine and is sometimes used in patients who have difficulty in maintaining sleep or falling asleep. Lormetazepam works by acting on receptors in the brain called GABA receptors. This causes the release of a neurotransmitter called GABA in the brain. As lormetazepam increases the activity of GABA in the brain, it increases its calming effect and results in sleepiness, a decrease in anxiety and relaxation of muscles.

INDICATIONS

Lormetazepam 0.5 mg and 1 mg Tablets are indicated for the short-term treatment of insomnia when it is disabling or subjecting the individual to extreme distress.

The indications are consistent with those for the reference products and are satisfactory.

POSODOLOGY AND METHOD OF ADMINISTRATION

The usual adult dose is 0.5 to 1.5 mg lormetazepam before retiring.

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of lormetazepam is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The clinical pharmacology of lormetazepam is well-known. With the exception of the bioequivalence studies, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics - Bioequivalence studies

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Lormetazepam 1 mg Tablets, to that of the reference product, Lormetazepam Tablets 1 mg (Genus Pharmaceuticals Holding Limited). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was an open-label, randomised, two-period, two-sequence, two-treatment, single-dose crossover bioequivalence study conducted in healthy adult human male subjects under fasting conditions. A single 1 mg dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 60.0 hours after administration of test or reference product. Plasma levels of lormetazepam were quantified by a validated LC/MS-MS method.

The primary pharmacokinetic parameters for this study were C_{max} , AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 80.00%-125.00%, for log-transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for lormetazepam.

Results:

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

Summary pharmacokinetic data for lormetazepam for a randomised, open-label, 2-way, single-dose crossover study; healthy subjects, dosed fasted; t=60 hours, washout period: 7 days

Pharmacokinetic Parameters (Units)	Ln- transformed Geometric Least Squares Mean			90% Confidence Interval (Parametric)	
	Test (T)	Test (R)	T/R %	Lower	Upper
	C_{max} (ng/mL)	1.9167	1.9426	97.44	93.96
AUC_{0-t} (ng.hr/mL)	4.2602	4.2478	101.25	96.42	106.31
$AUC_{0-\infty}$ (ng.hr/mL)	4.3180	4.2945	102.37	97.79	107.17

C_{max}	maximum plasma concentration
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent under fasting conditions, as the confidence intervals for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ for lormetazepam fall within the acceptance criteria ranges of 80.00-125.00%, in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Lormetazepam 0.5 mg Tablets. As Lormetazepam 0.5 and 1 mg Tablets meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 1 mg strength can be extrapolated to the 0.5 mg strength tablets.

EFFICACY

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate

bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of lormetazepam is well-established from its extensive use in clinical practice.

SAFETY

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of lormetazepam is well-known.

CLINICAL OVERVIEW

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those of the UK reference products and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSIONS

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Lormetazepam 0.5 mg and 1 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL

Bioequivalence has been demonstrated between the applicant's Lormetazepam 1 mg Tablets and the UK reference product, Lormetazepam Tablets 1 mg (Genus Pharmaceuticals Holding Limited).

As Lormetazepam 0.5 and 1 mg Tablets meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 1 mg strength were extrapolated to the 0.5 mg strength tablets, and omission of further bioequivalence studies on the lower strength can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs are consistent with those for the reference products and are satisfactory.

A mock-up PIL has been provided. The package leaflet is in line with the SmPCs and is satisfactory. 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 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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT- RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's Lormetazepam 0.5 mg and 1 mg Tablets are generic versions of the UK reference products, Lormetazepam 0.5 and 1 mg Tablets (Genus Pharmaceuticals Holding Limited). Extensive clinical experience with lormetazepam is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.

Lormetazepam 0.5 mg Tablets
Lormetazepam 1 mg Tablets

PL 17507/0131-2

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Marketing Authorisation applications on 17 February 2011.
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 23 February 2011.
- 3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 16 May 2011 and further information relating to the quality dossier on 09 May 2011, 06 July 2011 and 16 December 2011.
- 4 The applicant responded to the MHRA's requests, providing further information for the clinical sections on 29 June 2011 and further information for the quality sections on 29 June 2011, 18 November 2011 and 22 December 2011.
- 5 The applications were approved on 9 January 2012.

Lormetazepam 0.5 mg Tablets
Lormetazepam 1 mg Tablets

PL 17507/0131-2

STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Lormetazepam 0.5 mg and 1 mg Tablets (PL 17507/0131-2) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Lormetazepam 0.5 mg Tablets
Lormetazepam 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lormetazepam 0.5 mg: Each tablet contains 0.5 mg lormetazepam.
Lormetazepam 0.5 mg: Each tablet contains 83.125 mg of lactose.

Lormetazepam 1 mg: Each tablet contains 1 mg lormetazepam.
Lormetazepam 1 mg: Each tablet contains 166.25 mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Lormetazepam 0.5 mg Tablets are round, biconvex, white tablets, 6.5 mm in diameter with 'LMT 0.5' embossed on one side and plain on the other.

Lormetazepam 1 mg Tablets are round, biconvex, white tablets, 8.5 mm in diameter with 'LMT 1' embossed on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lormetazepam is indicated for the short term treatment of insomnia when it is disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest time possible. Generally, the duration of treatment varies from a few days to 2 weeks, with a maximum of 4 weeks including the tapering off process. Extension of the treatment period should not take place without re-evaluation of the need for continued therapy.

Since insomnia is often transient and intermittent, the prolonged administration of lormetazepam is generally unnecessary and is not recommended.

Treatment in all patients should be withdrawn gradually to minimise possible withdrawal symptoms (see Special warnings and precautions for use).

Dosage

Adults: 0.5mg to 1.5mg before retiring. Subsequently the initial dosage may be increased in individual cases if this proves necessary.

Elderly: The lower adult dose is preferable for elderly patients.

Children: Lormetazepam has not been evaluated for the treatment of children.

4.3 Contraindications

- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Hypersensitivity to benzodiazepines including Lormetazepam Tablets or their components.
- Myasthenia gravis
- Severe hepatic failure

4.4 Special warnings and precautions for use

Patients should be advised that since their tolerance for other CNS depressants will be diminished in the presence of lormetazepam, these substances should either be avoided or taken in reduced dosage. Lormetazepam may enhance the sedative effects of alcohol. Since this affects the ability to drive or use machinery, alcohol should be avoided while taking lormetazepam.

Lormetazepam is not intended for the primary treatment of psychotic illness or depressive disorders, and should not be used alone to treat depressed patients with associated insomnia. The use of benzodiazepines may have a disinhibiting effect and may release suicidal tendencies in depressed patients. Therefore, large quantities of lormetazepam should not be prescribed to these patients.

Pre-existing depression may emerge during benzodiazepine use.

The use of benzodiazepines may lead to physical and psychological dependence. The risk of dependence on lormetazepam is low when used at the recommended dose and duration, but increased with higher doses and longer term use. The risk of dependence is further increased in patients with a history of alcoholism or drug abuse or in patients with significant personality disorders. Therefore, use in individuals with a history of alcoholism or drug abuse should be avoided.

Dependence may lead to withdrawal symptoms, especially if treatment is discontinued abruptly. Therefore, **the drug should always be discontinued gradually.**

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating and the occurrence of "rebound" phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movement; vomiting; hallucinations; convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

It may be useful to inform the patient that treatment will be of limited duration and that it will be discontinued gradually. The patient should also be made aware of the possibility of "rebound" phenomena to minimise anxiety should they occur.

Abuse of benzodiazepines has been reported.

Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines may develop after repeated use for a few weeks.

Caution should be used in the treatment of patients with acute narrow-angle glaucoma.

Insomnia may be a symptom of several other disorders. The possibility should be considered that the complaint may be related to an underlying physical or psychiatric disorder for which there is a more specific treatment.

Patients with impaired renal or hepatic function should be monitored frequently and have their dosage adjusted carefully according to patient response. Lower doses may be sufficient in these patients. The same precautions apply to elderly or debilitated patients and patients with chronic respiratory insufficiency.

As with all CNS-depressants, the use of benzodiazepines may precipitate encephalopathy in patients with severe hepatic insufficiency. Therefore, use in these patients is contraindicated.

Some patients taking benzodiazepines have developed a blood dyscrasia, and some have had elevations in liver enzymes. Periodic haematologic and liver-function assessments are recommended where repeated courses of treatment are considered clinically necessary.

Transient anterograde amnesia or memory impairment has been reported in association with the use of benzodiazepines. This condition, which may be associated with inappropriate behaviour, usually occurs several hours after ingestion. Therefore, patients should ensure that they will be able to have a period of uninterrupted sleep which is sufficient to allow dissipation of drug effect (e.g., 7-8 hours).

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychoses, and inappropriate behaviour and other adverse behavioural effects have been occasionally reported during benzodiazepine use. Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued.

Although hypotension has occurred only rarely, benzodiazepines should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications. This is particularly important in elderly patients.

Lormetazepam tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The benzodiazepines, including lormetazepam produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression e.g., alcohol, barbiturates, antipsychotics, sedatives/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, and anaesthetics.

Concomitant use of alcohol is not recommended. The sedative effects may be enhanced when lormetazepam is used in combination with alcohol. This will affect the ability to drive or use machines.

An enhancement of the euphoria induced by narcotic analgesics may occur with benzodiazepine use, leading to an increase in psychic dependence.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines which are metabolised only by conjugation.

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including lormetazepam.

Enhanced hypotensive effects may occur when lormetazepam is given to patients treated with antihypertensive agents.

4.6 Fertility, Pregnancy and lactation

Benzodiazepines should not be used during pregnancy, especially during the first and last trimesters. Benzodiazepines may cause foetal damage when administered to pregnant women. If the drug is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the drug if she intends to become, or suspects that she is, pregnant.

Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnoea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.

Since limited data indicates that a small proportion of parent drug and its conjugate is excreted in breast milk, lormetazepam should not be given to breast-feeding women.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, dizziness and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (see also Interactions).

4.8 Undesirable effects

Adverse reactions, when they occur, are usually observed at the beginning of therapy and generally decrease in severity or disappear with continued use or upon decreasing the dose.

Most frequently reported adverse reactions associated with benzodiazepines include daytime drowsiness, dizziness, muscle weakness and ataxia.

Adverse reactions are listed by frequency: common (>1/100, <1/10); uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000); very rare (<1/10,000).

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leucopenia, agranulocytosis, pancytopenia

Immune system disorders

Very rare: Hypersensitivity including anaphylaxis/anaphylactoid reactions

Endocrine disorders

Very rare: Inappropriate antidiuretic hormone secretion, hyponatraemia

Psychiatric disorders

Rare: Confusion, depression and unmasking of depression, numbed emotions, disinhibition, euphoria, appetite changes, sleep disturbance, change in libido, decreased orgasm

Unknown: Dependence, Suicidal ideation/attempt

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, insomnia, nightmares, hallucinations, psychoses, sexual arousal, and inappropriate behaviour have been occasionally reported during use.

Nervous system

Very common: Daytime drowsiness, sedation

Common: Dizziness, ataxia

Rare: headache, reduced alertness, dysarthria/slurred speech, transient anterograde amnesia or memory impairment

Very rare: Tremor, extrapyramidal reactions, Coma (see 4.9 Overdose)

Eye disorders

Rare: Visual disturbances (diplopia, blurred vision)

Vascular disorders

Rare: Hypotension (see 4.4 Special warnings and precautions).

Respiratory thoracic and mediastinal disorders

Rare: Apnoea, worsening of sleep apnoea, worsening of obstructive pulmonary disease.
Respiratory depression (see 4.9 Overdose)

Gastrointestinal disorders

Rare: Nausea, constipation, salivation changes

Hepatobiliary disorders

Rare: Abnormal liver function test values (increases in bilirubin, transaminases, alkaline phosphatase), jaundice

Skin and subcutaneous tissue disorders

Rare: Rash, allergic dermatitis

Musculoskeletal disorders

Common: Muscle weakness

Reproductive system and breast disorders

Rare: Impotence

General disorders

Common: Asthenia, fatigue

Very rare: Hypothermia

Drug withdrawal symptoms (see 4.4 Special warnings and precautions)

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of "rebound" phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

4.9 Overdose

In the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy. In more serious cases, and especially when other CNS-depressant drugs or alcohol are ingested, symptoms may include ataxia, hypotension, hypotonia, respiratory depression, coma, and very rarely, death.

If ingestion was recent, induced vomiting and/or gastric lavage should be undertaken followed by general supportive care, monitoring of vital signs and close observation of the patient. If there is no advantage in emptying the stomach, activated charcoal may be effective in reducing absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Hypotension, though unlikely, may be controlled with noradrenaline. Lormetazepam is poorly dialysable.

The benzodiazepine antagonist, flumazenil may be useful in hospitalised patients for the management of benzodiazepine overdose. Flumazenil product information should be consulted prior to use.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Lormetazepam is a benzodiazepine with anxiolytic, muscle relaxant, sedative and hypnotic properties. Clinical studies have shown minimal effects on REM sleep and on psychomotor performance on the day after treatment with lormetazepam.

5.2 Pharmacokinetic properties

Lormetazepam is rapidly absorbed from the gastrointestinal tract and is metabolised by a simple one-step process to a pharmacologically inactive glucuronide. There are no major metabolites and little risk of accumulation. Lormetazepam has a terminal phase half-life of about 11 hours.

5.3 Preclinical safety data

Fertility in male and female rats was not adversely affected by oral lormetazepam.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Sodium starch glycolate
Talc
Magnesium stearate

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

PVC/aluminium blisters. Pack size of 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Auden Mckenzie (Pharma Division) Ltd
McKenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 17507/0131
PL 17507/0132

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/01/2012

10 DATE OF REVISION OF THE TEXT

09/01/2012

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

LORMETAZEPAM 0.5 MG & 1 MG TABLETS

Read all of this leaflet carefully before you start taking this medicine.

1. Keep this leaflet. You may need to read it again.
2. If you have any further questions, ask your doctor or pharmacist.
3. This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
4. If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. What is **LORMETAZEPAM** and what is it used for?
2. Before you take **LORMETAZEPAM 0.5 mg or 1 mg Tablets**
3. How to take **LORMETAZEPAM 0.5 mg or 1 mg Tablets**
4. Possible side effects
5. Storing **LORMETAZEPAM 0.5 mg or 1 mg Tablets**
6. Further information

1. What is **LORMETAZEPAM** and what is it used for?

The name of this medicine is Lormetazepam 0.5 mg or 1 mg Tablets. Lormetazepam is one of a group of medicines called benzodiazepines.

Lormetazepam is prescribed as a short-term therapy to help with sleeping difficulties which are significantly affecting normal daily life.

2. Before you take **LORMETAZEPAM 0.5 mg or 1 mg Tablets**

Do not take **LORMETAZEPAM** if you have:

- Severe breathing or chest problems
- An allergic reaction to benzodiazepines or any of the ingredients in Lormetazepam Tablets (see list under Section 6). An allergic reaction can be a rash, itchiness or shortness of breath
- Myasthenia gravis (very weak or tired muscles)
- Serious liver problems
- Sleep apnoea (breathing problems when you are asleep)

Special Precautions

Check with your doctor or pharmacist before taking your medicine if any of the following applies to you:

- You are pregnant, or trying to become pregnant (see below).
- You abuse or have in the past abused drugs or alcohol.
- You have a personality disorder. If so, you have a greater chance of becoming dependent on Lormetazepam.
- You have any kidney or liver problems.
- You have suffered from depression before, since it could re-occur during treatment with Lormetazepam.
- You are suffering from depression, since Lormetazepam may increase any suicidal feelings which you may have.
- You are suffering from an eye problem called glaucoma.
- You suffer from breathing problems.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking this medicine.

The beneficial effect of Lormetazepam Tablets may be less apparent after several weeks of use.

If you are given Lormetazepam for more than 4 weeks, your doctor might want to take blood samples occasionally to check your blood and liver, since drugs like Lormetazepam have occasionally affected liver function.

Lormetazepam Tablets are usually prescribed for short courses of treatment, lasting from a few days to 2 weeks. You should not usually take Lormetazepam Tablets for longer than 4 weeks including a dose reduction at the end. This reduces the risk of becoming dependent on Lormetazepam Tablets, or suffering unpleasant effects when

you stop taking it. (See "Stopping your medicine", at the end of section 3).

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Taking some medicines together can be harmful.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines as the dose of these drugs may need to be reduced before you take Lormetazepam:

- Sedatives
- Anti-anxiety drugs
- Antidepressants
- Strong pain-killers (e.g. methadone)
- Drugs for epilepsy
- Anaesthetics
- Antihistamines
- Drugs for mood or mental disorders (e.g. chlorpromazine)

If you are unsure of the types of medicines you are taking, ask your doctor or pharmacist.

Taking **LORMETAZEPAM** with food and drink

You should avoid alcohol while you are taking Lormetazepam Tablets, since this may make you very drowsy and seriously affect your ability to drive or use machines.

Pregnancy and breast feeding

Lormetazepam may cause damage to the foetus if taken during early pregnancy. Therefore, do not take this medicine if you are pregnant or might become pregnant without consulting your doctor. If you take this medicine during late pregnancy or during labour, your baby, when born, may be less active than other babies, have a low body temperature, be floppy, or have breathing or feeding difficulties for a while. Your baby's response to the cold might be temporarily impaired also. If this medicine is taken regularly in late pregnancy, your baby may develop withdrawal symptoms after birth.

Lormetazepam should not be used during breast feeding.

Driving and using machines

Lormetazepam may make you feel dizzy or sleepy during the day, or may affect your concentration. This may affect your performance at skilled tasks such as driving and operating machinery.

Important information about some of the ingredients of **LORMETAZEPAM**

This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, please contact your doctor before taking this medicinal product.

3. How to take LORMETAZEPAM 0.5 mg or 1 mg Tablets

Always take this medicine exactly as your doctor or pharmacist has told you. You should check with them if you are not sure. Lormetazepam Tablets should be taken orally.

Adults:

The usual adult dose of Lormetazepam Tablets is 0.5 mg to 1.5 mg. You should swallow your tablets with water just before you go to bed at night.

Make sure you can have 7 or 8 hours of uninterrupted sleep before taking Lormetazepam Tablets. Treatment usually lasts from a few days to 2 weeks. It should not usually last longer than 4 weeks including a dose reduction at the end.

Elderly:

The dose for elderly patients will be reduced to either half the adult dose or less.

Children:

This product should not be taken by children.

If you take more LORMETAZEPAM than you should:

Do not take more tablets than stated on the label of your medicine. If you take too many tablets you should seek medical attention immediately, either by calling your doctor, or going to the nearest casualty department. Always take the labelled medicine container with you, even if there are no tablets left.

If you forget to take LORMETAZEPAM:

If you forget to take a dose, don't worry, just take your next tablet when it is due. Never take a double dose of tablets to make up for a forgotten dose.

Stopping your medicine:

- After you have finished your prescribed treatment with Lormetazepam Tablets, your doctor will decide whether or not you need further treatment.
- The number of Lormetazepam Tablets and how often you take them should always be reduced slowly before you stop taking them altogether. This allows your body to get used to being without your tablets, and reduces the risk of unpleasant effects when you stop taking them. Your doctor will tell you how to do this.
- On stopping lormetazepam, you may experience symptoms such as headaches, muscle pain, anxiety, tension, depression, restlessness, sweating, confusion or irritability. Your original sleeplessness may also return. If you suffer from any of these symptoms. Ask your doctor for advice.

Do not stop taking your tablets suddenly. This could lead to more serious symptoms such as a loss of the sense of reality, feeling unreal or detached from life, and unable to feel emotion. Some have experienced numbness or tingling of the arms or legs, hallucinations, vomiting, tinnitus (ringing sounds in your ears), twitching and convulsions and hypersensitivity to light, sound and touch. If you suffer from any of these symptoms, ask your doctor for advice immediately.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Lormetazepam can have side effects, although not everybody gets them.

Occasionally you may have unwanted effects while taking Lormetazepam Tablets. These are usually not serious and do not last long. However, you should tell your doctor if any of the following symptoms are severe or become troublesome:

- Daytime drowsiness, dizziness, reduced alertness, sleep problems, confusion, depression, memory loss or forgetfulness, numbed emotions, fatigue, muscle weakness, poor muscle control, stomach upsets, nausea, changes in appetite, headaches, problems with vision, skin problems or changes in sex drive.

If you experience any of the following more rare unwanted effects, you should **tell your doctor immediately**. (These effects are more likely to occur in children and elderly patients):

- Restlessness, agitation, irritability, aggressiveness, violent anger, nightmares, hallucinations, personality changes, abnormal behaviour or false beliefs.

Other rare unwanted effects (which you may not be aware of whilst taking Lormetazepam Tablets) include blood or liver function changes or low blood pressure.

If any of the above side effects are troublesome or last more than a few days or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. Storing LORMETAZEPAM 0.5 mg or 1 mg Tablets

Keep all medicines out of the reach and sight of children. Do not use Lormetazepam Tablets after the expiry date on the carton and blister. The expiry date refers to the last day of that month.

Keep the tablets in the carton, in their blister pack, in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What LORMETAZEPAM contains:

Each tablet contains either 0.5 mg or 1 mg of Lormetazepam as the active ingredient.

The tablets also contain lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, talc and magnesium stearate.

What LORMETAZEPAM looks like and contents of the pack:

Lormetazepam 0.5 mg tablets are round white tablets with the marking 'LMT 0.5' on one side and plain on the other.

Lormetazepam 1 mg tablets are round white tablets with the marking 'LMT 1' on one side and plain on the other.

Lormetazepam tablets are available in boxes of 30 tablets.

Marketing authorisation holder:

Auden Mckenzie (Pharma Division) Ltd.
Mckenzie House
Bury Street
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Middlesex
HA4 7TL
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Manufacturer:

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3261 LW Oud-Beijerland
Netherlands

This leaflet was last approved in June 2011.

For information in large print, on tape, on CD or in Braille, phone 01895 627 420.

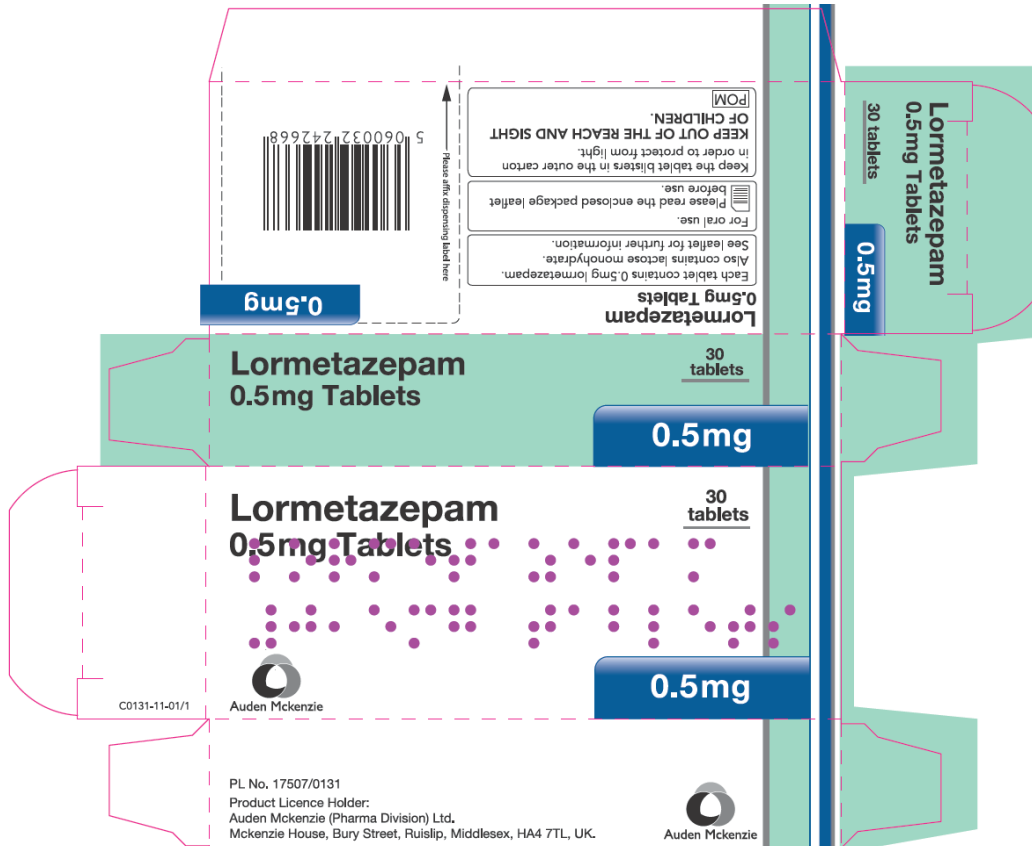


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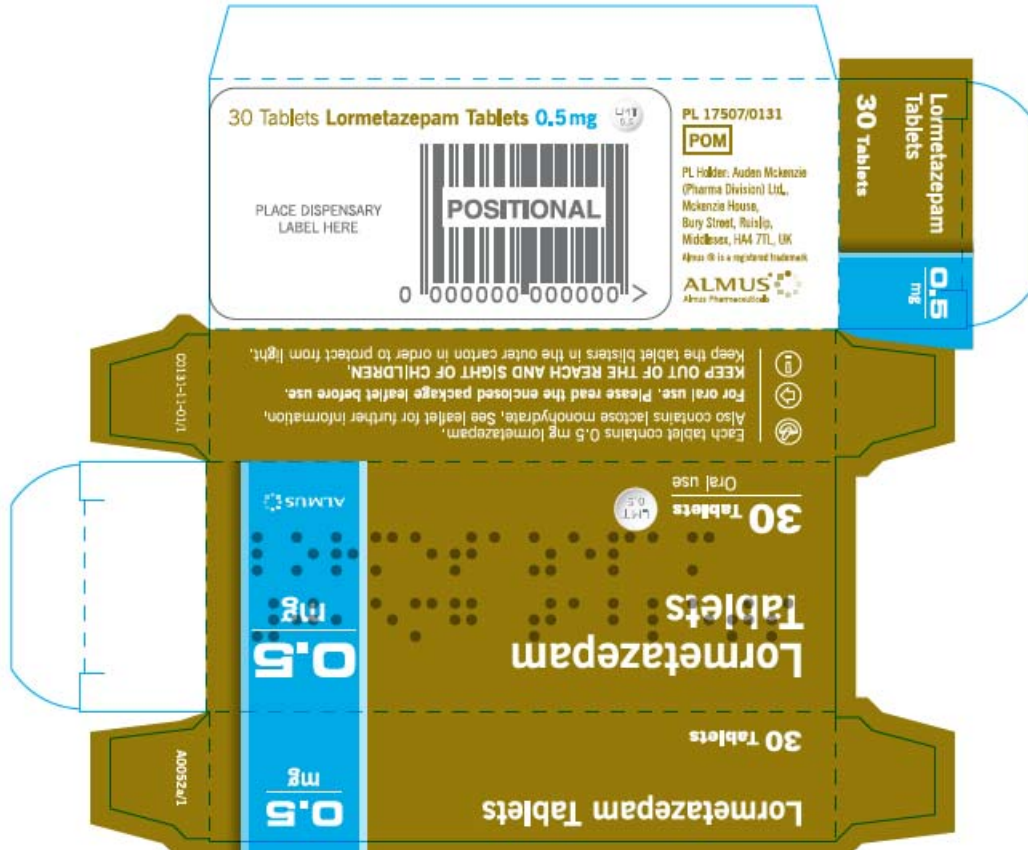
LABELLING

Lormetazepam 0.5 mg Tablets - PL 17507/0131

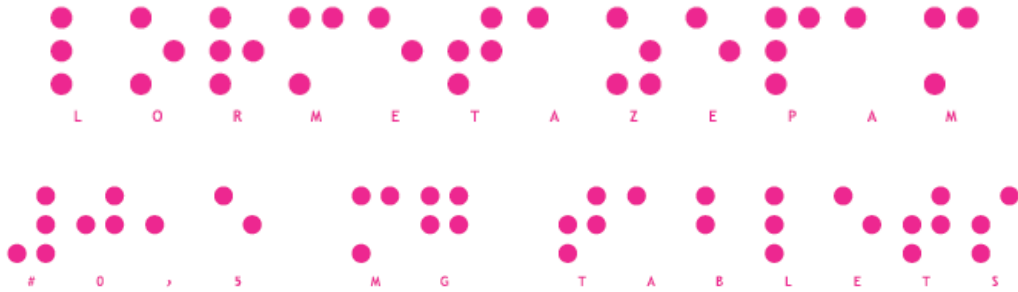
Carton



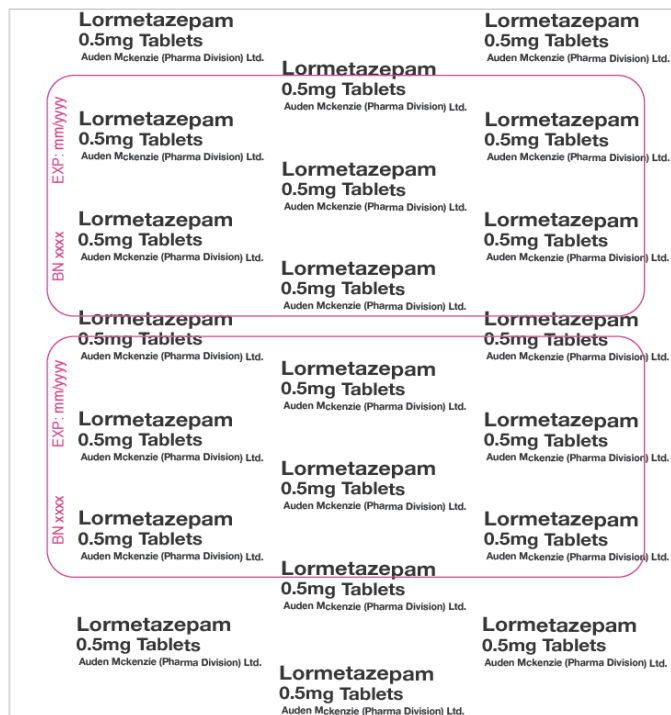
Alternative carton



Braille

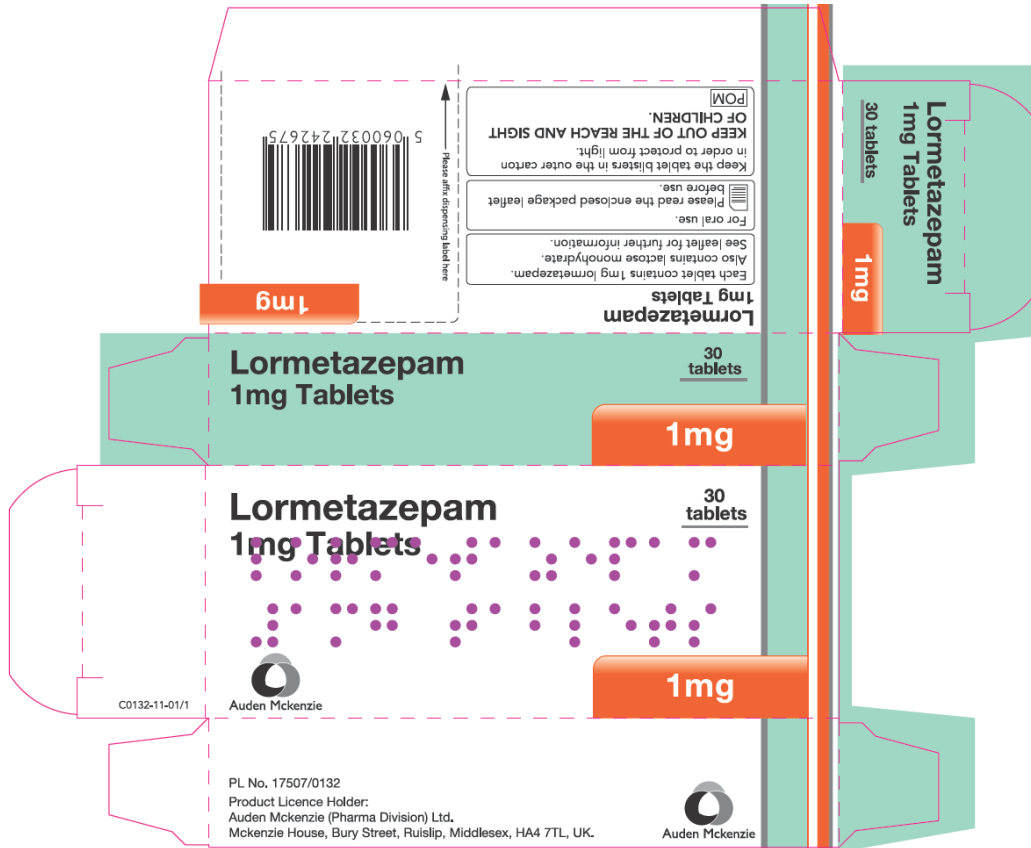


Blister foil

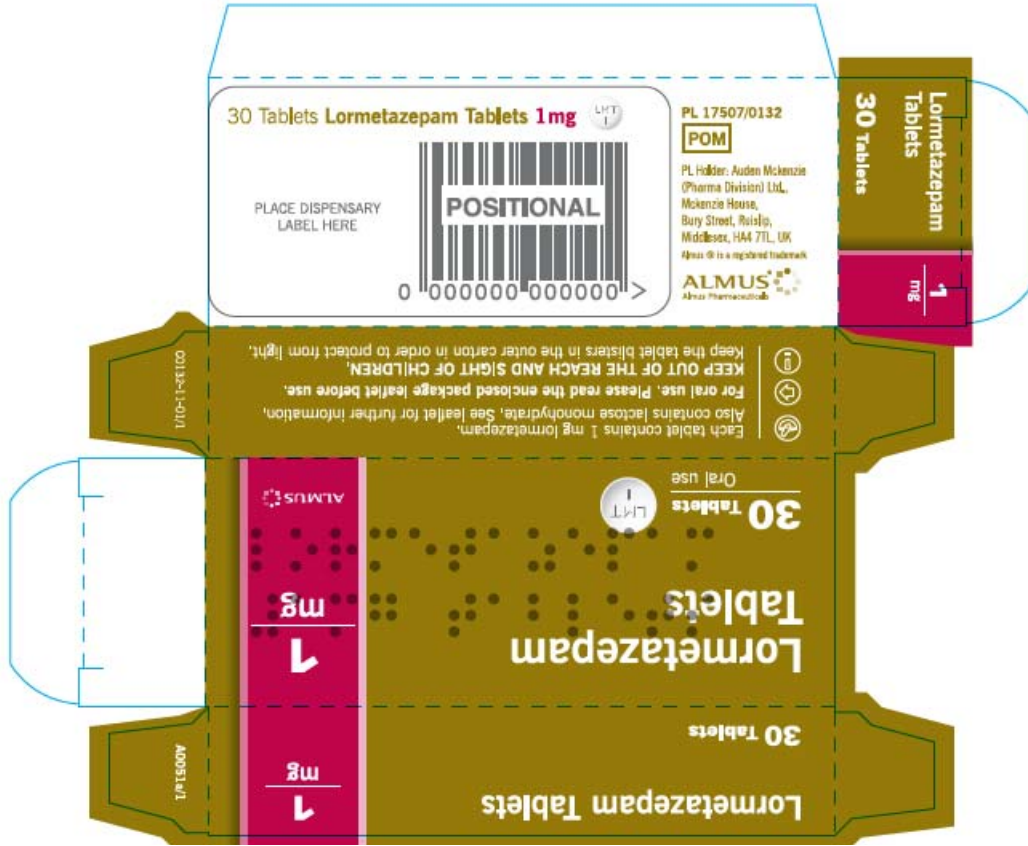


Lormetazepam 1 mg Tablets - PL 17507/0132

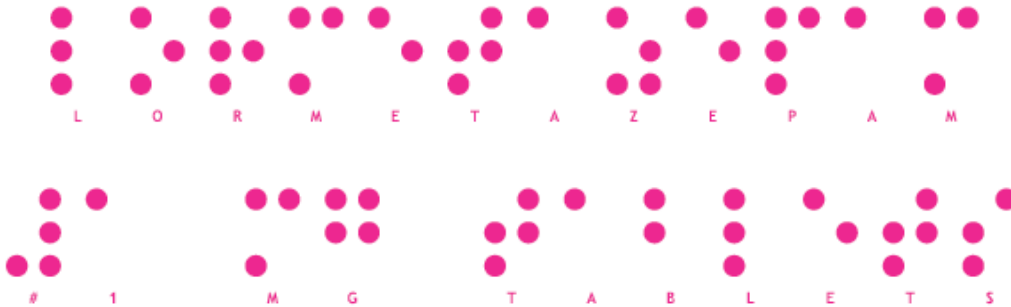
Carton



Alternative carton



Braille



Blister foil

