Public Assessment Report

Decentralised Procedure

CLONAZEPAM ROSEMONT 0.5MG/5ML ORAL SOLUTION
CLONAZEPAM ROSEMONT 2MG/5ML ORAL SOLUTION

Procedure No: UK/H/2487/001-2/DC

UK Licence No: PL 00427/0157-8

ROSEMONT PHARMAECUTICALS LTD
LAY SUMMARY

Clonazepam Rosemont 0.5mg/5ml and 2mg/5ml Oral Solution
(clonazepam, oral solution, 0.5mg/5ml and 2mg/5ml)

This is a summary of the Public Assessment Report (PAR) for Clonazepam Rosemont 0.5mg/5ml and 2mg/5ml Oral Solution (PL 00427/0157-8; UK/H/2487/001-2/DC). It explains how Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Clonazepam Rosemont 0.5mg/5ml and 2mg/5ml Oral Solution.

The products will be referred to as Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution throughout the remainder of this public assessment report (PAR).

For practical information about using Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What are Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution and what are they used for?
Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution are a ‘generic medicine’. This means that Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Rivotril 0.5 mg and 2 mg tablets (Roche Products Ltd).

Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution are used to treat epilepsy in adults, they lower the number of fits (seizures) that the patient has and any fits that the patient does have will be less serious.

How do Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution work?
Clonazepam belongs to a group of medicines called benzodiazepines.

A seizure or fit is a short episode of symptoms which is caused by a burst of abnormal electrical activity in the brain. Clonazepam controls the symptoms of seizures by reducing these abnormal electrical activities. It also relaxes muscles that contract, or stiffen, during a seizure. This means that the numbers of seizures are reduced and they are less severe.

How is Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution used?
The pharmaceutical form of this medicine is an oral solution.

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.

Clonazepam 0.5mg/5ml Oral Solution contains 0.5mg of clonazepam in one 5ml spoonful.

Clonazepam 2mg/5ml Oral Solution contains 2mg of clonazepam in one 5ml spoonful.

- Always use the 2.5ml/ 5ml double ended spoon with a 1.25ml dosing line within the 2.5ml end that is provided with the pack.
• Do not use a different spoon as it may be made of polystyrene or PVC and may react with the medicine.
• If a pharmacist gives the patient a different device such as an oral syringe or pipette, they may find that the plunger of the syringe may stop moving smoothly or the markings may fade over time. If this happens, the patient should take it back to their pharmacy and swap for a new one.

**How to take**
• Take this medicine by mouth.
• The patient must make sure that everything they are using is dry. This is because the medicine should not be mixed with water before they take it. The patient can drink water after taking the medicine if they want, this will not affect the medicine.
• This medicine can also be administered via specific nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. There is further information in the SmPC, the patient should ask their doctor, pharmacist or nurse for this information.
• Do not use with a tube which is made of PVC or polystyrene.
• It is recommended to administer the dose before feed is given via the tube, as the medicine is oily.

For instructions for use via NG or PEG tube, please refer to section 3 of the package leaflet.

**How much to take**
• The patient’s doctor will start them on a low dose of this medicine and gradually increase it over 2 to 4 weeks until the right dose has been found for them.
• The patient’s doctor will usually tell them to split their daily dose into four equal amounts which they will take at evenly spaced times throughout the day.
• If the patient’s daily dose cannot be split equally, they should take the largest dose at bedtime.

Once the patient’s doctor has found the right dose for them, they may tell them to take this medicine as a single dose in the evening.

**Adults**
• The usual starting dose is 1mg a day or less.
• This will be increased gradually, usually to between 4mg and 8mg a day.
• The maximum dose is 20mg a day.

**The elderly**
• The usual starting dose is 0.5mg a day or less.
• This will be increased gradually, usually to between 4mg and 8mg a day.
• The maximum dose is 20mg a day.

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.

For further information on how Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution is used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**What benefits of Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution have been shown**
in studies?
Because Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine Rivotril 0.5 mg and 2 mg tablets (Roche Products Ltd). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution?
Because Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution are generic medicines and are bioequivalent to the reference medicine Rivotril 0.5 mg and 2 mg tablets (Roche Products Ltd), their benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution, see section 4 of the package leaflet available on the MHRA website.

Why was Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution approved?
It was concluded that, in accordance with EU requirements, Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution have been shown to have comparable quality and to be bioequivalent to Rivotril 0.5 mg and 2 mg tablets (Roche Products Ltd). Therefore, the MHRA decided that, as for Rivortril 0.5 mg and 2 mg tablets (Roche Products Ltd); the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution?
Safety information has been included in the Summaries of Product Characteristics (SmPC) and the package leaflets for Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution including the appropriate precautions to be followed by healthcare professionals and patients.

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

Other information about Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution
Ireland and the UK agreed to grant Marketing Authorisations for Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution on 23 November 2011. Marketing Authorisations were granted in the UK on 20 December 2011.

Following the grant of these licences, the product names were changed to Clonazepam Rosemont 0.5mg/5ml Oral Solution and Clonazepam Rosemont 2mg/5ml Oral Solution via a variation approved on 16 April 2014.

The full PAR for Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution follows this summary.

For more information about treatment with Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2016.
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I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution (PL 00427/0157-8; UK/H/2487/001-2/DC) could be approved. These applications were submitted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS).

The products are prescription-only medicines (POM) indicated for all clinical forms of epileptic disease and seizures in adults, especially absence seizures (petit mal) including atypical absence; primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross referring to the reference products Rivotril 0.5 mg and 2 mg tablets (Roche Products Ltd) which have been authorised in the UK since 13 June 1974.

Clonazepam belongs to a group of medicines called benzodiazepines and it exhibits pharmacological properties which are common to benzodiazepines including anticonvulsive, sedative, muscle relaxing and anxiolytic effects. Animal data and electroencephalographic investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absence seizures (petit mal), slow spike wave, generalised spike wave, spikes with temporal or other locations as well as irregular spikes and waves. Generalised EEG abnormalities are more readily suppressed by clonazepam than are focal EEG abnormalities such as focal spikes. Clonazepam has beneficial effects in generalised and focal epilepsies.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support these applications, comparing the test product Clonazepam Rosemont 2 mg/5ml Oral Solution (Rosemont Pharmaceuticals Ltd) with the reference product Rivotril 2 mg tablets (Roche Products Ltd).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are being considered as generic medicinal products of an originator product that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP). The RMS 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, assembly and batch release of this products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 209) on 23 November 2011. After a subsequent national phase, the licences were granted in the UK on 20 December 2011.

Following approval, the product names were changed to Clonazepam Rosemont 0.5mg/5ml Oral Solution and Clonazepam Rosemont 2mg/5ml Oral Solution via a variation approved on 16 April 2014.
II.1 QUALITY ASPECTS

II.1 Introduction

Clonazepam Rosemont 0.5mg/5ml Oral Solution:
Each 5ml contains 0.5mg Clonazepam.

Clonazepam Rosemont 2mg/5ml Oral Solution:
Each 5ml contains 2mg Clonazepam.

Other ingredients (for both product strengths) consist of the pharmaceutical excipients saccharin, ethanol, levomenthol and medium chain triglycerides.

The finished products are packaged in amber (Type III) glass bottles with high-density polyethylene (HDPE), expanded polyethylene (EPE) wadded, tamper evident, child resistant closures and are available in pack sizes of 150 ml bottles. Each pack also contains a dosing device (2.5 ml/5ml double ended spoon with a 1.25 ml graduation mark).

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2. Drug Substance

INN: Clonazepam
Chemical name: 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one or 5-(o-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one

Structure:

![Structure of Clonazepam](image)

Molecular formula: $\text{C}_{15}\text{H}_{10}\text{ClN}_{3}\text{O}_{3}$
Molecular mass: 315.7
Appearance & solubility: Clonazepam is a slightly yellowish, crystalline powder. It is practically insoluble in water, slightly soluble in alcohol and methanol and very slightly soluble in ether.

Clonazepam is the subject of a European Pharmacopoeia 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 specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

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

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

II.3. Medicinal Product
Pharmaceutical Development
The objective of the programme was to develop two strengths of liquid formulation containing 0.5 mg/5ml and 2 mg/5ml clonazepam as the active substance.

Suitable pharmaceutical development data have been provided for these applications.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

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

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

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 12 months for the unopened product which reduces to one month once opened with the storage conditions “Do not store above 25°C. Store in the original package in order to protect from light”.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence studies.

Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PIL), Labels
The SmPCs, PILs and labels are acceptable.
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements.

**MAA forms**
The MAA forms are satisfactory.

**Expert report**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of these products from a pharmaceutical viewpoint.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
As the pharmacodynamic, pharmacokinetic and toxicological properties of clonazepam are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

**III.2 Pharmacology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.3 Pharmacokinetics**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.4 Toxicology**
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

**III.5 Ecotoxicity/environmental risk assessment (ERA)**
A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with other products already on the market it is not considered to increase the environmental risk. Thus, the applicant’s justification is accepted.

**III.6 Discussion on the non-clinical aspects**
There are no objections to the approval of these products from a non-clinical viewpoint.

**III.3 CLINICAL ASPECTS**

**IV.1 Introduction**
The clinical pharmacology of clonazepam is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of clonazepam.
Bioequivalence has been demonstrated between the applicant’s Clonazepam 2 mg/5ml Oral Solution and its respective reference product (Rivotril 2 mg tablets, Roche Products Ltd). As the 0.5 mg/5ml strength of the product meets the bioequivalency 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 2 mg/5ml strength can be extrapolated to the 0.5 mg/5ml strength.

IV.2 Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, randomised, single-dose, two-treatment, two-period, crossover, study to compare the pharmacokinetics of the test product Clonazepam 2 mg/5ml Oral Solution (Rosemont Pharmaceuticals Ltd) versus the reference product Rivotril 2 mg tablets (Roche products Ltd) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of 2mg of either the test or reference product as 5ml of the 2mg/5ml oral solution (test) or 1 x 2 mg tablet (reference) administered with 235 ml of water under fasting conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 144 hours post dose. The washout period between treatment periods was at least 21 days.

The pharmacokinetic results for clonazepam are presented below (log-transformed values; least squares mean, ratios and 90% confidence intervals):

<table>
<thead>
<tr>
<th>Clonazepam in Plasma</th>
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<td>Rosemont (A) vs Roche (Rivotril) (B)</td>
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<tr>
<td>PK Parameter</td>
<td>Ratio of LSM (A/B)</td>
</tr>
<tr>
<td>AUC 0-t</td>
<td>1.02</td>
</tr>
<tr>
<td>AUC 0-72</td>
<td>1.01</td>
</tr>
<tr>
<td>AUCinf</td>
<td>1.02</td>
</tr>
<tr>
<td>Cmax</td>
<td>1.12</td>
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AUC<sub>0-inf</sub> area under the plasma concentration-time curve from time zero to infinity
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
AUC<sub>0-72</sub> area under the plasma concentration-time curve from time zero to 72 hours
C<sub>max</sub> maximum plasma concentration

The 90% confidence intervals for AUC and C<sub>max</sub> for test versus reference product for clonazepam are within predefined acceptance criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 0.5 mg/5ml strength of the product meets 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 2 mg/5ml strength can be extrapolated to the 0.5 mg/5ml strength.
IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for these applications.

IV.5 Clinical safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products where appropriate. The PIL is consistent with the SmPCs and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these applications.

IV.7 Discussion on the clinical aspects
There are no objections to the approval of these applications from a clinical viewpoint.

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, as amended. 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

QUALITY
The important quality characteristics of Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solution 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 were required for applications of this type.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Clonazepam 2 mg/5ml Oral Solution and its respective reference product (Rivotril 2 mg tablets, Roche Products Ltd). As the 0.5 mg/5ml strength of the product meets the biowaiver 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 2 mg/5ml strength can be extrapolated to the 0.5 mg/5ml strength.

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of clonazepam is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate.

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 supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with clonazepam is considered to have demonstrated the therapeutic value of the compound. The benefit-risk 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 (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for the initial grant of this medicine is as follows:

**Carton:**

![Carton Image]

**Bottle label:**

![Bottle Label Image]
PAR Clonazepam 0.5mg and 2mg/5ml Oral Solution

Carton:

Bottle label:
## Table of content of the PAR update

The following table lists non-safety variations of clinical significance to the Marketing Authorisations for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

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<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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ANNEX 1

Our Reference: PL 00427/0157-0009
PL 00427/0158-0009

Product: Clonazepam Rosemont 0.5mg/5ml Oral Solution
Clonazepam Rosemont 2mg/5ml Oral Solution

Marketing Authorisation Holder: Rosemont Pharmaceuticals Ltd

Active Ingredient(s): Clonazepam

Type of Procedure: Mutual recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/2487/001-002/II/004

Reason:
To update sections 4.2 and 6.6 of the SmPC to add suitability of the Clonazepam 0.5mg/5ml and 2mg/5ml Oral Solutions to be able to administer via Nasogastric or Percutaneous Endoscopic Gastrostomy (NG or PEG respectively) tubes and in line with the QRD template. Consequently, the label and PIL has been updated.

Supporting Evidence
- Module 1: Revised SmPC fragments, PIL and labelling.
- Module 2: Quality overall summary addendum and Clinical overview Addendum
- Module 3: Pharmaceutical development
- Module 5: Literature references

Evaluation
Clinical evaluation:
The applicant has requested the addition of new text in sections 4.2 and 6.6 of the SmPC, with consequential changes in the PIL and the labelling. A clinical overview has been submitted and contains one reference dated 2006.

Proposed text to be added at the end of section 4.2:
Suitable for administration via non-PVC nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. Flush the tube with 5mL of water, before and after use for the administration of the Clonazepam Oral Solution. The dose may need to be adjusted according to the clinical response.

Proposed text to be added to section 3 of the PIL:
- This medicine can also be administered via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes.
- Do not use with the enteral tubes made up of PVC.
- Flush the tube with 5mL of water, before and after use for the administration of the Clonazepam Oral Solution.
- Your doctor may adjust your dose depending on how you respond to your medicine.
Current indication
All clinical forms of epileptic disease and seizures in adults, especially absence seizures (petit mal) including atypical absence; primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

The applicant’s argument can be found in the clinical overview as follows:
After oral doses, Clonazepam is quickly absorbed throughout the gastrointestinal tract, including the buccal and rectal mucosa, with a bioavailability of about 90%; peak plasma concentrations occur between 1 and 4 hours after ingestion. A therapeutic range of plasma concentrations has not been established.

As both NG and PEG tubes deliver drug directly to the stomach; delivery of clonazepam via either tube type is unlikely to significantly affect drug absorption and subsequently systemic delivery to the site of pharmacological action.

The conclusions from the evaluation of clonazepam 2mg/5mL are based on the mean of 3 determinations for each tube type and show that clonazepam was delivered at between 87 and 96% of target dose with water flushing with a tendency for slightly lower drug delivery with the wider bore tubes. Although these results fall short of the target of 95% drug delivery for some of the tube types and sizes studied, it should be noted that the tube length used for these determinations was 1250 mm i.e. longer than either NG and PEG tube lengths likely to be used in clinical practice (between 20 and 900 mm).

In summary, NG or PEG tube delivery of clonazepam is feasible when accompanied by water flushing achieving delivery of at least 90% in all but the 18Fr tubing. Whist this is unlikely to have any clinical significance, it is theoretically possible that the slight reduction in drug delivery could give rise to seizure recurrence which may necessitate the need to assess the dosage administered.

Given the incompatibility of the clonazepam formulation with PVC materials, NG or PEG tube delivery should be restricted to non-PVC tube types (e.g. silicone or polyurethane). Air flushing of Enteral Feeding Tubes to deliver the required dose of clonazepam is not recommended.

In the SmPC for the 2mg/ml oral solution the following can be found:
Mode of administration
A 2.5ml/5ml double ended spoon with a further 1.25ml graduation is supplied with the pack. The product is incompatible with polystyrene or PVC and therefore, other devices may react with the product. It should be noted that for oral syringes, the product may cause the plunger to stop moving smoothly or the markings may fade over time.

Assessment of the two strengths with data from the 2.5mg/5ml is acceptable as the composition of the two strengths is comparable. The quality assessor requested e.g. that the composition, diameter and length of the tubes tested be added in the SmPC as this affects the amount of drug delivered. In addition a technical leaflet or text in the PIL or label to refer to the SmPC has been requested. It should be noted that:
- NG tubes are used for short-term (< 30 days) feeding and PVC (for short-term need) as well as polyurethane tubes are used.
PEG tubes are for longer term feeding (> 30 days) and may be changed every 2-3 years. Also nasojejunal tubes are sometimes used which are longer than NG ones.

From a clinical point of view it is noted that the use of non-PVC tubes could result in a loss of 10% or more (depending on the length and diameter of the tube) of product from absorption of clonazepam on Enteral Feeding Tubes (EFT) even after water flushing.

The applicant was asked to clarify the potential loss of product depending on the type, length and diameter of the tube.

In the proposed text in section 4.2 of the SmPC the following wording is found: “The dose may need to be adjusted according to the clinical response.” Clear guidance should be provided regarding the management of the dose when the medicine is being given by enteral feeding tubes in order to avoid the occurrence of seizures.

The applicant provided the following response:

“Following further experimental the 5 ml flush volume which was recommended initially does not ensure more than 95% of the drug product is delivered through the tube. However, an experiment modelled to mimic a real life situation of multiple dosing of medication and feed showed that more that 95% of the drug product could be delivery using the majority of tube diameters and lengths. The shorter tube lengths and delivered of feed were found to improve the amount of dose delivered.

The tubes which were found not to deliver more than 95% of the drug product were at the longest lengths. Based on these results a table of tubes suitable for use with Clonazepam Oral Solution has been added into section 6.6 of the SmPC, including maximum tube lengths.

In practice, nasogastric (NG) tubes tend to be 90 to 100cm in length with external diameters of 6 to 12Fr units. Percutaneous gastrostomy (PEG) tubes tend to be shorter with wide external diameters. The tubes sizes included in the SmPC cover a wide range of scenarios which could be used in practice.

A recommendation to administer the dose prior to delivering feed through the NG or PEG tube has also been included in section 6.6, as this has been shown to help deliver the dose. The instructions for administration have been updated to reflect the method used during the real life simulation experiment.

No work has been performed on nasojejunal tubes as this product is not proposed to be a route of administration. This route would not delivery the product directly into the stomach as it is via NG or PEG tubes.”

**Conclusion**

Because the dose delivered is not 100% and because of the risk when not following the advice as per section 6.6, the following text has been added to the SmPC and consequentially to the PIL:

- Section 4.2 notes that over 95 % of the dose is delivered with the administration advice as given in section 6.6 is followed.
A warning has been added in section 4.4 to remind healthcare professionals that a fraction of the dose may be lost when administering through a tube and that the advice found in section 6.6 should be followed.
Quality evaluation

Introduction
The Company recognised that some patients require medicines to be administered via feeding tubes and that there are few products licensed for this route of administration. In addition instructions are often not provided in product information for this method of administration, which may be associated with increased risks to patients. It is the Company’s intention to provide information in the SmPC on the administration of clonazepam 0.5 and 2 mg/5ml oral solutions via feeding tubes. Pharmaceutical development work is reported in support of the application and is discussed below.

The scope of this licence variation is restricted to clonazepam 0.5 and 2 mg/5ml oral solutions administered via either percutaneous endoscopic gastrostomy tube (PEG) or nasogastric (NG) tubes.

Problem Statement
Despite regulatory guidance to include instructions, few medicines make mention of administration via a feeding tubes in their product information.
Tube occlusion is recognised as a potential risk for the patient which can result in the cessation of feeding and possibly interventions to re-site the tube which can be a complicated procedure particularly in very young children. The Company asserts that the administration of crushed tablets/capsule contents carries risks in this regard and that oral liquids carry a much lower risk.
A very wide variety of patients from neonates to geriatric patients require medicines to be administered via this route. It should be noted that clonazepam oral solution is not indicated for children as it contains ethanol.

The company has noted that the types of tube available vary greatly in terms of design, size and composition.

- Design: It was noted that there are feeding tubes inserted via the nasopharynx (e.g. nasogastric tubes) and directly into the gastro-intestinal tract through the skin (e.g. percutaneous endoscopic gastrostomy tubes). The tubes can deliver drugs to the stomach (gastric), or duodenum (post-pyloric) or jejunum, although this licence variation is limited to PEG and Nasogastric tubes terminating in the stomach.
- Size of tubes varied in length, external diameter and lumen. The external diameter of the tube is expressed using the French (Fr) unit, where each Fr unit is equivalent to 0.33mm. Silicone and latex tubes have thicker walls and therefore silicone or latex tubes with same Fr unit as polyurethane tubes will have a smaller internal diameter.
- Composition: feeding tubes are made of one of the following materials: polyvinylchloride (PVC), polyurethane (PUR), silicone or latex. The different materials of construction may interact differently with the different drug substances in products.

The company’s aim is to add information, helpful to Health Care Professionals and patients’ carers, to the SmPC that will cover this wide set of variables. Satisfactory data in support of SmPC claims has been generated.

The 2 mg/5ml clonazepam solution used for the assessment of dosing via a PEG / NG tube is already licensed in the UK by Rosemont Pharmaceuticals. This strength of product was deemed by the Company to be representative of both concentrations of clonazepam oral solution licensed by the Company. This is acceptable as the qualitative formulations are the same and the quantitative
differences relate to the drug substance required to provide the required dose. The formulation is interesting in that it is not water based.

**Assessor comment:**
It is confirmed that the composition of the 0.5mg/5ml and 2mg/5ml products are identical except for the levels of active substance, which are compensated by differing levels of the medium chain triglycerides (miglycol). This is not expected to affect the physicochemical properties of the product (e.g. viscosity), which is confirmed by identical finished product specifications. The higher strength product could be considered to be the ‘worse-case scenario’ from the perspective of absorption/adsorption. The choice of strength is considered acceptable.

The Analytical Method for Drug Substance Assay used for this licence variation work is the same one used to release the licensed products. The method is suitable for this purpose.

Tubes constructed of three materials have been tested namely; silicone, PVC and polyurethane. These are the most commonly used tubes in practise. The fourth potential material, latex has not been studied. Latex is used much less often in practise, so its omission is acceptable, but the tube materials tested should be noted on the SmPC.

A range of tube diameters of each material of construction have been tested and these cover an acceptable range with respect to clinical use.

**Assessor comment:**
The length of tube is justified. The BNPG’s ‘Drug Administration via Enteral Feeding Tubes’ states that NG tubes are typically 90-100mm long; PEG tubes will be much shorter. Details of the tubes tested, such as composition, diameter and length, should be included in the SmPC as this affects the amount of drug delivered.

**The Company has addressed the following points in the supporting pharmaceutical development**

- **i.** Feasibility of administration through feeding tubes of different diameters and materials of construction
- **ii.** Rinse or flush volume(s) and dose recovery
- **iii.** Risk of physical blockage of the tube
- **iv.** Air Flushing
- **v.** Compatibility

**i.  Feasibility of administration through feeding tubes of different diameters and materials of construction**
The Company has shown that clonazepam 2 mg/5ml solution can be delivered through all enteral feeding tubes bore sizes of all three materials of construction. This includes the finest bore size of 4 French units in all materials. A “high” thumb pressure on a 5 ml syringe was used by the analyst to deliver the solution down the finest tubes. No adverse events were seen and this is well noted as the Company has referenced the Handbook of Drug Administration which states that small syringes create high luminal pressures and may damage the tube. This data is acceptable and provides useful information to health care professionals.

**ii. Rinse or flush volume and dose recovery.**
The company has studied flushing the tube before and after the medicine is administered. The first flush is to simulate patient use where it removes enteral feed from the tube: the second flush washes the full dose of medicine out. Subsequent flushing should remove any residual
medicine. Water has been used as the solvent for tube flushing. The oral solution tested has been analysed prior to any dosing down a tube. The flush volume required (in terms of multiples of the volume of the tube) has been determined for each tube size and material of construction.

The drug delivery is more variable than would be expected. The amount of drug delivered based on a single flush using the tube volume of water appears to be dependent on tube diameter, with the amount delivered falling as tube diameter increases. For the finer tubes drug delivery is between 93 and 95%. This does not meet the target set by the company in the protocol of not less than 95% dose delivery. Clinically such a small difference of 2% may not impact the patient. With wider tubes especially the PVC 12Fr and PUR 18 Fr, the dose delivered is further reduced to between 85 and 90% of LC. This is important information for health care professionals and carers to take this into account when titrating the dose of the product appropriately. The Company has not studied the impact of multiple dosing.

The Company has determined a general statement for flushing to cover flushing of all tubes i.e. 5ml of water should be used for flushing and this in turn has been calculated as number of tube volumes for a given bore size of tube. Clinical comment is required on the suitability of this advice for patients and carers. From the drug delivery and subsequent flushing it appears that minimal dose is left behind in the dosing tube with fine tubes but more appears to be left if a wider tube is used. The drug delivery may be more variable since the flushing is done with water and the product is oil based.

The Company has not made any concession where a 5ml flush may be considered too large an amount for a child, which is reasonable since the product is not indicated for use in children.

The Company presents data that shows the use of air flushing gives low and variable drug delivery. Air flushing cannot be recommended.

The Company has not studied tubes that have been pre-treated with feed. From the data presented the amount of drug substance available to interact with feed post dosing is minimal and feed drug interactions are not reported as a major cause of tube blockage.

The Company has not studied tubes to determine if any adsorption of drug onto the tube occurs. Given the amount of drug delivered from the fine bore tubes after flushing this may be of little clinical significance, however the lower dose seen with the wider bore tubes requires some clinical comment. The patient should be titrated on the drug product to gain the correct clinical effect, so the data above may be sufficient to achieve a good clinical outcome. It would be interesting to know if the fraction of a dose which remains in the tube is “released” during normal use i.e. feeding the patient. As tubes are in place for a long time, but exposed to drug products for a very short time, the impact of drug absorption on the tube should be considered.

Assessor comment:
The amount of clonazepam delivered after the recommended flush volume of 5ml has been experimentally determined. It may be useful to provide this information in the product literature, i.e. this is the likely decrease in delivered drug if the administration advice is not followed.

In order to replicate real-life situations the applicant has investigated multiple dosing, interaction of an enteral feeding product when using the recommended flush volume, two types of tubing material, various tube lengths and internal diameters. At the end of the
experiment to examine the amount of Clonazepam Drug Product adhering to the inside of the tube wall, acetonitrile was flushed through the tubing.

In all cases after flushing with the recommended flush volume of water followed by a standard enteral feeding solution the mean results were >95% Label Claim (L.C) for all the tubing tested where the feed is held in the tubing for 10 or 60 minutes.

It was noted the % L.C. obtained if the Drug Product was flushed through the tubing using 5mL water that the results were lower although in all cases with the exception of one of the tubing (where the result was between 85-90 % L. C.) 90-95 % L.C. was achieved.

When the results obtained are summed together then ≥95% L.C. was achieved in all cases. These results mean the at least 5mL of water would be required to flush through the tubing tested three times to deliver ≥95% L.C. of Clonazepam Oral Solution.

In practice the length of tubing and diameter for nasogastric delivery of clonazepam is 90 to 100cm and between 6 – 12Fr units. The volume of water flushes are normally between 15 and 30mL.

During feeding up to 400mL of enteral feeding formulation can be delivered down the tube at any one time. This work demonstrates the worst possible case in terms of length and volumes of liquid (water and feed) and contact times that might be used.

The work in this report demonstrates that Clonazepam Oral Solution (providing sufficient water and/or feed are flushed down the tube) is suitable for use with the following enteral feeding tubes;

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Length</th>
<th>Fr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyurethane ≤10Fr (≤2.0mm i.d.)</td>
<td>≤125cm</td>
<td>≤10Fr</td>
</tr>
<tr>
<td>Polyurethane ≤12Fr (≤2.6mm i.d.)</td>
<td>≤75cm</td>
<td>≤12Fr</td>
</tr>
<tr>
<td>Polyurethane ≤8Fr (≤1.5mm)</td>
<td>≤100cm</td>
<td>≤8Fr</td>
</tr>
<tr>
<td>Polyurethane ≤18Fr (≤4.0mm)</td>
<td>≤75cm</td>
<td>≤18Fr</td>
</tr>
</tbody>
</table>

iii. Risk of physical blockage of the tube
The applicant has focussed on correct practise of flushing a tube before use to clear it of feed, dosing the clonazepam solution and then flushing the tube again. Since the drug does not need to be taken with food this is acceptable. In general no drug precipitation has been seen in these circumstances. The drug is therefore mixed with food in the stomach as it would be after oral dosing. The applicant has not considered mis-use of the product should the tube not be flushed before use, as this is against good practise and the instructions being given.

iv. Air flushing
Practices such as “air flushing” are sometimes required for fluid restricted patients. The company has shown that air flushing dose not give drug delivery at the required level and is not recommended.

Furthermore in patients with low gastric emptying, such techniques should not be advised due to the risk of gastro-oesophageal reflex. The company does not recommend air flushing the dose down the PEG or NG tube as the dose delivered is not within the limit of acceptability. For some patients this may not be a concern, but the comment is available to HCP.
v.  Compatibility of the drug product with the Enteral Feeding tube.
The Company asserts that the drug product will be dosed over a limited period of time, 60 seconds has been used for experimental purposes. Therefore the chemical compatibility of the drug product and the tube has not been considered. The Company has considered the physical compatibility of the tube with the drug product. Exposure of the tube to drug product for 16 hours at 37°C has not led to any visible deterioration of the tube. Since the drug product is in the tube for a short time (assuming good practise is followed and the tube flushed after dosing) the Company has not considered the possibility of leachables being removed from the tube or any changes to the stability of the product. No literature information or tube manufacturer’s information is presented to support this approach. This may be pragmatic but supporting evidence would be helpful to HCP.

The Company has not considered multiple medicine dosing and finds that difficult since there is a tremendous range of possible combinations to study.

Conclusion
The Company has demonstrated that clonazepam can be reliably dosed by EN tubes, however the delivered dose may be reduced. Work is included to show the proposed flush volumes work reasonably well for smaller bore tubes and less well with larger bore. The health care professional will find this advice helpful is titrating the dose appropriately. It should be noted that the drug delivery reported may still be more effective than the use of crushed tablets suspended in a viscous media. Air flushing is not recommended for this product. Compatibility issues such as leachables, impact of dose remaining on the tube after flushing have not been considered due to the short exposure times of the tube to the drug product in dosing. The company has also demonstrated that the dose can be delivered by a 5ml syringe across a wide range of tube diameters and materials of construction.

Product Information:

Assessor comment:

SmPC
The information on delivery of clonazepam through EFTs should be supplemented with the type of EFTs tested (material, length, internal diameter and external bore size) and the amount of clonazepam actually delivered (not estimated) using the recommended flush volume, preferably in a tabulated format. The information should also be supplemented with results from the requested multiple dosing and food studies. Those EFTs that would benefit from extra flushing (i.e. larger bore EFTs) should be annotated, providing it is clinically justified. The statement concerning using non-PVC EFTs should be justified. The aim is to give prescribers the maximum amount of information to make a judgement, whilst acknowledging that every clinical situation cannot be foreseen.

The SmPC will not be readily available to prescribers; therefore, a technical leaflet may be necessary. Alternatively, suitable advice to consult the SmPC when using the product with EFTs should be included the label or leaflet (to make the prescriber aware).

Applicant’s Response:
Section 6.6 of the SmPC has been updated to include a table which specifies the types of tubes (with material, external bore size, internal diameter and length) suitable for use with Clonazepam Oral Solution. This table is based on the experiment which mimicked a real life situation of multiple dosing of medication and feed. The results showed that more that 95% of the drug product could be delivered via these tubes by either:
• Flushing the enteral tube with a minimum volume of 5mL of water and then immediately deliver a minimum of 10ml of feed, or
• Flushing the enteral tube 3 consecutive times, using a minimum volume of 5mL of water each time.

Regarding non-PVC enteral tubes, in the initial licence application the following statement was added to SmPC section 6.2, ‘This product is incompatible with polystyrene and PVC’. This incompatibility is due to the medium chain triglycerides (miglyol) in the formulation. As PVC is a common material for NG and PEG tubes we also included a warning in section 6.6.

For clarity the wording in section 6.6 regarding non-PVC enteral tubes, has been amended as follows:
‘This product is not compatible with PVC and therefore should not be used with NG or PEG tubes made from PVC.’

To address the concern that the SmPC will not be readily available to the patient, the Company proposes to include the following wording on the labelling and leaflet.

Labelling Text:
Suitable for administration via NG or PEG tubes, for further instructions refer to the SmPC or leaflet.

Leaflet Text:
This medicine can also be administered via specific nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. There is further information in the SmPC, ask your doctor, pharmacist or nurse for this information.

The wording on the carton is directed at the pharmacist to alert them that there is more information in the SmPC. The leaflet text also alerts the patient/carer that there is more detail regarding the administration via NG/PEG tube. This is to avoid the patient/carer having to interpret information from the SmPC, which could lead to using the tubes/product incorrectly. It was felt that instructing the patient to discuss with a healthcare professional would reduce any risks. This ensures that the correct instructions are passed on to the patient/carer.

New proposed SmPC Sections 4.2 and 6.6 for Clonazepam Oral Solution:

4.2 Posology and method of administration
[...]
Suitable for administration via non-PVC nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. For further instructions see section 6.6. When these instructions are followed over 95% of the dose is delivered.

The product is incompatible with polystyrene or PVC and therefore, other devices may react with the product.

6.6. Special precautions for disposal and other handling
Instruction for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes:
Clonazepam Oral Solution is suitable for use with the following types of NG and PEG tubes:

<table>
<thead>
<tr>
<th>Material</th>
<th>External Bore Size (Fr Unit)</th>
<th>Internal Diameter (mm)</th>
<th>Maximum Length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicone</td>
<td>6</td>
<td>1.0</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.0</td>
<td>125</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>8</td>
<td>1.5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>2.6</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>4.0</td>
<td>75</td>
</tr>
</tbody>
</table>

This product is not compatible with PVC or polystyrene and therefore should not be used with NG or PEG tubes made from these materials.

**Care should be taken during administration due to the oily nature of the product.** It is recommended to administer the dose prior to delivering feed through the NG or PEG tube and to follow the instruction below:

Ensure that the enteral feeding tube is free from obstruction before administration.

1) Flush the enteral tube with water, a minimum flush volume of 10mL is required.

2) Administer the required dose of Clonazepam Oral Solution with a suitable measuring device.

3) Flush the enteral tube again by either of the methods below:
   i) Flush the enteral tube 3 consecutive times, using a minimum volume of 5mL of water each time.
   ii) Flush the enteral tube using a minimum volume of 5mL of water and then immediately deliver a minimum of 10mL of feed.

Healthcare professionals should be aware that if the instructions above cannot be followed (e.g. longer or wider tubes are used or in a specific clinical situations) there is a risk of under dosing (up to 15%) as the oily medicine may adsorb to the wall of the feeding tube. Extra flushing with water or feed may combat this. In these situations the patient should be monitored closely.

Any unused product or waste material should be disposed of in accordance with local requirements.

**New proposed Labelling for Clonazepam Oral Solution:**

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Administration:

For oral use.

Suitable for administration via NG or PEG tubes, for further instructions refer to the SmPC or leaflet.

This product is incompatible with polystyrene and PVC.

This product should not be mixed with water.
Read the package leaflet before use.

New proposed Leaflet Text for Clonazepam Oral Solution:

3. How to take Clonazepam Rosemont Oral Solution

[…]

How to take

- Take this medicine by mouth.
- Make sure that everything you are using is dry. This is because the medicine should not be mixed with water before you take it. You can drink water after taking the medicine if you want, this will not affect the medicine.
- This medicine can also be administered via specific nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. There is further information in the SmPC, ask your doctor, pharmacist or nurse for this information.
- Do not use with a tube which is made of PVC or polystyrene.
- It is recommended to administer the dose before feed is given via the tube, as the medicine is oily.
- Instructions for use via NG or PEG tube:
  1. Ensure the tube is clear before taking the medicine
  2. Flush the tube with a minimum of 10mL of water
  3. Administer the medicine with a suitable measuring device
  4. Flush the tube again by either:
     i) Flushing the tube 3 times, using a minimum of 5mL of water each time, or
     ii) Flushing the tube using a minimum of 5mL of water and then immediately delivering a minimum of 10mL of feed.
- Please consult your doctor if these instructions cannot be followed as the oily medicine may stick to the wall of the tube and therefore the dose you get may be less than required.

[…]

This leaflet was last revised in 03/2016

Assessor’s comment:
The product information (SmPC, leaflet and labelling) has been suitably updated. As previously mentioned, it is considered very useful to explain why the administration instructions should be followed and how much drug is likely to be delivered if the administration instructions are not followed (or if longer/wider tubes are used).

Overall conclusion (clinical and quality)
The overall benefit risk for these variations is positive; these variations are approvable.

The proposed changes to the SmPCs, PIL and labelling are acceptable and have been incorporated into the Marketing Authorisations.
The approved labelling is as follows:
PAR Clonazepam 0.5mg and 2mg/5ml Oral Solution

Decision- Approved on 06 May 2016.