Decentralised Procedure

Public Assessment Report

Clonazepam-neuraxpharm 2,5 mg/ml Tropfen zum Einnehmen

Clonazepam

DE/H/3295/001/DC

Applicant: neuraxpharm Arzneimittel GmbH

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Clonazepam-neuraxpharm 2,5 mg/ml Tropfen zum Einnehmen
INN (or common name) of the active substance(s):	Clonazepam
Pharmaco-therapeutic group (ATC Code):	N03AE01, Antiepileptics
Pharmaceutical form(s) and strength(s):	Oral drops, solution ; 2,5 mg/ml
Reference Number for the Decentralised Procedure	DE/H/3295/001/DC
Reference Member State:	DE
Member States concerned:	withdrawn NL
Applicant (name and address)	neuraxpharm Arzneimittel GmbH Elisabeth-Selbert-Straße 23, D-40764 Langenfeld, Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Clonazepam-neuraxpharm 2,5 mg/ml Tropfen zum Einnehmen, Lösung, in the treatment of

- most clinical forms of epilepsy in infants and children, especially typical and atypical absences (Lennox-Gastaut syndrome), and primary or secondary generalised tonic-clonic seizures and
- for the treatment of epilepsy - especially focal seizures - in adults,

is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

With Germany as the Reference Member State in this Decentralised Procedure, neuraxpharm Arzneimittel GmbH is applying for the Marketing Authorisations for "Clonazepam-neuraxpharm 2,5 mg/ml Tropfen zum Einnehmen" in NL. At Day 106 the applicant decided to withdraw the application in NL.

II.2 About the product

Clonazepam is a benzodiazepine derivative that is predominantly used as an anticonvulsant inthe treatment of practically all clinical forms of epileptic seizure disorders. The clinical benefit of the substance in these indications can be assessed to be evident without any doubt – as also claimed for the generic product. Clonazepam was investigated in clinical studies already in the late 1960s and has therefore been in clinical use for more than 4 decades.
Accordingly, a well-established clinical use of clonazepam has been established.
The generally accepted antiepileptic indications are:

- To treat the majority of clinical forms of epilepsy in infants and children, especially typical and atypical absence seizures, primary or secondary generalised tonic-clonic seizures.
- To treat epilepsies – in particular focal seizures – in adults.

II.3 General comments on the submitted dossier

This application of marketing authorisation for Clonazepam 2.5 mg/ml oral drops, solution is based on Directive 2001/83/EC Article 10(1), a "generic medicinal product", referring to a medicinal product, which has been authorised by Roche for more than 10 years in several countries under the product name Rivotril.
The marketing authorization of the reference product Rivotril was granted in The Netherland on 03/09/1975.

Clonazepam 2.5 mg/ml oral drops, solution and the reference product have exactly the same quantity of active ingredient, and exactly the same excipients with nearly the same quantities.
Both products will be administered as oral solution. This means, the active ingredient is in solution when administered, and is solved when it reaches the site of absorption. As in both cases, it is solved within the same solvent, with the same excipients in practicably the same concentrations; there is nothing to induce differences in extent and/or rate of absorption. Therefore, sufficient justification for a biowaiver approach is given.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The active substance clonazepam is described in the European Pharmacopoeia (Ph. Eur.). The quality of the drug substance clonazepam is controlled in compliance with the corresponding monograph of the European Pharmacopoeia (Ph. Eur.). The suitability of the monograph to test the drug substance has been verified.
For the manufacturer of the active substance the following valid certificate of suitability of the EDQM has been submitted. The CEP states a retest period of 60 month.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three pilot scale batches each filled both in 10ml, 30 ml and 50 ml bottles. The batch analysis results show that the finished products meet the specifications proposed. The same batches are used in process validation and were also placed on stability.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
Based on the currently available stability results for Clonazepam 2.5 mg/ml oral drops, solution a shelf life of 12 months is accepted. Due to the increasing of impurities at accelerated conditions the labelling advice "Do not store above 30 °C" is implemented.
Based on the results of in use stability testing the stability is 3 months after first opening.

III.2 Nonclinical aspects

Clonazepam is a substance with well-known pharmacodynamic, pharmacokinetic and toxicological properties, which have been satisfactorily summarised based on publicly available information in the Non-clinical Overview. The instructions on use of the product during pregnancy and lactation and the preclinical safety data contained in the proposed SmPC and PL, respectively, essentially reflect these characteristics.
There are hence no objections for marketing authorisation from a non-clinical point of view.

III.3 Clinical aspects

With respect to the adequate bioavailability of clonazepam from the product submitted for application, Clonazepam 2.5 mg/ml oral solution, and in particular the bioequivalence of this immediate-release oral formulation with the corresponding reference (innovator) product Rivotril®, the current revised "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev.1) points out that the concept of bioequivalence is fundamental in applications for generic medicinal products. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutical quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.
In this context, the revised EMA guideline also points out that if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However, if the excipients may affect gastrointestinal transit (e.g., sorbitol, mannitol, etc.), absorption (e.g., surfactants or excipients that may affect transport proteins), in vivo solubility (e.g., cosolvents) or in vivo stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data.
Regarding the formulations of the product and of the reference product, it has to be considered that these formulations are certainly not aqueous oral solutions. On the other hand, both products principally contain the active substance clonazepam solved in propylene glycol at the same concentrations (2.5 mg/ml solution). Accordingly, the formulations can be assessed as being practically identical, because the other excipients (i.e., flavouring, saccharin, and glacial acetic acid; the excipients are identical in the products) in the low concentrations used are definitely unproblematic and do not play any role concerning the bioavailability / bioequivalence of the active substance from the products.
Hence, it can be concluded that irrespective of the formulation as an aqueous or non-aqueous solution comparable bioavailability and therefore bioequivalence between practically identical oral solutions such as Clonazepam 2.5 mg/ml oral solution and its reference product Rivotril® can be expected in principle.

It can be summarised that bioequivalence between the formulations of Clonazepam 2.5 mg/ml oral solution and the reference product Rivotril® can be concluded and that bioequivalence studies on the solution formulation can therefore be waived.
Under the aspect of the potential side effects of the benzodiazepine in healthy volunteers, there are also ethical concerns to perform an additional clinical study although the positive result of bioequivalence can be expected in advance with sufficient certainty.
Accordingly, it can be concluded that with regard to safe conversion from the reference product Rivotril® to the product Clonazepam 2.5 mg/ml oral solution, the interchangeability between these products can be expected unambiguously, i.e., evident bioequivalence allows safe transfer of all the clinical experience obtained with the innovator product to the product submitted for application.

Pharmacokinetics
Clonazepam 2.5 mg/ml oral drops, solution were developed as generic version of Rivotril (Roche) identical in dosage form, strength and active ingredient. Clonazepam is the only active substance. The qualitative composition with respect to the excipients is the same for the generic medicinal product and the reference product. No clinical studies were performed.

Clonazepam is relatively insoluble in water but readily crosses biological membranes. Clonazepam is rapidly and well absorbed following oral administration to man. Peak plasma levels are usually reached within 1 to 4 hours, and decline slowly over several days. About 90% of an oral dose is bioavailable, suggesting minimal presystemic metabolism. There are wide individual variations in the levels reached at the same dose. Peak plasma concentrations appear to be poorly correlated with either the antiepileptic action or the side effects of the drug. Clonazepam is excreted mainly in the urine, but very little of the administered dose appears as unchanged drug. There is extensive metabolism to 7-amino- and 7-acetamino-clonazepam, which are excreted unchanged, as conjugates, or after further biotransformation to their 3-hydroxy derivatives (Browne 1978; Dollery 1999; Pinder et al. 1976).

Pharmacodynamics
The pharmacological properties of clonazepam, a benzodiazepine derivative, are qualitatively similar to those of other benzodiazepine derivatives; however, clonazepam is predominantly used for its anticonvulsant properties. Thus, clonazepam exhibits pharmacological properties which include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. As with other benzodiazepines, these effects are thought to be mediated mainly by post-synaptic GABA-mediated inhibition, although there are animal data showing in addition an effect of clonazepam on serotonin. 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 therefore beneficial effects in both generalised and focal epilepsies.

Clinical efficacy
The efficacy of Clonazepam in epilepsy has been well documented in literature. No new data were submitted. Clonazepam was investigated in clinical studies already in the late 1960s and has therefore been in clinical use for more than 4 decades. Thus, clonazepam has been well known worldwide with respect to the overall pharmaco-toxicological and clinical properties as well as its clinical use. Hence, a well-established clinical use of clonazepam has been established

Clinical safety
No new data were submitted. It is considered that the safety profile of Clonazepam 2.5 mg/ml oral drops will be comparable to that of other identical or similar products which are currently licensed and marketed in Europe.

User Test
From the results of the Readability User Test, it can be concluded that most patients who are prescribed this product will be able to find and understand the sought information in the PIL.
As a whole, the PIL is intelligibly written. Both the writing style and the clear presentation contribute to this assessment. This is primarily reflected by the fact that information can be found quickly.
The PL is a useful information source for patients and as such contributes towards preventing unintentional misuse of the medicinal product.
The reasons can be summarised as follows:
• 99.6% of the information of the PL was found and
• 100% of the information was understood by all participants
• from which 100% was understood in detail or good.
• At least 19 participants found and comprehended the information necessary to answer each individual question. All 16 questions achieved the necessary score of findings.
• The participants' subjective impression scores of the leaflet also backup the test results. Comprehensibility was rated 7.6 on a scale of 1 to 10, with 10 being the best.
• The layout, design and structure of the PL were rated 7.1.
• The font size was rated 8.2 by the participants.
The Readability Index Ratio is 0.99. This result substantiates the usability of this PL for every day life.
Therefore the PL can be rated as readable and comprehensible according to the guidelines of the European Commission.

Pharmacovigilance system

Description of Pharmacovigilance System
The applicant has provided documents that set out a detailed description of the neuraxpharm Arzneimittel GmbH system of pharmacovigilance (Version 09 dated 01 March 2011). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union 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.

Risk Management Plan

An EU-RMP may need to be submitted at any time of a product's life-cycle, i.e. during both the pre-authorisation and post-authorisation phases. In particular an EU-RMP should be submitted:

- with the application for a new marketing authorisation for:
- any product containing a new active substance
- a similar biological medicinal product
- a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product

- with an application involving a significant change in marketing authorisation (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication) unless it has been agreed with the competent authority that submission is not required

- on request from a competent authority (both pre- and post-authorisation)

- on the initiative of a applicant/marketing authorisation holder when they identify a safety concern with a medicinal product at any stage of its life cycle

As none of these conditions applies, a Risk-Management Plan has not been submitted yet.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published non-clinical and clinical data and bioequivalence can be concluded based on the scientifically justified biowaiver approach for the solution formulation. The benefit risk profile is positive. The application is approved.