LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Clonazepam Vital Pharma Nordic
(clonazepam)

SE/H/2122/01/DC

This module reflects the scientific discussion for the approval of Clonazepam Vital Pharma Nordic. The procedure was finalised on 2022-10-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Clonazepam Vital Pharma Nordic, 1 mg/ml, Concentrate for solution for injection/infusion.

The active substance is clonazepam. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Clonazepam Vital Pharma Nordic, 1 mg/ml, concentrate for solution for injection/infusion, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Vital Pharma Nordic ApS, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, IS and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Iktorivil 1 mg/ml, concentrate and solvent for solution for injection or infusion authorised in SE since 1995-01-01 (Date of first authorisation 1975-01-24), with Roche AB as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in DK, FI, IS and NO [Iktorivil 1 mg/ml, concentrate and solvent for solution for injection or infusion authorised in SE since 1995-01-01 (Date of first authorisation 1975-01-24), with Roche AB as marketing authorisation holder].
The justification to use this product is based on RMS's own files. The ERP information was circulated during validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: EU/3/16/1803, EU/3/05/315, EU/3/17/1836, EU/3/17/1920, EU/3/12/953.

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should update the report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2).

The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with an authorised orphan medicinal product under market exclusivity. The detailed RMS assessment of similarity is presented in the attached RMS Similarity AR.

Conclusion
Short comparison of known mechanism of action of clonazepam and cannabidiol was provided in the similarity report. In addition, the comparison of indication of two products was performed.
Thus, the Applicant's consclusion that the analysis of the available data regarding the similarity of the medicinal product Clonazepam to the Epidyolex *(cannabidiol)* has demonstrated, that they are not similar according to the EC regulation No 847/2000 is endorsed.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

At Day 70, the Applicant was requested to provide a safety assessment for the excipients benzyl alcohol, ethanol and propylene glycol. Accordingly, the non-clinical overview has been updated. At Day 120, the amount and combination of the excipients in the formulation, i. e. benzyl alcohol, ethanol and propylene glycol raised a major concern for the pediatric population and in particular the youngest patients. As all 3 excipients are substrates of alcohol dehydrogenase, a limiting step of the metabolism, there is a risk of accumulation of the excipients, especially in immature infants. Potential accumulation and consequences thereof, are difficult to estimate. This concern was raised as multidisciplinary and quality Major Objections.

In the response to the multidisciplinary MO, the Applicant proposes to remove the indication in patients below 12 years of age, and to contra-indicate use in children younger than 12 years. Given the concerns regarding the excipients included in the drug product for the youngest population, this is endorsed.

Following the proposed posology in SmPC 4.2, the recommended clonazepam dose is 1 ampoule (1 mg), that can be repeated as needed up to a maximum recommended dose of 20 mg clonazepam daily.

The daily dose of these excipients following the proposed posology in adolescents and adults (1 ampoule) is 31 mg benzyl alcohol, 158 mg ethanol and 805 mg propylene glycol. The maximum recommended dose in adolescents and adults is 20 mg daily (20 ampoules) corresponding to 620 mg benzyl alcohol, 3160 mg ethanol and 16100 mg propylene glycol. The estimated daily, and maximum excipient doses in mg/kg are presented below.

Age	**Weight span (kg)**	**Daily dose (mg/kg)**		
		benzyl alcohol	**ethanol**	**propylene glycol**
Adolescents (1 dose)	>40 kg	0.8	4	20
Adolescents max daily dose	>40 kg	16	79	402
Adults (1 dose)	50	0.6	3.2	16
Adults max daily dose	50	12	64	320

Regarding benzyl alcohol, the maximum daily doses are above the proposed ADI in food (0 to 5 mg/kg) but in line with that reported for other medicinal products used for parenteral administration. As outlined in the document questions and answers on benzyl alcohol used as an excipient in medicinal products for human use (EMA/CHMP/508188/2013), the median concentration of benzyl alcohol is 150 mg per injection, and the range of injected dose varies from 20 to 600 mg/day. Warnings are warranted if you are pregnant or breast-feeding as large amounts of benzyl alcohol can accumulate and may cause metabolic acidosis. The same is applicable if you have a liver or kidney disease. Relevant warnings are included in the SmPC.

Regarding ethanol, 1 ampoule (corresponding to 1 dose) contains 158 mg ethanol which is equivalent to 4 mL beer or 2 mL wine. The ethanol content per dose in mg/kg is 3.2 and 4 mg/kg in adults and adolescents, respectively. Doses below 15 mg/kg/dose are not expected to result in noticeable effects (EMA/CHMP/43486/2018).

As outlined in the document questions and answers on propylene glycol used as an excipient in medicinal products for human use, clinical data showed that in children from the age of 5 years and adult patients, up to 500 mg/kg/day of propylene glycol could generally be considered safe even for long term periods. However, at daily doses of 50 mg/kg/day and above, caution should be taken if you are pregnant or breast-feeding as administration of propylene glycol may reach the fetus and has been found in milk. The same is true for patients with liver or kidney disease. Adequate warnings are proposed in the SmPC.

As all three excipients are substrates of alcohol dehydrogenase, a limiting step of the metabolism, there is a risk of accumulation of the excipients. Given the age of the patient population from 12 years and above, and the short-term treatment, a risk for accumulation seems low. Overall, the composition seems acceptable for the intended population.

Environmental Risk Assessment (ERA)

The revised environmental risk assessment is not in agreement with the “Guideline on the environmental risk assessment of medicinal products for human use” (EMEA/CHMP/SWP/4447/00 corr 2, 01 June 2006). However, as the revised indications for Clonazepam Vital Pharma Nordic are comparable, and even more narrow, to the indications of the reference product, an increase in the environmental exposure is not to be expected. Thus, the absence of a complete environmental risk assessment is considered acceptable.

IV. CLINICAL ASPECTS

Pharmacokinetics
The applied product is to be administered as an intravenous or intramuscular solution containing the same active substance in the same concentration as the reference product. The applied product also contains the same excipients in similar amounts as the reference product. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.

The Applicant submitted a Clinical Overview dated June 2019. The Clinical Overview is written by J. Kuczyńska, PhD, Dep of Pharmacology Inst of Psychiatry and Neurology, Warsaw, Poland.

The Clinical Overview contained a summary of literature references in support of the sought indications in the treatment of epilepsy and panic disorder as well as other potential indications. The literature review of the clinical data is largely very dated.

The Applicant is seeking the following indications:

Status epilepticus, treatment of all forms of epilepsy in adults and children: particularly absence seizures (petit mal), including atypical absences (Lennox-Gastaut syndrome), primary or generalised tonic-clonic seizures (grand mal), simple or complex focal seizures, myoclonic seizures and atonic seizures (drop syndrome), epilepsy with infantile spasms (West syndrome)

Panic disorder - Use in treatment of acute conditions (sudden unexpected attacks of anxiety and fear with intense vegetative symptoms, acute exacerbation of symptoms in patients with chronic anxiety). Once the acute condition is managed, further treatment with clonazepam should be oral.

The reference product Iktorivil is approved for the following indications (both adults and children):

Epilepsy, generalized seizures (petil mal, myoclonic seizures, grand mal). Partial seizures. Status epilepticus.

The indication ‘panic disorder’ is not supported in the context of this hybrid application procedure. This indication is not approved for the reference product. The Applicant removed this indication in response to the MO raised.

In this context of this hybrid procedure and given the absence of adequate and well controlled studies that specifically support defined conditions such as Lennox-Gastaut syndrome and West syndrome, the Applicant should not deviate from the indication approved for the reference product. The following wording would be acceptable (in line with the current classification wording according to ILAE):

Epilepsy, generalized seizures (absences, myoclonic seizures, tonic clonic seizures). Partial seizures. Status epilepticus.

In response to the request the Applicant adjusted the indication and issue is resolved.

The Applicant accordingly addressed a number of concerns raised regarding the need to adjust the SmPC in agreement to the SmPC of the reference product.

Since the formulation of the product contains benzyl alcohol, ethanol and propylene glycol the

Applicant removed children younger than 12 years old from the indication and added additional contraindication as well as relevant warning to the SmPC. This is acceptable.

Risk Management Plan

The MAH has submitted a risk management plan (version 0.3 signed 16-05-2022), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to clonazepam.

Safety specification

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan is acceptable.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Polish. 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 user test is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Clonazepam Vital Pharma Nordic is found adequate. There are no objections to approval of Clonazepam Vital Pharma Nordic, from a non-clinical and clinical point of view. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Clonazepam Vital Pharma Nordic, 1 mg/ml, Concentrate for solution for injection/infusion was positively finalised on 2022-10-12.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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