LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Buripal
(buspirone, buspirone hydrochloride)

SE/H/2356/01-02/DC

This module reflects the scientific discussion for the approval of Buripal. The procedure was finalised on 2024-01-18. 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 Buripal, 5 mg, 10 mg, Tablet.

The active substance is buspirone, buspirone hydrochloride. 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 Buripal, 5 mg, Tablet, is a **hybrid application** (change in strength) submitted according to Article 10(3) of Directive 2001/83/EC.

The application for Buripal, 10 mg, Tablet, is a **generic application** submitted according to Article 10(1) of Directive 2001/83/EC.

The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Norway and Denmark as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Buspar 10 mg tablets authorised in SE since 1991 (MA withdrawn in 2010) with Bristol-Myers Squibb as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of buspirone hydrochloride are well known. As buspirone hydrochloride 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.

Environmental Risk Assessment (ERA)
Since Buripal is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

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

IV. CLINICAL ASPECTS

Pharmacokinetics
BCS-based biowaiver
The application is based on a Biopharmaceutical Classification System (BCS) based biowaiver and no bioequivalence study has been submitted.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), a BCS class I-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and complete absorption (BCS class I). Also, *in-vitro* dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be quantitatively and qualitatively the same.

Discussion and overall conclusion
The quality criteria for biowaiver (solubility) are fulfilled. Similar *in vitro* dissolution characteristics of the test and the reference product has been demonstrated.

Buspirone HCl is not considered to have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with buspirone HCl.

None of the excipients included in the drug product are known to influence bioavailability. The difference in excipients is acceptable for a BCS class I/III-biowaiver.

Based on submitted caco-2 cell permeability data, it can be concluded that buspirone is highly permeable and thus, buspirone can be classified as a BCS class I substance from a pharmacokinetic perspective.

In conclusion, the justification for a BCS (Biopharmaceutics Classification System) based biowaiver can be accepted.

As there is no reference product for 5 mg strength, the conditions for BCS-biowaiver (to have same strength as the reference product) cannot be applied. Normally, for a BCS-based biowaiver, comparison should always be made to the corresponding strength of the reference product. In this case,

however, no reference product is available for the 5 mg strength. The applicant has submitted *in vitro* data comparing the 5 mg test strength both to the 10 mg test strength and to the 10 mg reference strength. High solubility was shown for buspirone and the pharmacokinetics of buspirone is linear within the recommended dose range. Even though the general biowaiver criteria in section 4.1.6 of Bioequivalence Guideline is applicable for waiver of study for additional strengths only when a bioequivalence study has been performed, in the current case, considering the aspects stated above and considering that the general biowaiver criteria is fulfilled for the applied product, there is no concern regarding lack of study for the 5 mg strength. Further, it is of lesser concern as buspirone is BCS class I substance. Thus, the 5 mg strength is considered approvable.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted a risk management plan, 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 Buripal.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 2022-12-19 and proposed the following summary safety concerns:

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

Assessor's comment: The Applicant has proposed no safety concerns which is in line with other buspirone hydrochloride containing products and is accepted.

Part III Pharmacovigilance Plan

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

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

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 2022-12-19 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Anksilon 5 mg and 10 mg tablets, FI/H/893/001-002 regarding content and Dexamcol 1 mg/ml + 5 mg/ml eye drops, solution, DK/H/3155/001/DC regarding layout.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Buripal, is found adequate. There are no objections to approval of Buripal, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and 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 Buripal, 5 mg, 10 mg, Tablet was positively finalised on 2024-01-18.

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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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