IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dexamethasone Activase 2 mg Tablets
Dexamethasone
PA1567/002/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Dexamethasone 0.5mg & 2 mg Tablets, from Activase Pharmaceuticals Ltd on 3rd of June 2022 for the treatment of various inflammatory and autoimmune diseases e.g.:

- Rheumatism, as pain, stiffness or limitation of motion, especially in the joints and related structures, including muscles, bursae, tendons, fibrous tissue;
- Collagen disease, as lupus erythematosus, dermatomyositis, polyarteritis nodosa, thrombotic purpura and rheumatoid arthritis;
- Allergies, as status asthmaticus, bronchial asthma, contact dermatitis, inflammatory processes of the eye and its adnexa, severe hypersensitivity reactions to drugs or insect stings, anaphylactic shock, impending allograft rejection;
- Primary or secondary adrenocortical insufficiency, and adrenogenital syndromes.
- Besides Dexamethasone is used as an adjunct in the control of cerebral oedema (not in those cases where the oedema is caused by head injury), for treatment of lymphocytic leukaemia, as anti-emetic in antineoplastic regimens and for palliative treatment in terminal stages of neoplastic disease. This decentralised marketing authorisation application was submitted in accordance with Article 10(3) of Directive 2001/83/EC as amended (hybrid application). For the 2 mg Dexamethasone tablet, an application in accordance to Article 10(1) was requested. For the 0.5 mg strength, a biowaiver was sought. However, since the Reference Medicinal Product is not available in a 0.5 mg strength, an application under Article 10(3) was submitted as agreed with the RMS and CMS. The EU reference product is Dexamethasone tablet 2 mg marketed by Aspen Pharma Trading Ltd, which was first authorised in IE on 01/04/1978 (IE authorisation No: PA1691/014/001). With Ireland as the Reference Member State in this Decentralised Procedure, Activase Pharmaceuticals Ltd. is applying for a Marketing Authorisation for Dexamethasone 0.5 mg and 2 mg Tablets in CMS: NL. The product will be subject to medical prescription that may not be renewed. The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Dexamethasone 0.5mg & 2 mg Tablet
Name(s) of the active substance(s) (INN)	Dexamethasone
Pharmacotherapeutic classification (ATC code)	H02AB02
Pharmaceutical form and strength(s)	0.5mg & 2 mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA1567/002/001-002
Marketing Authorisation Holder	Activase Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1168/001-002/DC
Reference Member State	IE
Concerned Member State	NL

II. QUALITY ASPECTS

II.1. Introduction

This application is for Dexamethasone 0.5mg & 2 mg Tablet

II.2 Drug substance

The active substance is dexamethasone, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Active Ingredient	Function	0.5 mg tablet (mg/tablet)	2 mg tablet (mg/tablet)	Reference
Dexamethasone	Active substance	0.50	2.0	Ph. Eur.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Dexamethasone 0.5 mg and 2 mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for 44 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment is required.

III.2 Pharmacology

An overview of available scientific literature pertaining to the pharmacological activity of dexamethasone was provided. Dexamethasone acts mainly through the cytosolic glucocorticoid receptor to regulate genes involved in inflammatory and immune responses, as well as development and metabolism. The non-clinical pharmacology studies described are old were not performed according to current guidelines. Nevertheless, clinical experience over many years supports the use of dexamethasone and further nonclinical data are not required.

III.3 Pharmacokinetics

Dexamethasone is readily absorbed from the gastrointestinal tract, with bioavailability estimated at between 70-78%. Dexamethasone binds mainly to albumin in the plasma and this binding has low affinity but is of high capacity. Unlike hydrocortisone and prednisolone, however, dexamethasone does not bind to transcortin and as a result has been found to exhibit linear pharmacokinetics following intravenous administration. Dexamethasone is metabolised mainly in the liver, but also the kidney. Biotransformation in rats and humans is comparable and mainly involves hydroxylation. Dexamethasone is excreted in both the urine and the faeces.

There is no information on the excretion of dexamethasone in breast milk. However, as other corticosteroids are excreted in small amounts in breast milk it is likely that this will also be the case with dexamethasone. This is described in the SmPC in Section 4.6.

III.4 Toxicology

An acute toxicity study in mice indicates that there is a wide safety margin between therapeutic doses and those that cause lethal toxicity. Repeat-dose toxicity studies reported that dexamethasone was generally well tolerated, with decreased body weight gain being the main finding. The main target organs were the adrenal gland and thymus in both rats and dogs. Dexamethasone has a low potential for genotoxicity and the overall carcinogenic potential of dexamethasone is considered to be low. In common with other corticosteroids, dexamethasone was found to cause malformations including cleft palate when administered parenterally to animals. Overall, the results report no unexpected toxicity findings but may not form a complete basis for judgments on safety and efficacy, which is more appropriately made from the wide clinical experience gained with dexamethasone over several decades in humans.

III.5 Ecotoxicity/environmental risk assessment

The applicant has not conducted environmental risk assessment (ERA) studies; a justification for their absence is provided. Since dexamethasone 0.5 mg and 2 mg tablets are intended for generic substitution, no increased exposure to the environment is expected. Additional studies on environmental risk are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Dexamethasone is a widely used and well-known active substance. Dexamethasone was first used clinically in 1958 and has been marketed for several decades. The pharmacodynamic, pharmacokinetic and toxicological properties of dexamethasone and other glucocorticoids are well-understood and well-described in the literature. No new nonclinical studies are presented in this submission; an overview based on literature review was provided and is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dexamethasone is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Dexamethasone tablet 2 mg marketed by Aspen Pharma Trading Ltd, (IE authorisation No: PA1691/014/001).

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Dexamethasone 2 mg tablets of Activase Pharmaceuticals Ltd. is compared with the pharmacokinetic profile of the reference product Dexamethasone Tablets BP 2 mg of Aspen Pharma Trading Ltd.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Dexamethasone 2 mg tablets of Activase Pharmaceuticals Ltd., was compared to the reference product Dexamethasone Tablets BP 2 mg of Aspen Pharma Trading Ltd.

All pre-dose concentrations were lower than the LLOQ concentration and the residual area was <20% for all subjects demonstrating no carryover effect. The 90% confidence intervals for C_{max} and AUC_{0-t} were 89.69-107.21% and 100.16-110.92% respectively, all of which are within the accepted ranges.

PK Parameters (Unit)	Geometric Least Square Means and Its Ratio (N = 26)			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
C_{max} (ng/mL)	23.578	24.044	98.06	18.91	89.69% - 107.21%	99.16
AUC_{0-t} (hr*ng/mL)	130.646	123.947	105.40	10.76	100.16% - 110.92%	100.00

Based on the pharmacokinetic parameters of Dexamethasone, the reference tablet Dexamethasone Tablets BP 2 mg marketed by Aspen Pharma Trading Ltd. and test tablet Dexamethasone 2 mg tablets of Activase Pharmaceuticals Ltd. are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

With respect to the grant of a biowaiver for the Dexamethasone 0.5 mg tablets, the bioequivalence guidelines general requirements were found to have been met. The Dexamethasone 0.5 mg Tablets are manufactured by the same manufacturing process as the Dexamethasone 2 mg Tablets. The qualitative composition of the 0.5 mg and 2 mg tablet strengths are the same. While the composition of both strengths are not quantitatively proportional, the amount of the active substance is less than 5% of the tablet core weight and the amount of different core excipients are the same for the concerned strengths and only the amount of active substance is changed.

Finally, the in vitro dissolution data for the Dexamethasone 0.5 mg Tablets is comparable to that of the Dexamethasone 2 mg Tablets, which in turn is comparable to the reference product.

The above mentioned conditions of a biowaiver, as outlined in the relevant CHMP Note for Guidance are fulfilled, and as the pharmacokinetics of dexamethasone are linear, the bioequivalence guidelines state that it is sufficient to establish bioequivalence with only one dosage strength. Therefore a biowaiver for the Dexamethasone 0.5 mg Tablets is granted.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

No additional studies investigating the pharmacokinetic effects of Dexamethasone 0.5 mg and 2 mg Tablets were conducted which is acceptable for this generic application.

Absorption
After ingestion, dexamethasone is rapidly and well (around 80%) absorbed. Peak plasma levels are reached between 1 and 2 hours after ingestion.

Distribution
Dexamethasone is bound (up to 77%) by plasma proteins, mainly albumin. There is high uptake of dexamethasone by the liver, kidney and adrenal glands.

Biotransformation and Elimination
Metabolism in the liver is slow and excretion is mainly in the urine, largely as unconjugated steroids. The plasma halflife is 3.0-4.5 hours but, as the effects significantly outlast plasma concentrations of steroids, the plasma half-life is of little relevance and the use of the biological half-life is more applicable. The biological half-life of dexamethasone is 36-54 hours. Therefore, Dexamethasone is especially suitable in conditions where continuous glucocorticoid action is desirable.

IV.3 Pharmacodynamics

No additional studies investigating the pharmacodynamic effects of Dexamethasone 0.5 mg and 2 mg Tablets were conducted which is acceptable for this generic application.

For further information see the SmPCs Section 5.1.

IV.4 Clinical Efficacy

No new Applicant-generated efficacy studies or bibliographical data were submitted in this application.

IV.5 Clinical Safety

No new Applicant-generated safety studies or bibliographical data were submitted in this application.

The reference product for this application, Dexamethasone Tablets BP 2 mg has been on the market in IE since 1978. Therefore, dexamethasone has an established clinical safety profile.

During the pivotal bioequivalence study, both the test and reference products were well tolerated by the subjects. Two AEs were reported both of which were classified as mild in nature. AE occurring in the test product (raised bilirubin) could be expected in dexamethasone administration since its metabolism, to a small extent, occurs in the liver. There were no safety concerns raised and no report of SAEs or deaths during the conduct of the study.

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 Dexamethasone. Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:
• PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
• In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This decentralised marketing authorisation application was submitted in accordance with Article 10(3) of Directive 2001/83/EC as amended (hybrid application). For the 2 mg Dexamethasone tablet, an application in accordance to Article 10(1) was requested. For the 0.5 mg strength, a biowaiver was sought. However, since the Reference Medicinal Product is not available in a 0.5 mg strength, an application under Article 10(3) was submitted as agreed with the RMS and CMS.

One bioequivalence study was submitted, in which the pharmacokinetic profile of the test product Dexamethasone 2 mg tablets of Activase Pharmaceuticals Ltd. was compared with the pharmacokinetic profile of the reference product Dexamethasone Tablets BP 2 mg of Aspen Pharma Trading Ltd.

The 90% confidence intervals for C_{max} and AUC_{0-t} were 89.69-107.21% and 100.16-110.92% respectively, all of which are within the accepted ranges and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

With respect to the grant of a biowaiver for the Dexamethasone 0.5 mg tablets, the bioequivalence guideline requirements were found to have been met.

Dexamethasone is a well-known active substance with established efficacy and tolerability. Dexamethasone was first used clinically in 1958 and has been marketed for several decades. The reference product for this application, Dexamethasone Tablets BP 2 mg has been on the market in IE since 1978. The safety results reported in the bioequivalence study were found to be consistent with the known safety profile of Dexamethasone and no other safety studies were submitted in support of this study which is acceptable.

V. OVERALL CONCLUSIONS

Dexamethasone 2 mg and 0.5mg tablets are a generic form of Dexamethasone Tablets BP 2 mg. Dexamethasone Tablets BP 2 mg is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the IE reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Dexamethasone Activase 2 mg and 0.5mg Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

21.03.2027