IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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.

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I. INTRODUCTION

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulartory 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 EC Directive 2001/83, as amended by Directive 2004/27/EC. 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. Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Deximune 25, 50 & 100 mg Capsules from Dexcel-Pharma Limited on 31st January 2005 for Organ Transplantation, Bone Marrow Transplantation, Psoriasis, Atopic Dermatitis, Nephrotic Syndrome and Rheumatoid Arthritis

The marketing authorization in Ireland is granted based on article 10(3) formerly 10.1 (a) (iii) of Directive 2001/83EEC, as amended). It concerns a generic application claiming essential similarity with the innovator product, Sandimmun Neoral. A study demonstrating bioequivalence with this innovator has been provided.

Prevention of graft rejection following bone marrow transplantation and prophylaxis of graft-versus-host disease (GVHD).

Treatment of established graft-versus-host disease (GVHD).

Non-transplantation indications

Psoriasis: For treatment of patients with severe psoriasis in whom conventional therapy is ineffective or inappropriate.

Atopic Dermatitis: For treatment of patients with severe atopic dermatitis when systemic therapy is required.

Rheumatoid Arthritis: For treatment of patients with severe, active rheumatoid arthritis in patients in whom classical slow-acting anti-rheumatic agents are inappropriate or ineffective.

Nephrotic Syndrome: For treatment of adults and children with steroid-dependent and steroid-resistant nephrotic syndrome owing to glomerular diseases such as minimal change nephropathy, focal segmental glomerulosclerosis or membranous glomerulonephritis, to induce remissions and for maintenance treatment. It can also be used for the maintenance of steroid-induced remission, allowing withdrawal of steroids.

Special pharmaceutical aspects if any, e.g. novel delivery system: none

Name of the product	**Deximune 25mg, 50mg and 100mg capsules**
Name of active substance(s)	CICLOSPORIN
Prescription status	Prescription- only medicine
Pharmacotherapeutic classification (ATC code)	L04AA01 CICLOSPORIN
Pharmaceutical form and strength(s)	Soft gelatin capsule. Each capsule contains 25mg, 50mg or 100mg ciclosporin.
Packaging	blister pack of OPA/Al/PVC foil with Aluminium lid in an outer cardboard carton.
Pack sizes	30, 50 or 60 capsules per pack
Mode of action	Immunosuppressant
Approved indications and dosage	(See full SPC for details)
Marketing Authorisation Number(s) in Ireland (PA)	PA2261/001/001-003
Date of first authorisation	28th January 2005
Date of assessment report	6th September 2007
Marketing Authorisation Holder	Dexcel Pharma GmbH Carl-Zeiss-Strasse 2 63755 Alzenau Germany

MRP/DCP No.	IE/H/0164/001-003
Reference Member State	IE
EU Referral	No

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

II. QUALITY ASPECTS

II.1 II.1 Introduction

The product is a soft gelatin capsule containing ciclosporin in three strengths: 25mg, 50mg and 100mg.

II. ABOUT THE PRODUCT

II.2 II.2 Drug Substance

The active substance is ciclosporin, an established active substance described in the European Pharmacopoeia (Ph. Eur.), which is manufactured in accordance with Good Manufacturing Practice (GMP).
The active substance specification is considered adequate to control the quality and meets the current pharmacopoieal requirements. Batch analytical data demonstrating compliance with this specification have been provided for several batches.

II. 3 Medicinal Product

P.1 Composition

The product is a soft gelatin capsule containing a solution of ciclosporin.
Deximune capsules contain the active substance ciclosporin and the following other ingredients: Polysorbate 20, Sorbitan oleate, Lecithin, Triglyceride, macrogolglycerol hydroxystearate, Ethyl lactate, Gelatin, Glycerol, Ferric oxide black, Titanium dioxide and Purified water.
The composition contains no novel ingredients. EU guidelines on the use of gelatin derived from animal origin have been complied with.
Container/closure system
The product is presented as a blister pack of polyamide/aluminium/PVC foil with Aluminium lid in an outer cardboard carton.

P.2. Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The aim of the development was to produce a stable product essentially similar to the innovator product, Sandimmun Neoral, marketed by Novartis in Sweden. The latter is considered equivalent to the Irish reference product. Comparative dissolution data have been provided.

P.3 Method of preparation of the product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) and in accordance with conventional manufacturing techniques for this product type at suitably qualified manufacturing sites.
The manufacturing process has been validated according to relevant European / ICH guidelines, the process is considered to be sufficiently validated.

P.4 Control of substance(s) other than the drug substance (excipients)

All excipients comply with pharmacopoieal requirements or are adequately controlled by the manufacturer's specification.

P.5 Control tests on the finished product

The finished product specification is based on the monograph for soft gelatin capsules in the Ph. Eur.,.with some additional tests. 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 from the proposed production sites has been provided demonstrating compliance with the specification and thus demonstrate the ability of the manufacture to produce finished product of consistent quality.

P.6 Packaging Materials

The product is presented as a blister pack of polyamide/aluminium/PVC film with aluminium lid in an outer cardboard carton. Evidence has been provided that both the film and foil comply with Ph. Eur. / EU legislation for use in foodstuff requirements.

P.7 Stability tests on the finished product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for two years when stored below 25°C with the additional warning "Do not refrigerate or freeze".
EU guidelines on the use of gelatin derived from animal origin have been complied with. Other ingredients, are of plant or synthetic origin.
Conclusion on quality
The quality of these products has been demonstrated satisfactorily and thus has been recommended for marketing.

III. NON-CLINICAL ASPECTS

III.1 Medicinal Product

IV. CLINICAL ASPECTS

The product is generic, that is, it is based on the demonstration of pharmacokinetic equivalence with the innovator product Neoral Capsules. In order not to waste the lives of experimental animals the developer is not required to repeat the non-clinical (animal) development work done by the innovator company.

The marketing authorisation was granted on the basis of Study 008/00 a two way cross over, single dose, open bioequivalence study comparing the test ciclosporin with Sandimmun Neoral both as 100 mg soft capsules. Twenty-four healthy volunteers participated in the study.

The pharmacokinetic indices of the two preparations of ciclosporin are shown in Table 1.

Table 1: Pharmacokinetics indices for test and reference brands of ciclosporin

AUC (0- t) ng.hr/ml
Cmax (ng/mL)
Tmax (h)

Test	**Reference**	**Geometric Mean Ratio T/R (90% CI)**	**Median Difference T/R (90% Aparametric CI)**
4930 ± 1283	4866 ± 1107	1.01 (0.93 – 1.09)	
1184 ± 215	1203 ± 231	0.99 (0.90 – 1.09)	
1.65 ± 0.48	1.63 ± 0.52		0.00 (-0.25 – 0.25)

V. OVERALL CONCLUSIONS

Discussion in CMD(h), Specific obligations, follow-up measures, if applicable

VI. REVISION DATE

June 2018