

Public Assessment Report

Scientific discussion

Lakrimont
(carbomer)

SE/H/1517/01/E/02

**This module reflects the scientific discussion for the approval of Lakrimont.
The Public Assessment Report was written in September 2011 by the previous RMS FR
after initial procedure FR/H/430/01/DC. RMS transfer from FR to SE was completed
2015-05-25.
For information on changes after this date please refer to the module 'Update'.**

Information about the initial procedure:

Application/Legal Basis	Article 10(3)
Active substance	Carbomer 980 (Carbopol 980)
Pharmaceutical form	Eye Gel
Strength	2 mg/g
Applicant	Laboratoires Blumont Pharma
EU-Procedure number	FR/H/430/01/DC
End of procedure	19/10/2010

I. INTRODUCTION

This is a hybrid application from Blumont Pharma for the tear substitute Lakrimont 2 mg/g eye gel which is submitted through a decentralised procedure under Article 10(3) of Directive 2001/83/EC.

Lakrimont is an ophthalmic gel based on a 2 mg/g (0.2% w/w) carbomer 980 packaged in a multidosis tube of 10g. Lakrimont 2 mg/g, eye gel is preserved with 0.1 mg/g (0.01 % w/w) of cetrimide.

Lakrimont 2 mg/g, eye gel is indicated for the symptomatic treatment of dry eye syndrome in adults with a recommended dosing regimen of 1 drop into the inferior conjunctival sac of the affected eye(s), 3-4 times daily or as required, depending upon symptoms resolution. A comprehensive description of the indications and doses is given in the SPC.

The medicinal product was claimed to be essentially similar to the originator Civigel 2 mg/g, eye gel marketed in France by Novartis Pharma. Civigel is registered from 1997 and therefore this eye gel of carbomer 980 is marketed in France for more than 10 years (or 6 years in two EU countries).

Carbomers and cetrimide, a quaternary ammonium, are well established as pharmaceutical ingredients; both are frequently used in ophthalmic products.

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for Lakrimont 2 mg/g, eye gel from Laboratoires Blumont Pharma on 03/05/2011.

Dry eye is a very common disorder affecting a significant percentage (approximately 10-30%) of the population, especially those older than 40 years. Dry eye is also known to be slightly more common in women. It is a multifactorial disease of the tears and the ocular surface that results in symptoms of discomfort, visual disturbance, and tears film instability with potential damage to the ocular surface.

The basis of dry eye treatment consists in most cases in a substitution of the lachrymal fluid by various types of tear substitutes which are considered as symptomatic treatments only. The main objective of tear supplementation/lubricants is to improve the ocular comfort and quality of life of patients with dry eye disease. Although symptoms can rarely be totally eliminated, the ocular surface and tear conditions improved with tear substitutes.

II. QUALITY ASPECTS

II.1 Introduction

The medicinal product Lakrimont 2 mg/g eye gel is a clear, colourless, odourless and particle free aqueous gel for ophthalmic use. It is presented in a 10 g white laminated polyfoil tube with white canula/dropper tip and white screw cap.

The formulation comprises the following excipients: Cetrimide, Disodium edetate, Sorbitol, Sodium hydroxide and Water for injections.

II.2 Drug substance

The drug substance Carbomer (trade name: Carbopol 980 NF) is described in the European Pharmacopoeia. An ASMF was submitted by the Active substance manufacturer.

The drug substance is a fluffy, white hygroscopic powder.

The substance was characterised and impurities were investigated. Adequate specifications are described for the Drug product manufacturer. The analytical procedures are adequately described.

Batch analysis results show compliance with the specifications.

II.3 Medicinal product

The medicinal product Lakrimont 2 mg/g eye gel is claimed to be similar to the innovator product Civigel 2 mg/g eye gel, marketed by Novartis Pharma.

Comparative data are provided which confirm that physicochemical parameters of hybrid and reference products are similar.

The pharmaceutical development of the formulation, the manufacturing process and the container closure system is satisfactorily documented.

The description of the manufacturing process, which includes an aseptic filling step, is provided with manufacturing flow-chart. Operating parameters, in-process controls and maximum processing durations are specified. Satisfactory process validation has been conducted at the declared Drug product manufacturing site.

All excipients are described in the European Pharmacopoeia and controlled according to their corresponding monograph.

The product specifications cover appropriate parameters for this kind of product.

Adequate analytical methods are proposed for the control of the drug product. Their validations have been presented.

Batch analysis has been performed on three industrial scale batches. The batch analysis results show that the drug product meet the proposed specifications.

The primary packaging material is sterilized as per Ph. Eur. standard requirements. Acceptable quality specifications and routine tests are proposed for the packaging.

On the basis of the submitted stability data, a shelf life of 3 years with the storage restriction “do not store above 25°C” can be granted.

III. NON-CLINICAL AND CLINICAL ASPECTS

III.1 Introduction

Carbomer 980 (Carbopol 980) is a well-known active substance with established efficacy and tolerability.

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Civigel® 2 mg/g, eye gel marketed by the company Novartis Pharma.

III.2 Discussion on the non-clinical and clinical aspects

Consistent with the guidance on 'Clinical requirements for locally applied, locally acting products containing known constituents' (CPMP/EWP/239/95/final) and the 'Note for guidance on the investigation of bioavailability and bioequivalence',
-No preclinical trials, bioavailability or pharmacodynamic trials have been performed with Lakrimont 2 mg/g, eye gel, which is locally applied, locally acting and has no known pharmacologic activity.

-No clinical equivalence trial has been performed to compare Lakrimont 2 mg/g, eye gel and the originator Civigel 2 mg/g, eye gel as the applicant has requested a biowaiver.

Justification for the claimed exemption from therapeutic equivalence study is based on identical compositions with respect to both the active and inactive ingredients.
To verify that Lakrimont 2 mg/g, eye gel is similar to Civigel 2 mg/g, eye gel, *comparative physicochemical characterisation* of the test product and the innovator have been appropriately conducted. In addition an *in vitro* comparison using intestinal porcine mucosa to compare the rheological and mucoadhesive behaviour of Lakrimont and Civigel was conducted showing that both formulations were equal as regards their mucoadhesive properties.

Therefore, since the equivalence of the product to the originator has been established through this approach, the Applicant used it as a basis to support the claim of *physicochemical* and *in vitro equivalence*. The lack of a therapeutic equivalence study as per the Note for Guidance on the Clinical Requirements for Locally Applied is an approach accepted. It is also agreed that the slight differences in eye drop size and viscosity which were observed between both products are not of significance from a clinical view: the drop size being around 24.5 mg vs 27.8 mg to 30 mg, and for viscosity 680 to 705 mPas vs 710 to 786 mPas for Lakrimont and Civigel, respectively.

Efficacy and safety data of Carbomer 0.2 % eye gels (generally preserved with cetrimide) are currently referred in published non clinical data and clinical trials as efficient symptomatic treatment of dry eye syndrome with prolonged ocular retention time.

The safety profile can be considered as well-established and no product-specific pharmacovigilance issues were identified which are not adequately covered by the current SPC. During the procedure, no potential serious risk to public health concerns was raised. Additional risk minimisation activities have not been identified for the reference medicinal product. A detailed Risk management Plan is not necessary for this product.

III.3 Pharmacokinetics

Carbomer Gel (Lakrimont) is intended for local use without systemic absorption. The product does not contain pharmacologically active ingredients and absorption or accumulation in eye tissues and the human body can presumably be excluded due to the high molecular weight of carbomer (about 4 million Daltons). Therefore, the approach to determine bioequivalence based on systemic measurements is not applicable ('Note for guidance on the investigation of bioavailability and bioequivalence').

III.4 Pharmacodynamics

The action of this eye gel is based on moistening cornea as well as conjunctiva. This effect is physical in nature and limited to the outer eye. Carbomer does not display its efficacy to relieve symptoms of dryness through a pharmacological mechanism of action but works by physical and mechanical means. As carbomer gel has a high binding power to water, a stable fluid film is formed on the outer eye. This is distributed evenly over the ocular surface with every lid movement and reduces mechanical irritation to the outer eye.

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The chemical-pharmaceutical quality of Lakrimont 2 mg/g, eye gel is demonstrated and it is a hybrid form of Civigel 2 mg/g eye gel, marketed by the company Novartis Pharma, which is a well-known medicinal product with an established favourable efficacy and safety profile.

The originator Civigel 2 mg/g, eye gel was approved in France in 1997, and therefore with more than 10 years (or 6 years in two EU country) of experience.

No new preclinical and clinical studies were conducted for Lakrimont 2 mg/g, eye gel which is acceptable for this kind of application.

The SPC, Package Leaflet (PL) and Labelling are in the agreed template.

The Member States recognised the French evaluation of the marketing authorisation. There was no discussion in the CMDh.

Agreement between Member States was reached through a written procedure.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

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