

## **Public Assessment Report**

### **Scientific discussion**

**Hylan 0.15/0.15 mg/ml, eye drops, solution  
(sodium hyaluronate/carbomer 981)**

**NL License RVG: 115288**

**Date: 5 July 2018**

This module reflects the scientific discussion for the approval of Hylan 0.15/0.15 mg/ml, eye drops, solution. The marketing authorisation was granted on 28 May 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

## List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
HA	Hyaluronic Acid
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SH	Sodium Hyaluronate
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Hylan 0.15/0.15 mg/ml, eye drops, solution from Tramedico B.V.

The product is indicated in adult patients, for:

- The protection and symptomatic treatment of dehydration of the eyes caused by imminent keratoconjunctivitis sicca (dry eye syndrome) as part of Sjogren's Syndrome.
- (Imminent) desiccation of the cornea resulting from (traumatic) injury of the eyelid or peripheral nerve palsies due to which the eye cannot be closed.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a bibliographic application based on well-established medicinal use. The MAH submitted non-clinical and clinical overviews based on scientific literature. The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. Additional non-published studies were added to the dossier.

Hylan contains the active substance sodium hyaluronate. Although no eye drop solutions containing this active substance are registered in the Netherlands as a medicinal product, sodium hyaluronate formulations are on the market as contact lens solutions or 'eye-wetting' products.

Hylan also contains carbomer, a substance which is used in artificial tears for the protection and symptomatic treatment of ocular dehydration. The Dutch society of general practitioners (NHG) recommends artificial tears such as carbomer eye gel or hypromellose eye drops 0.3% for the treatment of keratoconjunctivitis sicca (NHG-standard Red eye 2006).

Scientific advice was given by the MEB concerning this product in 2012, regarding the dossier requirements.

The MAH initially indicated sodium hyaluronate as the only active substance in this medicinal product. However, in the MEB's view, in this specific case, carbomer 981 should be considered an active substance as well. Both sodium hyaluronate and carbomer 981 are registered as active substances in the dossier, and indicated as such in the product information (see section II.4 of this report for further discussion).

## II. QUALITY ASPECTS

### II.1 Introduction

Hylan 0.15/0.15 mg/ml is a clear, colourless solution with pH 6.0 – 8.0 and osmolality of 250 - 320 mOsm/kg. One ml of solution contains 0.15 mg sodium hyaluronate and 0.15 mg carbomer 981.

The solution is packed in 0.65 ml transparent low density polyethylene single-dose containers.

The excipients are: glycerol, sodium hydroxide (for pH-adjustment) and water for injections.

### II.2 Drug Substance

The active substance sodium hyaluronate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, very hygroscopic powder or a fibrous aggregate which is sparingly soluble or soluble in water, and practically insoluble in acetone and in anhydrous ethanol.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can

apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

#### Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

#### Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. and the additional specifications of the CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided for a total of three production scale batches.

#### Stability of drug substance

Stability data on the active substance have been provided for four batches stored at  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$  for 36 months in the commercial package. Storage did not lead to significant physicochemical and microbiological changes. The active substance was also stored at elevated temperature ( $25 \pm 2^{\circ}\text{C}$ ) for six months in the commercial package. This did not lead to significant physicochemical changes. Based on the data submitted, a retest period could be granted of three years when stored at  $2 - 8^{\circ}\text{C}$ .

### **Carbomer 981**

The MAH has informed the MEB that there is no European Active Substance Master File (EU ASMF) available for carbomer 981. Although this substance is widely used, it is manufactured as an excipient rather than a pharmaceutical active substance.

Along the lines of the EMA position with regard to GMP for 'atypical' active substances<sup>1</sup>, the MAH submitted a comprehensive data package on the quality of the active substance and requested a derogation from the obligation to submit an Active Substance Master File for carbomer 981 until further regulatory guidance will have been developed for 'atypical' active substances.

Based on the data provided, the MEB considered that the MAH has sufficiently demonstrated that carbomer 981 is produced in accordance with the GMP standards applicable to active substances. The active substance carbomer 981 can be regarded as 'atypical'. The MEB has been ascertained that carbomer 981 meets the appropriate active substance quality standards.

## **II.3 Medicinal Product**

### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main goal of the development was to obtain a high viscosity eye drop comparable with the eye drops as described in the literature (well established use). Furthermore additional information has been provided that the drug product is comparable, with respect to pH and osmolality to artificial tears (eye gels) that are currently registered on the Dutch market, containing carbomer as active substance. The viscosity differs due to a difference in pharmaceutical form (eye gel versus eye drop). The drug product is however fully comparable with a product that has been available on the German market for more than ten years, Hylan eye drops (German MA Number: 43357.00.00).

The pharmaceutical development of this preservative-free formulation is based on current standards of pharmaceutical science as preservatives are well known for producing reactions of hypersensitivity in many patients. In order to avoid microbial contamination of non-preserved eye drops, they are filled in unit dose containers which are designed for single use only.

For the manufacturing process a blow-fill-seal technique is used. The MAH has sufficiently justified that terminal sterilisation by heat is not possible. Aseptic manufacturing is performed.

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<sup>1</sup> GMP Q&A [#6] van de European Medicines Agency (EMA);  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000027.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp)

#### Manufacturing process

The drug substance is dissolved in water for injections and the solution is filtered. A separate solution is made by dissolving glycerol, carbomer 981 and sodium hydroxide in water for injection. This solution is sterilised by heat. The two solutions are added together and filled into the single used containers by means of an aseptic blow-fill-seal process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches.

#### Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

#### Quality control of drug product

The product specification includes tests for appearance, identification, assay, relative density, pH, osmolarity, viscosity, filling volume and sterility. Viscosity was found to be a stability indicating parameter. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches, demonstrating compliance with the release specification.

#### Stability of drug product

Stability data on the product has been provided for three full scaled batches stored 25°C/60% RH (36 months) and 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in their commercial package with and without the protective aluminium pouch (secondary packaging).

Some changes in the assay were seen (the upper limit was slightly exceeded at several time-points). This was most likely caused by the analytical method. The analytical method for assay determination has been revised and the method has been validated.

When stored in the protective pouch no increase in weight loss due to evaporation is seen in any of the batches and for all three storage conditions. However, when the batches are stored without the aluminium pouch the weight loss increases significantly. Therefore a storage period after opening of the aluminium pouch of four weeks is proposed. This period is acceptable.

All other parameters tested remained relatively stable throughout the storage period. A photostability study was performed and the drug product was found to be susceptible with respect to degradation under the influence of light.

On the basis of the provided stability data a shelf-life before opening of the aluminium pouch of three years without temperature restriction can be granted. However, the drug product should be stored in the original container in order to protect from light.

#### Specific measures for the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

## **II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the MEB considers that Hylan 0.15/0.15 mg/ml, eye drops solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances sodium hyaluronate and the finished product. However, based on its physicochemical properties carbomer 981 should be considered an active substance as well.

The MAH committed to submit an active substance dossier for carbomer 981 within six months after the date at which the marketing authorisation would be granted (i.e. 28 May 2015).

### **Post-approval commitment**

#### Addition of carbomer 981 active substance dossier

On 27 November 2015, the MAH indicated to the MEB that there is no European Active Substance Master File (EU ASMF) available for carbomer 981. Although this substance is widely used, it is manufactured as an excipient rather than a pharmaceutical active substance.

Along the lines of the EMA position with regard to GMP for ‘atypical’ active substances<sup>2</sup>, the MAH requested a derogation from the obligation to submit an active substance dossier for carbomer 981 until further regulatory guidance will have been developed for ‘atypical’ active substances.

This matter was discussed in the Board meeting of 5 January 2017. Based on the data provided, the Board considered that the MAH has sufficiently demonstrated that carbomer 981 is produced in accordance with the GMP standards applicable to active substances. It was agreed that the active substance can be regarded as ‘atypical’. The MEB has been ascertained that carbomer 981 meets the appropriate active substance quality standards.

### III. NON-CLINICAL ASPECTS

#### III.1 Pharmacology

Sodium hyaluronate is a salt of hyaluronic acid (HA). Hyaluronic acid is present in the extracellular matrix of all tissues and is particularly abundant in vitreous humour, skin, cartilage and the synovial fluid of joints. Its long chain molecules form a filter matrix interspersed with cellular fluids, which provide viscoelastic properties to the tissues. In the normal eye, HA forms a layer over the corneal endothelium. It serves to protect the corneal cells and reduce cell damage. The applicant intends to demonstrate by literature that hyaluronate does not only protect corneal cells but also promotes corneal epithelial wound healing via interaction with the receptor CD44, a cell surface adhesion molecule found on human corneal cells.

According to the non-clinical overview, a study by Gomes *et al* (2004)<sup>3</sup> shows that increased expression of CD44 receptors has been shown to be associated with corneal re-epithelialisation. In this *in vitro* experiment in human corneal epithelial cell cultures, sodium hyaluronate (at 0.6 mg/ml = 0.06%) caused increased migration of cells compared to vehicle. This effect is thought to be related to rapid migration of cells leading to rapid wound closure. However, no effect on corneal epithelial cell proliferation was found in this study. A stimulating effect of hyaluronic acid on corneal epithelial migration was also observed in rabbit cornea tissue culture (Nishida *et al*, 1991<sup>4</sup>).

In a study by Camillieri *et al* (2004<sup>5</sup>), it was shown that sodium hyaluronate stimulated corneal epithelial migration *in vitro* using tissue cultures of rabbit cornea and that *in vivo* treatment in rabbits with eye drops containing hyaluronate in physiological saline induced faster wound reparation compared to control of a denuded area in the corneal epithelium. Both effects were dose-dependent. The lowest concentration of 0.015% did not induce an effect in both experiments, while 0.2% and 0.4% induced maximal effects. In the *in vitro* experiment, the effect of molecular weight was also investigated by applying three weight ranges (800-1400, 1400-2000 and 2000-2600 kD). No effect was observed of molecular weight and the *in vivo* experiment was performed using the 800-1400 kD range only. Hylan eye drops contain sodium hyaluronate of 1.5 – 1.65 million Da. According to the MAH, the high molecular weight of hyaluronate in the drug product enables it to be effective in solution at low concentration. Two publications by Saetonne (1989<sup>6</sup> and 1991<sup>7</sup>) are cited. However, these publications do not address the effect of hyaluronate on corneal wound healing, but on miosis and ocular retention using high- and low molecular weight fractions of sodium hyaluronate as adjuvants for

<sup>2</sup> GMP Q&A [#6] van de European Medicines Agency (EMA);

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000027.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp)

<sup>3</sup> Gomes JAP, Amankwah R, Powell-Richards A, Dua HS. Sodium hyaluronate (hyaluronic acid) promotes migration of human corneal epithelial cells *in vitro*. *Br J Ophthalmol* 2004; 88: 821-825

<sup>4</sup> Nishida T, Nakamura M, Mishima H, Otori T. Hyaluronan stimulates corneal epithelial migration. *Experimental Eye Research* 1991 Dec; 53(6):753-8

<sup>5</sup> Camillieri G, Bucolo C, Rossi S, Drago F. Hyaluronan-Induced Stimulation of Corneal Wound Healing is a Pure Pharmacological Effect. *Journal of Ocular Pharmacology and Therapeutics* 2004; 20(6): 548-53.

<sup>6</sup> Seattone MF, Chetoni P, Tilde M et al. Evaluation of muco-adhesive properties and *in vivo* activity of ophthalmic vehicles based on hyaluronic acid. *Int.J.Pharmaceutics* 1989; 51:203-12

<sup>7</sup> Seattone MF, Giannaccici B, Chetoni P et al. Evaluation of high-and low-molecular weight fractions of sodium hyaluronate and an ionic complex as adjuvants for topical ophthalmic vehicles containing pilocarpine. *Int.J.Pharmaceutics* 1991; 72:131-9

topical ophthalmic vehicles containing pilocarpine. In a study by Brignole *et al* (2005<sup>8</sup>), specimens were collected of conjunctiva from patients with moderate dry eye syndrome and superficial keratitis. Flow cytometry was performed on these specimens. Patients were treated with either sodium hyaluronate (SH) or carboxymethylcellulose. After 56 days, a significant decrease in CD44 expression was found in the SH group but not in the CMC group. According to the authors, CD44 is known to be overexpressed in patients with dry eye syndrome. It proves that SH has a significant affinity for the CD44 hyaluronic acid receptors present on conjunctival cells. The authors also state that little is known about the effect of SH on the CD44 receptor.

The rheological behaviour of Hylan was investigated in study F-1-2-1. The rheological behaviour of Hylan was compared with six other artificial tear preparations. The study shows that the viscosity of Hylan reduced in an exponential fashion as the shear rate increased. This implies that Hylan will be most viscous when the eyelid is at rest and the shear rate is low; this will enable it to be retained on the corneal surface. The viscosity of Hylan will be low during blinking when the shear rate is high; this will enable the eye drops to spread quickly across the cornea.

The refractive index of Hylan (and of another product, Unilarm) was investigated in study F-1-3. Sight is often blurred by instilling artificial tears. This is due to an uneven thickness of the tears resulting from poor mixing between an excessively viscous solution with natural tears and a rupture of the refractive index at the interfaces which promotes partial reflection and diffusion of the incident light. Tear film consists of three layers: the mucous layer, the aqueous layer and the lipid layer, with refractive indices of 1.376, 1.336 and 1.5 respectively. The aqueous layer accounts for more than 95% of the light path through the tear film. The refractive index of Hylan was found to be 1.3354; the refractive index of Unilarm was 1.3342. It was concluded that the refractive index of Hylan was similar to the index of the aqueous layer of natural tears.

The light absorption spectrum of Hylan was investigated in study F-1-3. The light absorption spectrum of Hylan was determined using a UV-visible spectrophotometer. It was compared with a solution of physiological saline. Hylan showed a similar light absorption spectrum to 0.9% NaCl. There was no notable absorption between 350-900 nm, especially in the visible range. It was concluded that Hylan will promote an accurate optical transmission of the visible light spectrum.

### **III.2 Pharmacokinetics**

Hyaluronate is not metabolised to any significant amount and diffuses into the plasma. Circulating serum levels in man are reported in the range of 10-100 µg/l.

### **III.3 Toxicology**

Carbomer 981 and glycerol comply with the relevant monographs of the Ph.Eur. These are established substances commonly used in pharmaceutical products, including those approved for ocular use.

#### Single dose toxicity

A mouse study is available. Five male and five female mice were treated by oral gavage with 1500 mg/kg sodium hyaluronate. Animals were observed for 14 days. No abnormalities were observed in clinical signs or body weight or after autopsy.

#### Repeated dose toxicity

Three male and three female albino rabbits were treated in one eye with one eye-drop six times daily for 28 consecutive days, the other eye was untreated. A control group was treated with 0.9% NaCl in one eye. Investigated parameters were clinical signs, food consumption, body weight, macroscopic pathological ocular changes, visual reflexes, ophthalmological examination, haematology, necropsy, organ weights and histopathology. No abnormalities were observed.

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<sup>8</sup> Brignole F, Pisella P-J, Dupas B, Baeyens V, Baudouin C. Efficacy and safety of 0.18% sodium hyaluronate in patients with moderate dry eye syndrome and superficial keratitis. *Graefes Arch Clin Exp Ophthalmol* 2005; 243:531-8

Repeated dose studies from the literature were reported in rats (up to six months), rabbits (up to three months), dogs (up to six months) and monkeys (up to nine years).

#### Genotoxicity

An Ames test was performed using *Salmonella typhimurium* TA1535, TA1537, TA100 and TA98 and *Escherichia coli* WP2 uvrA. Sodium hyaluronate was tested up to 1000 µg/plate. Sodium hyaluronate was not genotoxic in this test.

#### Carcinogenicity

No data are available.

#### Reproductive and developmental toxicity

No study reports were provided. In the literature, segment two studies are described in rats and rabbits as well as a combined segment 2/segment 3 study in rats. No teratogenic effects were observed. Hyaluronate was secreted into breast milk of rats.

#### Local tolerance

An eye irritation study was performed in male albino rabbits. 15.7 mg sodium hyaluronate powder was administered to the conjunctival fornix of a single eye of nine rabbits. In three rabbits, this was followed immediately by irrigation with water for 30 seconds. Clinical signs, body weight and macroscopic pathological ocular changes were observed for up to 96 hours after dosing. Slight reversible eye irritation (redness and discharge) were observed in most of the rabbits. All symptoms were disappeared after 48 hours.

A skin sensitisation study was performed in male guinea pigs. Sodium hyaluronate 1.5% (n=20) was compared with the positive control 2, 4-dinitrochlorobenzene 0.05% (n=5); there was a corresponding vehicle control for each test substance, distilled water (n=10) and olive oil (n=5) respectively. Induction at Day 0 was by intra-dermal injection (0.05ml) followed by topical induction (0.05ml) at Day 7 with closed patch application for 48 h. Topical challenge was at Day 21 with closed patch application for 24h. Scoring was at Day 23 & Day 24. Sodium hyaluronate did not exhibit any skin sensitisation potential in this study. The positive control scored positive.

### **III.4 Ecotoxicity/environmental risk assessment (ERA)**

Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted according to the Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 1) from the obligation to provide an environmental risk assessment for new products. Sodium hyaluronate is the sodium salt of hyaluronic acid, a high molecular weight biopolysaccharide. As hyaluronic acid is a naturally occurring carbohydrate, it is considered that Hylan eye drops are exempted from the requirement to provide an environmental risk assessment. Also for carbomer 981, no ERA has been performed.

### **III.5 Discussion on the non-clinical aspects**

Hyaluronate is a substance naturally occurring in the body. It is a well-known compound of eye drops also at higher concentrations than in the present product. Its systemic availability will not be significant after application of the eye drops. Overall, efficacy and safety of the active substance in the proposed indications are sufficiently justified. No further non-clinical studies are required for this application.

The MEB considers the claim that sodium hyaluronate stimulates healing of corneal damage not sufficiently substantiated. Also it seems that if there is such an effect, the concentration of 0.015% may be too low to achieve this. Sodium hyaluronate stimulated corneal epithelial cell migration *in vitro*, which may have a beneficial effect on corneal wound healing, but to what extent this will be clinically relevant is not known. However in the study by Camillieri (2004) there was only a clear effect at concentrations of 0.2% and higher. Gomes *et al* found no effect on corneal epithelial cell proliferation. Camillieri *et al* found a stimulating effect on cell proliferation but only at concentrations of 0.2% and higher. The MAH has amended the SmPC to remove any claims that Hylan eye drops, solution stimulates corneal wound healing.

Carbomer is a well-known compound of eye drops, for which no concerns on efficacy and safety exist.



## IV. CLINICAL ASPECTS

### IV.1 Introduction

For this application a clinical overview has been provided, which is based on scientific literature as well as the results of two additional clinical trials.

The MAH indicated that the formulation of the product applied for is identical to the product Hylan sodium hyaluronate eye drop solution, authorised in Germany for the symptomatic treatment of dry eyes since 2002. Reference is made to the clinical trial data obtained with this product. A clinical pharmacology study has also been conducted on Hylan sodium hyaluronate eye drops to demonstrate its retention on the cornea after application.

### IV.2 Pharmacokinetics

Pharmacokinetics is not relevant due to the lack of systemic absorption of sodium hyaluronate and carbomer upon topical application.

### IV.3 Pharmacodynamics

Sodium hyaluronate and carbomer are well-known substances with the capacity to absorb water. In this way, a protective layer over the cornea surface is established. This may protect the cornea from the damage that can be caused by inflammatory mediators.

Hylan eye drops contain both sodium hyaluronate and carbomer. These constituents are applied topically as tear substitutes in the management of dry eyes. A comparability study has been performed, comparing the physicochemical characteristics of Hylan 0.15 mg/mL sodium hyaluronate eye drops solution, against a placebo-solution without sodium hyaluronate (but otherwise same qualitative and quantitative composition). The physicochemical characteristics appearance (clarity and opalescence, as well as colouration), pH, viscosity and relative density have been determined. The MAH demonstrated that sodium hyaluronate influences the viscosity of the eye drop solution to a larger extent than the carbomer excipient alone. Due to the viscosity of sodium hyaluronate lubricating effects are enhanced. In the Netherlands, several artificial tears have been registered because of their physicochemical properties rather than a pharmacodynamic effect (e.g. hypromellose or carbomer eye drops).

### IV.4 Clinical efficacy

No new clinical studies were provided. In line with the requirements of a well-established use application, the MAH has submitted an overview of general efficacy of sodium hyaluronate eye drop treatment over the period of 1970 to 2012. The dossier included the results of two non-published pivotal clinical trials.

- **Efficacy of different doses of sodium hyaluronate**

The MAH has provided an overview of available dosages of sodium hyaluronate eye drops, varying between 0.1% and 0.4%. The respective eye drops have been applied three times daily up to ½ hourly initially.

- **Trial of the precorneal residence time of Hylan eye drops vs placebo in healthy volunteers (Study EC-914-1B)**

Design, objective and methods

This was a randomised single-blind cross-over study. The objective was to assess the precorneal residence time of Hylan sodium hyaluronate-carbomer eye drops compared to placebo eye drops in healthy volunteers using a fluorophotometric method.

Six healthy volunteer subjects received a single administration of Hylan sodium hyaluronate-carbomer eye drops to one eye, and placebo (sterile isotonic buffer) to the other eye, both labeled with 0.05% fluorescein. The fluorescence was monitored for four minutes after application using a slit lamp fluorophotometer and the decay curves were recorded. Tolerance parameters and adverse events were recorded.

**Results**

The AUC was significantly greater for Hylan eye drops than placebo ( $p = 0.048$ ). There was no difference between the tear film elimination coefficient ( $k$ ) and tolerance parameters recorded between the two groups. There were no adverse events.

It was concluded that the study results could be interpreted as an effect of the Hylan Sodium hyaluronate-carbomer eye drop solution on the thickness of the corneal film, but that the elimination of fluorescein was unchanged.

• **Pivotal clinical trial Sodium hyaluronate-carbomer vs. carbomer (Study EC-921-3)**

Design, objective and methods

This was a randomised, multicentre, single-blinded parallel study of three months duration. Patients were randomised to receive either test or control treatment by block randomisation (block size= 4).

The study evaluated the efficacy and safety of sodium hyaluronate-carbomer 0.015%/0.015% eye drops (test treatment) versus carbomer 0.3% eye gel (control treatment) in dry eyes disease. The aim of the study was demonstrate the 'equivalence' of both treatments.

The study was performed in 1993. At the time the study was performed the control treatment was a registered product. However, the control treatment is different from the test treatment in more than one aspect e.g. different carbomer content/eye gel formulation versus eye drops.

One hundred patients were included in this trial. These were patients aged over 18 years with moderate to severe dry eye syndrome. The diagnostic of dry eye syndrome was based on a combination of observations on the tear film. Both test and control treatment were applied in the affected eyes four times a day during three months.

Primary outcome measure was the subjective assessment by the patient of the improvement under treatment on a 9-point rating scale. Secondary outcome measures were the total score indicative of the severity of the syndrome, and the Rose Bengal score.

Results

Five patients were lost after the enrolment visit (2 test treatment, 3 control treatment). One patient (in test treatment group) received concomitant local treatment and was therefore excluded. In total, 94 patients received treatment; 46 of these patients received test treatment, the others received control treatment.

**Table 1. Overall evaluation of improvement assessed by the patient at the final visit**

	Test treatment (0.015% sodium hyaluronate-carbomer)	Control treatment (0.3% carbomer)	p-value
Worsening	2.2%	12.8%	0.134
Stability	19.6%	19.1%	
Improvement	78.3%	68.1%	

88.4% of patients who had received test treatment wished to continue their treatment compared to 69.7% of patients who received control treatment ( $p= 0.043$ ).

37.8% of patients treated with test treatment improved their total score by 4 points or more for the right eye, and 51.1% for the left eye. 42.6% of patients who received control treatment improved their total score with 4 points or more for the right eye and 34% for the left eye.

For both treatment groups, total scores tend to decrease upon treatment. Tear film break-up time and Rose Bengal staining also tend to change during treatment. No comparisons between test and control treatment were made with respect to these outcome measures.

**IV.5 Clinical safety**

The safety evaluation of the 0.15 mg/ml sodium hyaluronate eye drops solution relies on non-clinical safety data, literature reports, and post-marketing data. Local burning, eye pain, and blurred vision might occur upon treatment. In study EC-921-3 adverse events and discontinuation occurred more often in the control group as compared to the test group, although the validity of these findings might be questioned considering the study was not blinded. Nevertheless, the reported adverse events and their incidences indicate acceptable safety of the product.

The safety of carbomer is well-established and is deemed acceptable.

**IV.6 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 Hylan.

- Summary table of safety concerns as approved in RMP

Important identified risks	Local burning eye pain and blurred vision (including transient eye irritation)
Important potential risks	Hypersensitivity Potential for off label use
Missing information	Use in patients younger than 18 years Use in patients who may be pregnant Long term clinical safety

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

**IV.7 Discussion on the clinical aspects**

The composition of the product applied for is identical to Hylan eye drop solution, authorised in Germany. Carbomer is a well-known component in artificial tears. Although carbomer has no pharmacodynamic effect, its physicochemical properties are held responsible for the clinical effect. The additional effects of sodium hyaluronate to carbomer appear to be based on an increased viscosity. An additional pharmacodynamic effect of sodium hyaluronate in dry eyes has not been demonstrated. This would require comparative data of the current product with its vehicle.

The MAH demonstrated that the viscosity of Hylan eye drops solution is twice as high as that of its carbomer-containing vehicle. In this way, sodium hyaluronate enhances lubrication of the eyes. Hence, the clinical effect of sodium hyaluronate is rather due to its physicochemical properties than its pharmacodynamic effects. Due to its viscosity, sodium hyaluronate enhances clinical effects of carbomer-containing artificial tears.

Study EC-921-3, performed in 1993, in which efficacy and safety of the product applied for was compared to an at that time registered artificial tear product, does not meet the current standards for demonstrating superiority and/or equivalence of one product to another. The absence of blinding might have biased the assessment of the efficacy, especially the subjective patient rated endpoints. It appears, however, that the effect of the test product was similar to control treatment.

Based on the provided data, the MEB concluded that both sodium hyaluronate and carbomer are responsible for the effect of the eye drops solution, based on their physicochemical properties. It has been adequately demonstrated that the physicochemical properties of Hylan are similar to those of other artificial tears available for at least ten years within the European Union. Risk management is adequately addressed.

**V. USER CONSULTATION**

The package leaflet (PL) 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 test consisted of a pilot test with five participants, followed by two rounds with 10 participants each. Participants were asked 12 questions. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL 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.

## **VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Hylan 0.15/0.15 mg/ml, eye drops, solution has a proven chemical-pharmaceutical quality. The Board discussed the application in the Board meeting of 14 June 2014.

The MEB considers that sodium hyaluronate, as well as carbomer 981 are active substances based on physicochemical properties. The MAH has submitted adequate data on this 'atypical' active substance post approval (see section II.4 of this report)

Both sodium hyaluronate and carbomer have been used in artificial tear solutions for decades. The medicinal use of the active substances can be considered well-established, and products that are comparable to Hylan have been on the European market for over ten years. The product has a favourable efficacy and safety profile, which has been substantiated by adequate non-clinical and clinical literature data and the results of additional clinical trials.

In conclusion, the MEB considered that well-established use has been demonstrated for this medicinal product and has therefore granted a marketing authorisation. Hylan 0.15/0.15 mg/ml, eye drops, solution was authorised in the Netherlands on 28 May 2015.

**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Post-approval commitment: Addition of carbomer 981 active substance dossier	PAC	27-11-2015	20-1-2017	Approval	N See section II.4
Addition of information in the SmPC and PL that the product can be used when contact lenses are worn by the patient.	II	20-6-2017	5-4-2018	Approval	N
Submission of an updated Ph. Eur. certificate of suitability for the active substance sodium hyaluronate.	IA/G	27-7-2017	8-8-2017	Approval	N
Change of address of the MAH.	IA	11-1-2018	10-2-2018	Approval	N