



European Medicines Agency  
Evaluation of Medicines for Human Use

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**WITHDRAWAL ASSESSMENT REPORT  
FOR  
VEKACIA**

International Nonproprietary Name (INN):  
0.05% Eye Drops  
(Ciclosporin)

**Procedure No. EMEA/H/C/904**

Day 120 List of Questions as adopted by the CHMP with  
all information of a commercially confidential nature deleted.

This should be read in conjunction with the “Question and Answer” document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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## **I. RECOMMENDATION**

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Vekacia, an orphan medicinal product, in the treatment of vernal keratoconjunctivitis (VKC) is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies: efficacy.

## **II. EXECUTIVE SUMMARY**

### **II.1 Problem statement**

Vernal keratoconjunctivitis (VKC) is a potentially severe, recurrent chronic ocular immune disease that belongs to the group of allergic conjunctivitis. It typically affects young males (sex ratio reported in the literature: 4/1 to 2/1) living in warm and dry climates worldwide such as the Mediterranean area (Italy), Middle east, Africa, Indian subcontinent but cases are also observed in Northern part of Europe such as UK, France, Scandinavia and North America. Onset is typically in the first decade, usually between 5 and 12 years of age. VKC is a chronic disease with seasonal variations in severity, being worst during warm spring. In warm countries symptoms may persist all year , and the longer the disease is active, the more likely it is that the patients could develop perennial disease.

VKC is considered as a chronic allergic inflammatory disease such as asthma and not as a simple allergic disease. The most common symptoms of patients suffering from VKC are an intense ocular itching, associated with tearing, photophobia, foreign body sensation (sand dots) and burning.

Patients with VKC have a bilateral severe conjunctivitis with corneal involvement leading to serious visual disturbances, including vision loss, the major risk of the disease. There are two forms of VKC: the tarsal(or palpebral) form, more frequent in temperate countries, and the limbal (or bulbar) form, more commonly found in tropical areas.

### **II.2 About the product**

Ciclosporin is practically insoluble in water (6-20µg/ml) and it cannot be formulated in aqueous solution. CsA should be made soluble in oily solubilising agent allowing use as emulsions or in oily solutions.

Novagali Pharma developed VEKACIA eye drops (NOVA22007), a cationic (positively charged) ophthalmic emulsion that contains ciclosporin A (CsA) at a concentration of 0.05% (w/w), as a treatment for vernal keratoconjunctivitis (VKC). Ciclosporin A is a lipophilic cyclic endecapeptide immunosuppressant drug widely used after organ transplant to reduce the activity of the patient's immune system and avoid the graft rejection of organ/tissue. It is also used in the treatment of various immune diseases, including ocular diseases such as uveitis.

### **II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice**

The clinical development programme of VEKACIA consisted of 2 studies:

- One phase IIa, dose-ranging safety study of NOVA22007 (0.025%, 0.05%, 0.1% (w/w) CsA) and its vehicle was conducted in France in Sjögren patients (and therefore adult) with moderate to severe Keratoconjunctivitis sicca (KCS). This multicentre double-masked study (N09F0502) compared the safety and efficacy of three different doses of NOVA22007 and vehicle after 85 days of treatment with 2 instillations per day.

- the NOVATIVE study (NVG 05L101)

The pivotal phase II/III study, conducted in children with VKC, was an international, multicentre, double-masked, randomised, parallel group, dose ranging and controlled study (NVG 05L101) of efficacy and tolerance of NOVA22007 (CsA 0.05% and 0.1% ophthalmic cationic emulsion) versus vehicle in patients with VKC.

Scientific advice was sought on quality, preclinical and clinical aspect of this development in late 2006.

### **II.4 General comments on compliance with GMP, GLP, GCP**

The CHMP has requested a GCP inspection of the clinical study NVG05L101.

The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure.

### **II.5 Type of application and other comments on the submitted dossier**

This is a full application for a product which has been designated an orphan medicinal product in the EU.

### **III. SCIENTIFIC OVERVIEW AND DISCUSSION**

#### **III.1 Quality aspects**

Vekacia, eye drops, emulsion is an oil-in-water ophthalmic emulsion of ciclosporin 0.5 mg/g (0.05%) presented as a single dose product.

As ciclosporin is practically insoluble in water the product is formulated as a cationic emulsion where the ciclosporin is dissolved in the oily phase.

##### **Drug Substance**

The quality of the drug substance ciclosporin is given by a Ph.Eur. certificate of suitability.

##### **Drug Product**

The drug product is formulated whereby ciclosporin is dissolved in the oily phase, medium chain triglycerides (MCT) with Tyloxapol and Poloxamer 188, benzalkonium chloride and glycerol.

The method of manufacture consists in a standard method involving high shear mixture and high pressure homogenization.

Once the pouch is opened, an in-use period of 7 days has been proposed. A shelf life of two years without storage conditions has been assigned to the marketed products. Both periods are subject to a possible change.

#### **III.2 Non clinical aspects**

##### **Pharmacology**

Pharmacology studies were not submitted for the application of NOVA22007. Oral ciclosporin has been used for many years in the treatment / prophylaxis of organ rejection. Its mechanism of action is via passive entry into cells and reversible binding to cyclophilin causing inactivation of calcium dependent activation of the cell. The resultant immunosuppressive effect caused by the inhibition of IL2 production, inhibition of clonal expansion of T lymphocytes (mainly helper CD4 cell and its subsets) is non-toxic and reversible when treatment is stopped. Efficacy of ocularly administered ciclosporin has been documented mainly in published literature in the treatment of VKC which is a severe form of ocular allergy characterised by CD4/Th2 overexpression., not well associated with allergens. Animal models for this condition are not available and efficacy was considered best demonstrated by clinical trials in humans.

The absence of primary pharmacodynamic studies was considered acceptable. Comparison between bioavailability of 0.05% NOVA22007 and the commercially (formulated ad-hoc in non-pharmaceutical premises) available 2% oily solution suggested that similar efficacy could be achieved with the 0.05% oil in water emulsion. It represented a safer alternative formulation, because of a lower dose and hence an enhanced safety profile.

## **Pharmacokinetics**

Validated assays were conducted for the measurement of ciclosporin in ocular tissues and in whole blood. These assays were specific, sensitive, accurate and precise for determination of ciclosporin tissues concentrations in rabbits (aqueous humor, cornea, conjunctivae, plasma and in pigmented and albino rabbit whole blood).

After a single instillation of NOVA22007 containing up to 0.1% ciclosporin into pigmented rabbit eyes, it can be stated that ciclosporin diffuses rapidly in the cornea and conjunctiva and absorption in blood is undetectable. In the cornea, high levels are maintained for at least 72 hours, while they tend to decrease rapidly in the conjunctiva. Ciclosporin absorption in the cornea and conjunctiva increases with increasing dose. After twice daily administration for ten days 0.05% NOVA22007 showed none (conjunctiva) or slight (cornea) ciclosporin accumulation. No systemic passage was detected. On the basis of this data, there is the assumption that a qid dosing regimen as proposed for the clinical use of the product will also not result in accumulation, but this was not clearly outlined in the pharmacokinetic studies and needs to be discussed by the Applicant.

The extent of tissue accumulation may be measured by the ratio of C<sub>max</sub> from multiple dosing to the C<sub>max</sub> after a single dose and if greater than one, accumulation can be considered to occur. From study N09F0407 (a multiple dose study), measurements were taken at 1 hour and 24 hours, rather than at 0.33 hr (C<sub>max</sub>) in the cornea and conjunctiva at the 0.05% dose. Comparing the ratio of corneal and conjunctival measurements after seven days made at 1 hour (0.05% NOVA22007 qid) to the same measurements made at C<sub>max</sub> in study N09F1205 (a single dose study), the ratios for cornea and conjunctiva are 5.66 and 15.68 respectively (in actually the ratio may be slightly higher than this because numerator figure was at a time point past C<sub>max</sub>). This suggests that there may be accumulation of ciclosporin with time using the qid dose regimen and the Applicant should discuss the possibility of accumulation in the cornea and conjunctiva over time with clinical use of the product.

Following repeated (qid – clinical dose regimen) topical ocular administration for 7 days (by which time steady state was achieved) with instillations of NOVA22007 0.05% or 0.1% <sup>3</sup>H-ciclosporin emulsion or Restasis<sup>®</sup> 0.05% <sup>3</sup>H-ciclosporin emulsion in both eyes of pigmented rabbits, the highest radioactivity levels were found in external ocular structures (conjunctivae, cornea and sclera). Low concentration of radioactivity was found in the back of the eye, whole blood and organs. The non-ocular tissues containing the highest concentration of radioactivity included nasolacrimal duct and orbital fat. For all formulations, fixation of <sup>3</sup>H-ciclosporin was located preferentially in cornea and conjunctiva. No significant differences were observed at 1 h and 24 h after instillation for the different formulations. In terms of systemic distribution of NOVA22007, varying amounts of radioactivity, considered related to radioactive metabolites, were found in various organs but particularly, in the liver (7-20 % of conjunctival levels) and the right kidney (5–17 % of conjunctival levels). However, given that CsA is a well-known medicinal active substance and the amount of radioactivity found in the liver and right kidney is comparable to that found with Restasis<sup>®</sup>, the apparent residual activity present is considered unlikely to have an impact on the overall safety evaluation of NOVA22007.

Qualitatively and quantitatively, the studies have demonstrated that the cornea and conjunctiva are the principle sites of ciclosporin distribution and there is very minimal distribution to other areas of the eye and significant reassurance that systemic absorption and distribution are limited. Corneal and conjunctival CsA concentrations seem to be proportional to the administered dose. The cornea appears to act as a reservoir and releases ciclosporin slowly with a long retention time.

No metabolism, excretion or other pharmacokinetic studies were conducted and their absence was considered acceptable.

## **Toxicology**

Repeat-dose toxicity studies with CsA or NOVA22007 were not performed by the Applicant. A 28-day local tolerance study was conducted in rabbits with NOVA22007 in accordance with the note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00). To justify the lack of such studies, two categories of data were provided. First, results of oral studies conducted during the development of Neoral<sup>®</sup> /Sandimmune<sup>®</sup> show that the non toxic effect levels in various species are well above the maximal CsA dose administered in humans. Second, the Applicant has submitted supporting data from repeat-dose toxicity studies performed with Restasis<sup>®</sup> – an ophthalmic oil-in-water emulsion containing CsA and authorized in the USA for the treatment of dry eye – by ocular route were taken into consideration due to similarities between the ocular pharmacokinetics of NOVA22007 and Restasis<sup>®</sup>. In a 6-month study in rabbits, and in a 52-weeks study in dogs, the main findings reported were related to ocular application of Restasis (conjunctival hyperaemia/ discharge, and ocular discomfort) and of limited severity. No non-ocular effect or histological lesion was noted.

CsA was shown to be non-genotoxic in various tests. It was classified by IARC as carcinogenic to humans, but it acts as an epigenic carcinogen in which immunodepressive activity is involved and a threshold exists. Taking into consideration the weak dose of CsA administered topically to patients (0.014 mg/kg/day) compared to systemic doses used e.g. for the prophylaxis of organ rejection, and the negligible systemic exposure to CsA following NOVA22007 treatment, it is agreed with the Applicant that no carcinogenicity study is needed. However, concerning this specific population (children with inflamed eyes) it is a potential risk that epithelial conjunctival neoplasms may develop as a response to treatment which may last for several years. Despite this, it is considered of limited relevance to perform ocular carcinogenicity studies since the risk is already identified and these tumours are rare; it is generally believed that chronic ocular inflammation is a risk factor. In this specific case, it is therefore considered that the issue is considered best in the clinical section.

No reproductive and developmental toxicity studies, as well as no specific juvenile toxicity study were performed. This is acceptable taking into account the negligible exposure to CsA following NOVA22007 treatment and/or available published data with oral CsA. Additionally, no studies in juvenile animals were considered necessary since the systemic and intraocular exposure is very low and the external parts of the eye are fully developed in the target population.

Local tolerance studies demonstrated that NOVA22007 at 0.025%, 0.05% or 0.1% CsA was well tolerated following repeated administration (4 times a day for 28 days) in eyes of rabbits. The few ocular reactions observed were not different between the treated and the untreated eye and histopathological examination did not reveal particular findings. NOVA22007 0.1% CsA and its vehicle did not cause any anaesthesia of the cornea in New Zealand White albino rabbits. The vehicle of NOVA22007 did not induce delayed contact hypersensitivity in the murine Local Lymph Node Assay.

Vekacia was also devoid of phototoxic and photoallergic potential in the Guinea pig. The UV-visible spectra of NOVA22007 indicate that the product is photosafe.

No risk to the environment is posed by NOVA22007 at the maximum daily dose of 0.2 mg/day although it is not clear how the Applicant arrived at a maximum daily dose of 0.2mg/day.

## **Clinical aspects**

### **Pharmacokinetics and Pharmacodynamics**

Considering the route of administration, the Applicant has performed no specific studies to examine pharmacokinetic or pharmacodynamic aspects of this application. Ciclosporin levels taken at day 28 in the pivotal studies suggest limited absorption especially with the dose level chosen for treatment.

### **Clinical efficacy**

*Dose-response studies and main clinical studies*

Dose response studies per se were not performed. The pivotal study did attempt to compare the efficacy and safety of two different concentrations..

Administration in the pivotal study (four times a day) is in contrast to the twice a day administration in the three month KCS study. The dose regimen was derived from the literature and “general current practice”. It is stated that important tearing and abundant mucous secretions in VKC justifies the interest of four instillations a day, as well as the need for eye-washing associated in every treatment of VKC requires a minimum frequency of drop instillations. Moreover, anti-allergic eye drops (anti-histaminic, MCS, sodium cromoglycate) are frequently used four times a day.

The Applicant notes that in many published studies 2% concentration of CsA in an oily preparation is frequently used, but considered that 0.1% should be the highest dose level in their study. However, four times a day application in practice is likely to be difficult and it is possible that a less frequent administration might be equally efficacious and safe. The pivotal study did allow patients to reduce to twice a day if there were problems with tolerability, but during the first 28 days this appears to have been done relatively infrequently. The Applicant should further justify their choice of four times a day administration, providing appropriate evidence.

The pivotal NVG05L101 study was an international, multicentre, double-masked, randomised, parallel groups, dose ranging and controlled study (NVG 05L101) of efficacy and tolerance of NOVA22007 (CsA 0.05% and 0.1% ophthalmic cationic emulsion) versus vehicle in patients with VKC.

The trial was divided in two treatment periods:

Period I: a 4-week prospective, randomised, multicentre, double-masked, three parallel-groups, vehicle-controlled treatment period. The IMP was instilled four times daily.

Period II: a 3-month prospective, multicentre, double-masked treatment period where patients were to continue treatment with NOVA22007 0.05% or 0.1% instilled four times of twice daily.

Male or female patients of at least 4 years of age with active VKC (acute or chronic) needing treatment entered in the study if the following clinical criteria were present:

At least the two following signs, in at least one eye: Presence of giant papillae with a diameter  $\geq 1$  mm on the upper tarsal conjunctiva and superficial keratitis.

At least two of the following ocular symptoms with a score  $> 2$  in at least one eye (same eye as above): burning/stinging, tearing, itching, pain, sticky eyelids, foreign body sensation, mucus discharge, and photophobia;

Hyperaemia score equal to or greater than 2.

The primary objective of the study was:

- To assess the efficacy of NOVA22007 0.05% and 0.1%, a CsA cationic emulsion administered four times daily versus vehicle in patients with VKC after a 4-week treatment period.

The secondary objectives were:

- To compare the safety and ocular tolerance (objective and subjective) of NOVA22007 0.05% and 0.1%, four times daily versus vehicle in patients with VKC after a 4-week treatment period.
- To assess the long-term safety and ocular tolerance (objective and subjective) of NOVA22007 0.05% and 0.1% administered four times daily (or twice daily) in patients with VKC after three additional months of treatment.
- To assess long-term efficacy of NOVA22007 0.05% and 0.1% administered four times daily (or twice daily) or as a maintenance dosing of twice daily for 3 to 4 months.
- To assess the decrease in frequency of artificial tears use.



**Table 1: Primary analysis; overall rating of subjective symptoms of VKC at day 28 (FAS)**

		<b>Vehicle (N=40)</b>	<b>NOVA22007 0.05% (N=39)</b>
Treatment success at Day 28	1- Overall worsening of the subjective findings	7 (17.5%)	1 (2.6%)
	2- No change in the symptoms	5 (12.5%)	3 (7.7%)
	3- Slight improvement (*)	10 (25.0%)	15 (38.5%)
	4- Marked improvement (**)	15 (37.5%)	19 (48.7%)
	5- Completely free of all symptoms	3 (7.5%)	1 (2.6%)
<b>Mantel-Haenszel-Chi-square</b> (comparison of each active arm vs Vehicle)			1.2187
p-value (exact)			0.2699

(\*) 3=Slight improvement with the child still unable to participate in all normal daily activities

(\*\*) 4=Marked improvement despite temporary mild itching or mucus discharge

The primary efficacy criterion was based on a scale for treatment success used in a pilot trial performed in 1986 by Professor BenEzra, who was an investigator in this trial. The Applicant states that “few data were available from previous trials using the same scale for treatment success i.e. a pilot trial in 12 patients, all treated with active product (BenEzra et al 1986) and a prospective randomized placebo controlled trial in 24 patients”. The actual definition of treatment success is stated to be to demonstrate that a score of at least 3 would be recorded in at least 55% of the patients in each of the active arms, while this percentage should not exceed 25% in the placebo arm, assuming the following distribution in the placebo arm: overall worsening of subjective findings (score 1) in 25% of the patients; no change (score 2) in 50% of the patients, slight improvement (score 3) in 25% of the patients and marked improvement in none and no patients scoring 4 or 5. 55% of the patients in each of the active treatment arms showing at least a slight improvement.

In fact, the placebo/vehicle arm greatly exceeded the 25% at a total of 70%, and 37.5% and 7.5% had improvements at 4 and 5 respectively. Even taking account of the scale used, the proposal to take slight improvement with the child still unable to participate in all normal daily activities (score 3), as an acceptable level of efficacy is not considered appropriate.

It could be suggested that for the primary efficacy criterion, the study demonstrates no significant difference from placebo

The Applicant has chosen to use an unbalanced, unvalidated scale to demonstrate efficacy. In addition, the Applicant has chosen to emphasise subjective symptoms. Compared to allergic conjunctivitis, where subjective improvement is often greater, vernal keratoconjunctivitis is associated with more marked subjective and objective findings.

Note that a different scale is used for objective signs. The objective signs are discussed in detail in the clinical assessment section of this report.

With regard to the secondary objectives, to assess long-term efficacy of NOVA22007 0.05% and 0.1% administered four times daily (or twice daily) or as a maintenance dosing of twice daily for 3 to 4 months, as no comparison with placebo/vehicle is provided, it can only be stated that there appeared to be some effect on subjective and objective symptoms and signs and there was no significant difference between the two doses chosen. The subjective symptoms appeared to improve further with time. With regard to

objective signs, whilst there was improvement at day 28 which improved further at days 56 and 112, 30% of patients had still not reached level 5 by day 112.

There appeared to be little effect on the frequency of artificial tears use and vehicle had as great an effect as active.

## **Clinical safety**

### *Patient exposure*

Trial duration for Period I: 26.2 to 27.6 days (mean values) in all groups with ranges: that varied from 3 to 31 days, 23 to 30 days and 7 to 35 days for the vehicle, NOVA22007 0.05% and NOVA22007 0.1% groups respectively.

Mean extent of study drug exposure for Period II was 83.1 days (ranging from 28.0 to 119.0 days for the NOVA22007 0.05% group and 85.5 days, ranging from 6.0 to 131.0 days for the NOVA22007 0.1% group).

### *Adverse events*

The most common AE classified by organ system were eye disorders and general and administration site disorders. This is probably due to the pathological condition and route of the study medication. Nevertheless, the incidence of AEs related to study medication was generally low. The incidence of instillation site pruritus was the most prevalent.

### *Serious adverse events and deaths*

There were no deaths or serious adverse event (SAEs) in this trial in the first 28 days. There were no deaths. However one serious adverse event (SAE) was reported in this trial during the course of period II. SAE: One patient in the NOVA22007 0.05% group experienced a serious TEAE (patient 104): he had an asthma crisis that started and resolved the same day. The treatment was permanently discontinued.

### *Laboratory findings*

The majority of laboratory values were within the normal ranges. Few instances of values that were out of range were recorded in all treatment groups. However, none of these values were clinically significant. Laboratory values (ALAT; ASAT; creatininaemia) and changes in values from Screening to Day 28 were generally similar in all treatment groups. No trends were observed.

Laboratory tests were not performed during Period II.

### *Discontinuation due to AES*

In period I, three patients in the vehicle group withdrew because of worsening of disease after 2 weeks of treatment. Two patients in the 0.1% group withdrew on the basis of withdrawal of consent.

In period II, 2 patients from each of the active groups withdrew because of worsening of disease, 1 patient in the 0.1% group because of ocular intolerance, 1 patient in the 0.05% group because of adverse reactions, and one each for investigator and patient decision. One patient developed a new corneal ulcer (0.05%) and two patients developed significant worsening of vision (one in 0.1% group and one in 0.05% group).

## **Risk Management Plan**

### **Safety specification**

The Applicant comments that there are no important identified or potential risks and has identified the following as important missing information:

- Concomitant eye drops

- Children < 4 years

The Applicant's contention that there are no important identified and potential risks is not endorsed.

Important identified risk:

Local toxicity associated with the use of benzalkonium chloride (BAK) as preservative is an important identified risk, both in terms of its presence and its concentration – This is particularly significant given the product's intended long-term use in a paediatric population with a compromised ocular surface.

Important potential risks:

Systemic effects: Although for ocular administration, and systemic absorption of Vekacia is unlikely, this potential risk and its implications e.g. potential hypertensive, renal and hepatic effects has not been specifically addressed by the Applicant in the safety specification and should be.

Long term effects: With regard to ciclosporin, the potential risks for local and carcinogenic effects have not been addressed in the safety specification. The long term effects of high local concentrations of ciclosporin on the cornea and eye have not been studied in children with VKC. Major risk factors for the development of such malignancies are chronic inflammation and exposure to immunosuppressive drugs . In addition, even though photophobia is a general symptom in VKC, ciclosporin has a photo-co-carcinogenic potential. This consideration is of particular importance in children with vernal keratoconjunctivitis (VKC), who could potentially be using this type of treatment for several months over consecutive years.

**Pharmacovigilance Plan**

The Applicant proposes the following pharmacovigilance actions to address the important missing information; it proposes to record, review and analyse both aspects six months after marketing authorisation.

<b>Safety concern</b>	<b>Planned actions</b>
Important missing information <ul style="list-style-type: none"> <li>• Concomitant eye drops</li> <li>• Age &lt; 4 years</li> </ul>	<ul style="list-style-type: none"> <li>• To record, review and analyse concomitant eye drops in any reported ADR.</li> <li>• To record, review and analyse reported ADRs in children &lt; 4 years of age.</li> </ul>

Concomitant eye drops:

The Applicant intends to identify and evaluate the use of concomitant eye drops, related adverse events and the likelihood of interactions in *adverse events* (presumably suspected adverse drug reactions) reported through the standard PV system (including from compassionate use).

Use in children < 4 years of age:

The Applicant intends to identify *adverse events* (presumably suspected adverse drug reactions) occurring in this subpopulation as reported through the standard PV system.

**Evaluation of the need for risk minimisation activities**

The Applicant proposes that risk minimisation measures are required for the missing information only. This is not endorsed.

## **Risk Minimisation Plan**

With regard to risk minimisation measures, only concomitant eye drops is addressed via an SPC (and PL) warning; the rationale for which has been requested.

Ocular carcinogenicity is an important potential risk, which should also be subject to risk minimisation measures.

## **IV. ORPHAN MEDICINAL PRODUCTS**

Vekacia was designated as an orphan medicinal product in the EU on 6<sup>th</sup> April, 2006 (EU/3/06/360). According to the conclusion of the COMP (Opinion dated 08/03/06) the prevalence of the vernal conjunctivitis is between 1 and 3 per 10,000 individuals in the EU.

## **V. BENEFIT RISK ASSESSMENT**

### **V.1 Benefits**

The issues identified in relation to the pivotal study are such as to make it impossible to judge the benefit of Vekacia at this time. Comparison to vehicle is limited to four weeks, and the results of the study suggest no statistically significant difference between vehicle and active or between the two doses of active.

The improvement in subjective symptoms used in the primary efficacy criterion is not considered to be clinically significant by the CHMP.

In addition, there is no study comparing Vekacia against a comparator such as corticosteroids.

With regard to the issue of significant benefit, the dossier does not *demonstrate* a benefit over available therapies

### **V.2 Risks**

On the basis of the results of the pivotal study, there are no major safety concerns in relation to ophthalmic use of Vekacia.

### **V.3 Balance**

The pivotal study does not allow any conclusions to be drawn on the benefit risk ratio at this stage.

### **V.4 Conclusions**

The overall B/R of Vekacia is unknown.