



Australian Government

Department of Health  
Therapeutic Goods Administration

## AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for fluticasone propionate and azelastine hydrochloride

Proprietary Product Name: Dymista/Dylastine

Sponsor: Meda Pharmaceuticals Pty Ltd

Date of CER: 28 April 2013

## About the Therapeutic Goods Administration (TGA)

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- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

## About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

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## List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
ANCOVA	Analysis of co-variance
ARIA	Allergic Rhinitis and its Impact on Asthma (Guidelines)
AUC	Area under the curve
C <sub>max</sub>	Maximum concentration
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical practice
ICH	International Conference on Harmonisation
iTNSS	Instantaneous Total Nasal Symptom Score
iTOSS	Instantaneous Total Ocular Symptom Score
LOCF	Last Observation Carried Forward
LS	Least Squares
MP29-02	Fluticasone propionate and azelastine hydrochloride nasal spray
mcg	Micrograms
OTC	Over the counter
PAR	Perennial allergic rhinitis
PI	Product information
PK	Pharmacokinetics
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
rTNSS	Reflective Total Nasal Symptom Score
rTOSS	Reflective Total Ocular Symptom Score
S2	Schedule 2 of the Standard for the Uniform Scheduling of Medicines and Poisons

Abbreviation	Meaning
S4	Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons
SAE	Serious adverse event
SAR	Seasonal allergic rhinitis
TGA	Therapeutic Goods Administration
T <sub>max</sub>	Time of maximum concentration

## 1. Introduction

This is an abbreviated submission to register a new fixed dose combination of fluticasone propionate and azelastine hydrochloride, presented as a nasal spray, for the treatment of moderate to severe allergic rhinitis and rhino-conjunctivitis.

Throughout the sponsor's submission, and in many of the tables included in this report, the product is referred to by the codename MP29-02.

Fluticasone propionate is a glucocorticoid. Azelastine hydrochloride is a 2<sup>nd</sup> generation (non-sedating) antihistamine, belonging to the phthalazinone class.

## 2. Clinical rationale

Allergic rhinitis/rhinoconjunctivitis is a very common disorder that affects approximately 20% of the Australian population.<sup>1</sup> It is a disorder that occurs in individuals who have developed a type I hypersensitivity reaction to inhaled antigens. It has traditionally been classified into two forms – seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) – depending on the timing of exposure to the precipitating allergen(s). SAR develops in response to allergens that only occur in certain seasons (for example pollens) whereas PAR develops in response to allergens that are present year-round (for example dust mites, animal dander).

The ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines<sup>2</sup> are a contemporary set of evidence-based clinical guidelines for the treatment of allergic rhinitis, developed by international consensus. They no longer recommend use of the terms SAR and PAR, and instead classify the disease as either intermittent (occurring less than 4 days per week, or for less than 4 weeks at a time) or persistent (occurring more than 4 days per week, or for more than 4 weeks at a time).

Currently registered therapies for allergic rhinitis in Australia include the following:

- Topical decongestants such as oxymetazoline, xylometazoline and phenylephrine nasal sprays, which are generally only recommended for short term use (< 1 week)
- Oral decongestants such as pseudoephedrine and phenylephrine

<sup>1</sup> Walls RS, Heddle RJ, Tang MLK, et al. Optimising the management of allergic rhinitis: an Australian perspective. Med J Aust 2005; 182:28-33.

<sup>2</sup> ARIA (Allergic Rhinitis And Its Impact On Asthma) Guidelines; 2008 Update. Available from: <<http://www.whiar.org>>; ARIA (Allergic Rhinitis And Its Impact On Asthma) Guidelines; 2010 Revision. Available from: <<http://www.whiar.org>>.

- Topical antihistamines such as azelastine and levocabastine nasal sprays
- Oral antihistamines, of which there are multiple formulations available in Australia, including first generation (sedating) and second generation (non-sedating) agents
- Topical glucocorticoids including budesonide, fluticasone propionate, fluticasone furoate, triamcinolone, beclomethasone, mometasone and ciclesonide nasal sprays
- Sodium cromoglycate nasal spray, which is indicated for the prophylaxis of allergic rhinitis
- Ipratropium nasal spray, which is indicated for the treatment of rhinorrhoea associated with allergic rhinitis
- Immunotherapy, with repeated administration of specific allergen extracts, is generally reserved for subjects whose symptoms are not controlled with drug therapy.

The two active ingredients of the proposed combination product are available as individual nasal sprays in Australia.

The sponsor is seeking approval for use of the product in moderate to severe allergic rhinitis and rhino-conjunctivitis. The ARIA guidelines recommend the use of intranasal glucocorticoids for the first line treatment of moderate to severe disease. Where control is not achieved, additional treatment (for example with an antihistamine) is recommended. The use of an antihistamine alone is only recommended for the treatment of mild, intermittent allergic rhinitis. It is likely that some of these patients would progress to moderate or severe disease and hence require the addition of an intranasal glucocorticoid. Hence the concomitant use of fluticasone and azelastine would be appropriate in a proportion of patients with allergic rhinitis.

Prior to submission of this application the sponsor submitted a justification for the fixed combination and this was accepted by the TGA.

There are currently no other registered fixed combination nasal sprays for allergic rhinitis. There are many registered OTC products for oral administration that combine an antihistamine with a decongestant.

In Australia, any azelastine preparation for nasal use is available as an OTC (S2) product. A fluticasone nasal spray can also be an OTC (S2) product provided that it fulfils all of the following criteria:

- Each actuation delivers 50 mcg or less of fluticasone
- The maximum recommended daily dose is no greater than 400 mcg
- The pack contains 200 actuations or less
- The indication is for the prophylaxis or treatment of allergic rhinitis
- The proposed population is adults and children aged 12 years and over
- The proposed duration of use is no more than 6 months.

The product that is the subject of this application fulfils all these criteria except the last. The sponsor seeks to have no limit applied to the duration of use and hence the product will be prescription only if approved.

## 2.1. Formulation

At the time of evaluation by the Clinical Evaluator, it was not clear from the submission whether the formulation proposed for registration in Australia is the same as that used in the submitted clinical trials. The sponsor should be asked to comment on this point.

## 2.2. Guidance

The following regulatory guidelines, published by the European Medicines Agency (EMA) and adopted by the TGA, are relevant to the current submission:

- Guideline On The Clinical Development Of Medicinal Products For The Treatment Of Allergic Rhinoconjunctivitis<sup>3</sup>
- Guideline On Clinical Development Of Fixed Combination Medicinal Products<sup>4</sup>
- Clinical Requirements For Locally Applied, Locally Acting Products, Containing Known Constituents.<sup>5</sup>

Compliance with these guidelines will be discussed in this report where appropriate.

## 3. Contents of the clinical dossier

### 3.1. Scope of the clinical dossier

The clinical dossier documented a development program that included pharmacokinetic studies and efficacy and safety studies.

The submission contained the following clinical information:

- 2 clinical pharmacology studies that provided pharmacokinetic data.
- 1 pivotal efficacy/safety study.
- 3 other supportive efficacy/safety studies.
- 1 study that specifically examined long-term safety.
- Pooled analyses of efficacy, and an Integrated Summary of Safety.
- The sponsors Clinical Overview, Summary of Biopharmaceutics, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

### 3.2. Paediatric data

Allergic rhinitis occurs commonly in children. Fluticasone propionate nasal spray (the S4 version of Flixonase) is approved in Australia for use in children aged 4 years and over. Azelastine hydrochloride nasal spray (Azep) is approved in Australia for use in children aged 5 years and over.

The sponsor has not provided any clinical data on the use of the proposed fixed combination product in children under the age of 12 years and the proposed indication restricts use of the product to patients aged 12 years and over. No justification was provided for omitting children under the age of 12 from the development program.

The EMA granted a waiver for the development of the product in children aged between 2 and 11 years on the grounds that the product does not represent a significant therapeutic benefit over existing treatments in this patient group.<sup>6</sup>

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<sup>3</sup> European Medicines Agency. Guideline On The Clinical Development Of Medicinal Products For The Treatment Of Allergic Rhinoconjunctivitis (CHMP/EWP/2455/02); 2005.

<sup>4</sup> European Medicines Agency. Guideline On Clinical Development Of Fixed Combination Medicinal Products (CPMP/EWP/240/95/Rev. 1); 2009.

<sup>5</sup> European Medicines Agency. Clinical Requirements For Locally Applied, Locally Acting Products, Containing Known Constituents (pp 381 – 391 of Rules 1998 (3C) – 3CC29a); 1996.



**Comment:** This reviewer agrees with EMA's assessment that this product does not represent a significant advance over available therapies (that is the two single agents administered separately). The lack of clinical data in subjects aged less than 12 years is not considered a major deficiency.

### 3.3. Good clinical practice

For each clinical study included in the dossier the sponsor gave assurances that the study was conducted in accordance with the International Conference of Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki.

## 4. Pharmacokinetics

### 4.1. Studies providing pharmacokinetic data

The submission included two studies that examined the effect of the fixed combination nasal spray on the systemic PK of fluticasone and azelastine respectively. Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

**Table 1. Submitted pharmacokinetic studies.**

PK topic	Subtopic	Study ID	*
PK interactions	Effects of azelastine on systemic fluticasone PK	3282	*
	Effects of fluticasone on systemic azelastine PK	3283	*

\* Indicates the primary aim of the study.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

### 4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

#### 4.2.1. Pharmacokinetic interactions

##### 4.2.1.1. Pharmacokinetic interactions demonstrated in human studies

In Study 3282, the co-administration of azelastine hydrochloride with fluticasone propionate (through the proposed fixed combination product) did not result in any change in the systemic fluticasone exposure, compared to that seen with a fluticasone propionate monotherapy product formulated in the same vehicle. It could therefore be reasonably concluded that co-administration of azelastine does not affect systemic PK of fluticasone.

However, both the fixed combination product, and the fluticasone propionate monotherapy product which was formulated in the same vehicle, produced an approximately 50% increase in systemic fluticasone exposure when compared to a fluticasone propionate monotherapy

<sup>6</sup> European Medicines Agency. Decision P/82/2011. Note: Clinical trials were not conducted in children 12 years and under.

product that is commercially available in the USA. This suggests that the vehicle used in the fixed combination facilitates the systemic absorption of fluticasone.

**Comment:** The monotherapy product used in this study that is commercially available in the USA is not registered in Australia. It is therefore not clear how the systemic absorption of fluticasone produced by the fixed combination compares to that produced by the Flixonase formulations registered in Australia. The sponsor has conducted an in vitro comparison of physicochemical characteristics of the Roxane and Flixonase products. This study found that the two products were very comparable. The validity of this conclusion would need to be assessed by a pharmaceutical chemistry evaluator.

The lack of PK data comparing the fixed combination with the Australian Flixonase product is not considered to be a major deficiency in the submission. The approved dosage regimen for Flixonase in Australia permits doses of up to 400 mcg of fluticasone propionate per day. With the proposed fixed combination the maximum dose of fluticasone propionate will only be 200 mcg per day. Hence even if systemic absorption of fluticasone was greater with the fixed combination than with Flixonase, the lower recommended dose provides some reassurance regarding safety.

In Study 3283, the co-administration of fluticasone propionate with azelastine hydrochloride (through the proposed fixed combination product) did not result in any increase in the systemic azelastine exposure, compared to that seen with an azelastine hydrochloride monotherapy product formulated in the same vehicle. It could therefore be reasonably concluded that co-administration of fluticasone does not affect systemic PK of azelastine.

Also the fixed combination product and the azelastine nasal spray marketed in the USA ("Astelin") produced equivalent systemic exposure to azelastine. Hence the combination product would not be expected to produce a higher incidence of systemic adverse events than the marketed product.

**Comment:** The azelastine monotherapy product used in this study ("Astelin") is not identical to the azelastine monotherapy product marketed in Australia ("Azep"). The main difference is that the USA product contains benzalkonium chloride (BAC). The Australian product is identical to the product in Europe which is marketed under the trade name "Allergodil".

The sponsor has conducted an in vitro comparison of physicochemical characteristics of the USA and European/Australian products. This study found that the two products were very comparable. The validity of this conclusion would need to be assessed by a pharmaceutical chemistry evaluator.

The sponsor states that the BAC-containing formulation was marketed in Europe until the late 1990's, when it was changed to the BAC-free formulation. It is noted that on the ARTG, the Australian product (Aust R 104853) is described as a 'reformulation'. If the BAC-containing formulation was also the original formulation approved in Australia, then the TGA would have concluded that it has an acceptable systemic safety profile, and hence its use as a comparator in Study 3283 is acceptable. The sponsor should be asked to comment on this issue.

## 5. Pharmacodynamics

No new clinical pharmacodynamic data were included in the submission.

## 6. Dosage selection for the pivotal studies

No dose-ranging studies were conducted for the product. The dosage of the fixed combination product used in the submitted studies, and proposed for registration, is consistent with the recommended dosages of the approved monotherapy products.

**Comment:** The fluticasone dosage regimen proposed for the fixed combination product is 100 mcg twice daily. The recommended dosage for the Flixonase products registered in Australia is 200 mcg once daily. The sponsor has provided two review articles<sup>7</sup> which included summaries of the published literature on 200 mcg once daily versus 100 mcg twice daily dosing of fluticasone propionate nasal spray. All studies found comparable efficacy between the two regimens. The product information for the S4 version of Flixonase also allows twice daily dosing if the daily dose needs to be increased to 400 mcg per day. The twice-daily dosing regimen for fluticasone propionate is therefore considered acceptable.

## 7. Clinical efficacy

**7.1. Indication: “Symptomatic treatment of moderate to severe allergic rhinitis and rhino-conjunctivitis in adults and children 12 years and older where use of a combination (intranasal antihistamine and glucocorticoid) is appropriate.”**

**7.1.1. Pivotal efficacy studies**

**7.1.1.1. Study MP4001**

*7.1.1.1.1. Study design, objectives, locations and dates*

Study MP4001 was a randomised, double blind, placebo-controlled trial with four parallel groups, conducted in patients with seasonal allergic rhinitis (SAR). All subjects received placebo during a 1 week run-in period (Day -7 to Day 1). On Day 1 they were randomised to one of the four treatments, and these were continued for a 14-day treatment period.

The objective of the study was to compare the efficacy and safety of the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray to placebo and each product alone.

The study was conducted in 8 centres in Texas in the United States, during the pollen season for Texas Mountain Cedar (*Juniperus ashei*). Subjects enrolled in the study had documented allergy to this pollen. The first patient was enrolled on [information redacted] and the last patient completed on [information redacted]. The study report was dated 27 April 2010.

**Comment:** The use of a parallel group design with comparison of the fixed combination with its individual substances and placebo is consistent with the recommendations of the EMA guideline on fixed combination products.<sup>8</sup>

*7.1.1.1.2. Inclusion and exclusion criteria*

Subjects were required to be at least 12 years of age. They were required to have at least a 2-year history of SAR during the Texas Mountain Cedar pollen season as well as a positive skin

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<sup>7</sup> Bryson HM, Faulds D; Intranasal fluticasone propionate. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in allergic rhinitis. *Drugs*. 1992 May; 43(5): 760-75; Wiseman LR, Benfield P. Intranasal fluticasone propionate. A reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. *Drugs*. 1997 May; 53(5): 885-907.

<sup>8</sup> European Medicines Agency. Guideline On Clinical Development Of Fixed Combination Medicinal Products (CPMP/EWP/240/95/Rev. 1); 2009.

prick test to this antigen. Efficacy in this study was assessed using symptom scores and subjects were required to have a certain degree of symptoms at baseline (as measured by these symptom scores). Subjects were required to have a Total Nasal Symptom Score (TNSS) of at least 8 (out of a possible 12), together with a nasal congestion score of at least 2 (out of a possible 3) at Day -7. Similar criteria had to be met on Day 1.

**Comment:** The inclusion and exclusion criteria are appropriate and comply with the requirements of the EMA guideline on products for allergic rhinitis. According to the ARIA guidelines,<sup>9</sup> "moderate/severe" allergic rhinitis means that one or more of the following items are present:

- sleep disturbance,
- Impairment of daily activities, leisure and/or sport,
- impairment of school or work or
- troublesome symptoms.

Given the inclusion criteria in this study for severity of symptoms at baseline it would be expected that patients enrolled would have moderate to severe disease.

#### 7.1.1.1.3. Study treatments

Subjects were randomised to receive one of the following four treatments for the 14 days of the randomised treatment period:

- The proposed fixed combination of fluticasone propionate (50 mcg per actuation) and azelastine hydrochloride (137 mcg per actuation) nasal spray – one spray in each nostril twice daily
- Fluticasone propionate (50 mcg per actuation) nasal spray (using a formulation marketed in the USA) - one spray in each nostril twice daily
- Azelastine hydrochloride (137 mcg per actuation) nasal spray (using the Astelin formulation marketed in the USA)– one spray in each nostril twice daily
- Placebo spray - one spray in each nostril twice daily.

The placebo spray was the vehicle used for the fixed combination but without the active ingredients.

The use of rescue medications such as decongestants was prohibited.

**Comment:** Both comparator products are considered acceptable, as the FDA, a regulatory authority with similar standards to the TGA, has approved them.

The dosage of azelastine used in the study is consistent with the only azelastine dosage regimen approved in Australia (daily dose of 548 mcg). The dosage of fluticasone used in the study (200 mcg per day) is in the middle of the range approved for Australia (100 to 400 mcg per day). The dosing regimen for the fixed combination does not allow an assessment of whether using 400 mcg per day of fluticasone alone is superior to using the combination. It also does not allow down-titration of the steroid dose to 100 mcg per day in subjects whose symptoms are controlled. These limitations are typical of the issues that arise with fixed combination products.

#### 7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

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<sup>9</sup> ARIA (Allergic Rhinitis And Its Impact On Asthma) Guidelines; 2008 Update; ARIA (Allergic Rhinitis And Its Impact On Asthma) Guidelines; 2010 Revision.

- The severity of symptoms of rhinitis and conjunctivitis scored by the patient and recorded twice daily in a study diary.
- Quality of life as assessed by the patient using an Adult Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).

The primary efficacy outcome was:

- Change from baseline to Day 14 in the 12-hour reflective TNSS for the entire double blind period compared to placebo.

Secondary efficacy outcomes included:

- Change from baseline in instantaneous TNSS for the entire 14-day study period compared to placebo
- Change from baseline in 12-hour reflective individual symptom scores (including postnasal drip) for the entire 14-day study period compared to placebo
- Daily change from baseline in 12-hour reflective and instantaneous TNSS compared to placebo
- Change from baseline in 12-hour reflective TOSS for the entire 14-day study period
- Change from baseline in 12-hour reflective and instantaneous individual ocular symptom scores for the entire 14-day study period
- Change from baseline to Day 14 in the RQLQ compared to placebo in subjects 18 years of age and older.

**Comment:** Use of the rTNSS as the primary endpoint, and the use of other symptom scores and the RQLQ as secondary endpoints, is consistent with the EMA guideline on products for allergic rhinitis. The RQLQ is a validated and widely used QoL instrument.

#### *7.1.1.1.5. Randomisation and blinding methods*

Subjects were randomised 1:1:1:1 by a biostatistical group engaged by the sponsor, using a validated system that assigned random permutations of treatments to consecutive groups of 4 subjects. Allocation to treatment was accomplished through an interactive voice recognition system (IVRS).

Blinding was achieved by enclosing all nasal sprays in identical foil pouches.

#### *7.1.1.1.6. Analysis populations*

The Intention To Treat (ITT) population included all randomised subjects with at least one post-baseline observation. The Per Protocol (PP) population included all subjects completing the 2-week treatment period. The safety population included all randomised subjects who received at least one dose of study medication.

#### *7.1.1.1.7. Sample size*

When the AM and PM rTNSS scores are combined, possible scores range being between 0 and 24. Based on a previous study, which used this method and which used co-administration of azelastine and fluticasone nasal sprays, the expected change in rTNSS for the fixed combination product was -5.92 points. In other previous studies, placebo nasal spray produced changes of up to -3.41 points. Using an expected standard deviation of 5.0 points (based on the same previous studies), a two-tailed test with an alpha value of 0.05 and 90% power and allowing for a 10% dropout rate, approximately 95 subjects were required per treatment group, to test the combination product against placebo.

Based on previous studies, the expected change in rTNSS for the fluticasone group was -4.19 units. Using the value of -5.92 points for the combination product, along with an alpha of 0.05,

80% power, a two-tailed test and a 10% dropout rate, the calculated sample size was approximately 150 subjects per treatment group for this comparison. As azelastine nasal spray had been demonstrated to produce less of an effect on rTNSS than fluticasone, this sample size would be adequate for comparing the fixed combination with azelastine monotherapy.

#### 7.1.1.1.8. *Statistical methods*

For the primary endpoint, all absolute changes in combined (AM plus PM) rTNSS from Day 1 PM to Day 14 AM were included as repeated measures in an analysis of covariance (ANCOVA) model. The model contained study day as the within-subject effect, treatment group and site as the between-subject effects, and baseline as a covariate. Missing TNSS values were imputed using the last observation carried forward (LOCF) method. The analysis was done on the ITT population.

Two-sided confidence intervals for the differences in overall mean changes, that is, the combination compared to placebo, the combination compared to azelastine, and the combination compared to fluticasone, were also calculated.

In order to adjust for multiplicity, a gatekeeping strategy was employed. The combination versus placebo comparison was first tested at the 0.05 significance level. If this was significant, then the combination versus azelastine comparison was also done at the 0.05 level. If the combination versus azelastine comparison was not significant at the 0.05 level, no comparison of the combination versus fluticasone was made. Otherwise the comparison was made at the 0.05 level.

Sensitivity analyses included a raw data analysis without data imputation, and an analysis of the PP population.

A large number of analyses of symptom score secondary endpoints were conducted also using the ITT population and with LOCF for missing values. Analyses were done for both the combined AM and PM scores and for the AM and PM scores separately. Analyses were also provided for both absolute change from baseline and percent change. Comparisons were made for the entire 14-day treatment period as well as for each individual day. The ANCOVA model was used to compare scores over the entire 14-day treatment period. A reduced model, without study day as a factor, was used for treatment comparisons for individual days. No adjustments for multiplicity of testing were made for these secondary endpoints.

For the RQLQ, the total score as well as the 7 domain scores were analysed by applying an ANCOVA model as for the other individual day comparisons.

For all endpoints, within-subject changes from baseline for each treatment group were compared by calculating p-values based on paired t-test.

#### 7.1.1.1.9. *Participant flow*

A total of 610 subjects were randomized and 94.6% of these completed the study. Reasons for discontinuation were well balanced between the four treatment groups.

#### 7.1.1.1.10. *Major protocol violations/deviations*

One subject in the azelastine group and two in the fluticasone group did not have any post-baseline efficacy assessments and were therefore excluded from the ITT analysis. A total of 49 randomised subjects were excluded from the PP population. Most of these (n = 33) were excluded because they did not complete the study. Reasons for exclusion for the remaining 16 subjects included not meeting inclusion/exclusion criteria, poor compliance based on diary dosing records and the final visit being outside the required window of plus or minus 2 days. These violations were reasonably evenly distributed across the four treatment arms.

A tabulation of concomitant medications used in the study was provided in the report. Use of medications that might have represented rescue treatment (for example promethazine, loratadine, triamcinolone) was rare and occurred only in the azelastine and placebo groups.

**Comment:** The protocol violations would not have affected the outcome of the study.

*7.1.1.1.11. Baseline data*

**Comment:** The four groups were well balanced for these variables. Mean rTNSS scores were greater than 18 (out of a possible 24) in all groups, which would be consistent with subjects having moderate to severe rhinitis.

*7.1.1.1.12. Results for the primary efficacy outcome*

For statistical analysis of symptom scores, the AM and PM values were combined. Score values could therefore range between 0 and 24.

There was significant improvement in rTNSS from baseline in all treatment groups, including placebo. The improvement seen with the fixed combination (LS Mean -5.31) was significantly greater than that seen with fluticasone alone (-3.84;  $p = 0.003$ ), azelastine alone (-3.25;  $p < 0.001$ ) and placebo (-2.20;  $p < 0.001$ ).

**Comment:** The placebo-corrected improvement obtained with azelastine alone was -1.05 and with fluticasone it was -1.64. The value with the combination was -3.11. Therefore the absolute benefit of the combination over fluticasone alone was -1.47. This value is comparable to the benefit seen with the monotherapies over placebo. As both the monotherapies are registered in Australia, it could be concluded that the additional benefit provided by the combination is clinically significant.

*7.1.1.1.13. Results for other efficacy outcomes*

The sponsor presented a large number of other analyses of secondary endpoints. Results included the following:

**Nasal symptoms**

- Sensitivity analyses of the primary endpoint gave comparable results to the primary analysis. These included the per-protocol analysis, a raw data analysis without data imputation and an analysis that included a treatment-by-site term in the analysis model.
- The study report stated that the change from baseline in the primary endpoint was also statistically significant for both monotherapy comparators versus placebo ( $P < 0.05$ ), although no further information or tabulations were provided.
- For rTNSS (AM+PM) by individual day, the combination product was significantly more effective than placebo and azelastine for all days, and superior to fluticasone for most days. This was true for both change in absolute score from baseline, and percentage change from baseline.
- For rTNSS (AM only), the combination was superior to all 3 comparators when compared over the entire double-blind period, for both absolute and percentage change. For individual days, it was superior to placebo on all days and superior to azelastine and fluticasone on most days, whether assessed by absolute change or percentage change. The same overall pattern of results was seen for rTNSS (PM only).
- For the individual symptom of itchy nose (AM+PM), the combination was superior to all 3 comparators when compared over the entire double-blind period, for absolute change from baseline. When examined in terms of percentage change, it was superior to placebo and azelastine but not fluticasone ( $p = 0.055$ ). Individual day scores were consistent with this pattern.

- For the individual symptom of nasal congestion (AM+PM), the combination was superior to all 3 comparators when compared over the entire double-blind period, for both absolute and percentage change. Comparison of scores for individual days gave similar results.
- For the individual symptom of sneezing (AM+PM), the combination was superior to all 3 comparators when compared over the entire double-blind period, for both absolute and percentage change. Comparison of scores for individual days gave similar results.
- For the individual symptom of runny nose (AM+PM), the combination was superior to placebo and azelastine but not fluticasone ( $p = 0.068$ ) for absolute change from baseline when compared over the entire double-blind period. When examined in terms of percentage change, it was superior to all 3 comparators. Individual day scores were consistent with this pattern.
- For instantaneous TNSS (iTNSS – AM+PM) the combination was superior to all 3 comparators for both absolute change from baseline and percentage change from baseline when compared over the entire double-blind period.
- For iTNSS (AM only), and iTNSS (PM only) the combination was superior to all 3 comparators when compared over the entire double-blind period, for both absolute and percentage change. For individual days, the combination was superior to placebo on all days, superior to azelastine on most days, but not significantly better than fluticasone on most days.
- For individual nasal symptoms assessed using iTNSS (AM+PM), the combination was generally superior to placebo and azelastine for all four symptoms. However there were no significant differences between the combination and fluticasone for the symptoms of itchy nose and runny nose assessed over the entire double-blind period. It was significantly superior to fluticasone on nasal congestion and sneezing.

### Ocular symptoms

- For rTOSS (AM+PM), the combination product was superior to placebo and fluticasone when compared over the entire double-blind period. However, it was not superior to azelastine alone. The findings were the same for absolute and percentage change from baseline, and after a per-protocol analysis.
- For rTOSS (AM alone), the combination was superior to placebo and fluticasone but not to azelastine. For rTOSS (PM alone), the combination was superior to placebo and fluticasone. It was also superior to azelastine in terms of absolute change from baseline, but not by percentage change from baseline ( $p = 0.072$ ).
- For individual eye symptoms using rTOSS (AM+PM), the combination was superior to placebo and fluticasone on all 3 symptoms. It was superior to azelastine in terms of itchy eyes, but not for the other two symptoms.
- These analyses were repeated using iTTOSS and similar results were obtained. The combination was consistently superior to placebo, not consistently superior to fluticasone and not significantly different from azelastine.

### Postnasal drip

- For the reflective score (AM+PM) of postnasal drip, the combination was superior to placebo and azelastine but was not significantly different to fluticasone. This was also true following a per-protocol analysis, and analysis of AM only and PM only scores.

#### 7.1.1.1.14. RQLQ

- There was an improvement from baseline in all 4 treatment groups. The improvement obtained with the combination was significantly greater than that obtained with placebo or



azelastine, but there was no significant difference compared to fluticasone ( $p = 0.286$ ). The differences between groups in mean improvement were small, with only the combination versus placebo difference (LS means of -1.60 versus -1.01) being greater than the clinically important difference of 0.50 points.

- The p-values for the comparisons between treatments of the individual domains of the RQLQ are broadly consistent with the results seen for the overall score, with the combination being superior to placebo and azelastine, but with no difference being seen between the combination and fluticasone.

### 7.1.2. Other efficacy studies

The submission included three other Phase III randomised controlled trials (MP4002, MP4004 and MP4006) which were very similar in design and conduct to the pivotal study. Each was a randomised, double blind, placebo-controlled study with four parallel groups. The four treatment groups in each study were:

- The proposed fixed combination of fluticasone propionate (50 mcg per actuation) and azelastine hydrochloride (137 mcg per actuation) nasal spray – one spray in each nostril twice daily
- Fluticasone propionate (50 mcg per actuation) nasal spray (formulated in the same vehicle as the combination product) - one spray in each nostril twice daily
- Azelastine hydrochloride (137 mcg per actuation) nasal spray (formulated in the same vehicle as the combination product) – one spray in each nostril twice daily
- Placebo spray - one spray in each nostril twice daily.

The placebo spray was the vehicle used for the fixed combination but without the active ingredients.

**Comment:** The azelastine and fluticasone monotherapy products used in these studies are not commercially available, and appear to be “in-house” formulations developed by the sponsor. A fixed combination product should have superior efficacy to the monotherapy products currently been used by patients (that is the marketed monotherapy products). The submission did not provide any evidence that the “in-house” formulations used in these studies had comparable efficacy to marketed formulations of azelastine hydrochloride and fluticasone propionate. Therefore, in this reviewer’s opinion, the three studies cannot be considered pivotal due to the use of inappropriate comparators.

It would be of interest to know the sponsor’s rationale for not using marketed comparators in these three studies.

The submission also included another Phase III randomised controlled trial (MP4000), which had, as it’s the primary objective, the evaluation of long term safety of the combination product. The study compared the combination with fluticasone propionate nasal spray and included rTNSS and RQLQ as secondary endpoints. However the study enrolled patients with either PAR or non-allergic chronic rhinitis, and the rTNSS results were only presented for the entire population, so that efficacy results in those patients with PAR could not be dissected out. The study was also not blinded. For these reasons the efficacy data from the study are not considered useful.

#### 7.1.2.1. Study MP4002

The study objectives and design were virtually identical to those of the pivotal Study MP4001. It was conducted in patients with SAR, with a documented hypersensitivity to a local spring pollen. An additional inclusion criterion was that subjects must have had moderate-to-severe rhinitis, defined as rhinitis with one or more of the following being present:

- Sleep disturbance
- Impairment of daily activities, leisure and/or sport
- Impairment of school or work or
- Troublesome symptoms.

The study was conducted at 44 sites in the USA. The first patient enrolled on [information redacted] and the last patient completed on [information redacted]. The study report was dated 3 May 2010.

The primary efficacy outcome was rTNSS over the entire 14-day treatment period and the secondary efficacy outcomes were essentially the same as those used in the pivotal study. In addition, the study assessed onset of action by recording iTNSS at the following time points after the initial use of study medication on Day 1: 0, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes.

A total of 832 subjects were randomised and of these 798 (95.9%) completed the study.

All four treatments were associated with significant improvement in rTNSS from baseline. The three active treatments were all superior to placebo and the combination was significantly more effective than the two monotherapies.

**Comment:** The “in-house” formulations of fluticasone and azelastine were both significantly superior to placebo. However this does not establish that they are of comparable efficacy to the monotherapy products that are marketed in Australia (or elsewhere).<sup>10</sup>

There were multiple secondary endpoints based on nasal symptom scores including individual symptoms and iTNSS. On these endpoints, the combination was consistently superior to placebo and azelastine. However, for the majority of the secondary endpoints there was no significant difference between the combination and fluticasone.

Results for the change in iTNSS over the first four hours on Day 1 (onset of action) showed a statistically significant difference between the combination and placebo at the 45-minute time point ( $p = 0.021$ ) and remained so over the whole 4-hour period. No significant differences were observed at any time point for the combination versus fluticasone or combination versus azelastine comparisons.

**Comment:** These findings would support a claim for rapid onset of action for the product (that is within 45 minutes). However, for this study, they do not support a claim that the product will have a more rapid onset of action than fluticasone propionate alone.

For post-nasal drip, the combination was superior to placebo and azelastine, but not to fluticasone.

With regard to ocular symptoms, the results for the rTOSS over the entire 2-week treatment period in this study, the combination was superior to placebo, but was not significantly better than either of the monotherapy comparators. Secondary endpoints (individual symptoms, iTOSS) gave similar results.

The analysis of RQLQ overall score demonstrated that the combination was superior to placebo and azelastine, but not fluticasone. The differences in LS means between the combination and the two active comparators were less than 0.50 points, indicating that the combination has no clinically significant advantage over the monotherapy products.

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<sup>10</sup> European Medicines Agency. Clinical Requirements For Locally Applied, Locally Acting Products, Containing Known Constituents (pp 381 – 391 of Rules 1998 (3C) – 3CC29a); 1996.

### **7.1.2.2. Study MP4004**

The design and methods for Study MP4004 were identical to those used for Study MP4002, except that the subjects had to have a documented hypersensitivity to a local autumn antigen and the study was conducted during the North American autumn season. The study was conducted at 41 sites in the USA, with the first subject being enrolled on [information redacted] and the final subject completing on [information redacted]. The study report was dated 4 May 2010.

The efficacy endpoints used in the study were the same as those used in Study MP4002, including the secondary endpoint of onset of action as assessed by iTNSS over the first 4 hours of Day 1. The statistical analysis plan differed from MP4002 in that rTOSS was made a key secondary endpoint, with additional control introduced for multiplicity testing. Once the 3 test comparisons of rTNSS (the combination versus placebo, azelastine and fluticasone) were shown to be significantly different in favour of the combination, the rTOSS was examined in the same order specified for rTNSS.

A total of 779 subjects were randomised and of these 739 (94.9%) completed the study.

All four treatments were associated with significant improvement in rTNSS from baseline. The three active treatments were all superior to placebo and the combination was significantly more effective than the two monotherapies.

As with the previous studies, there were multiple secondary endpoints based on nasal symptom scores including individual symptoms and iTNSS. On these endpoints, the combination was consistently superior to placebo, and usually superior to azelastine. However, for approximately half of the secondary endpoints there was no significant difference between the combination and fluticasone.

Results for the change in iTNSS over the first four hours on Day 1 (onset of action), difference between the combination and placebo, was statistically significant at the 30-minute time point ( $p = 0.032$ ) and remained so over the whole 4-hour period. As in Study MP4002, no significant differences were observed at any time point for the combination versus fluticasone or combination versus azelastine comparisons.

For post-nasal drip, the combination was superior to all 3 comparators in terms of absolute change in score from baseline, but was only superior to placebo in terms of percentage change in score from baseline.

For ocular symptoms, the results for the rTOSS over the entire 2-week treatment period, in this study, the combination was superior to placebo and fluticasone, but was not significantly better than azelastine ( $p = 0.069$ ). Other secondary endpoints (individual symptoms, iTOSS) gave similar results.

The analysis of RQLQ overall score demonstrated that the combination was superior to placebo and azelastine, but not to fluticasone. The differences in LS means between the combination and the two active comparators were less than 0.50 points, indicating that the combination had no clinically significant advantage over the monotherapy products.

### **7.1.2.3. Study MP4006**

The design and methods for Study MP4006 were essentially identical to those used for Study MP4004. Subjects had to have hypersensitivity to prevailing individual seasonal pollen documented by positive skin prick testing within the last year. The study was conducted at 49 sites in the USA, with the first subject being enrolled on [information redacted] and the final subject completing on [information redacted]. The study report was dated 4 May 2010.

In Studies MP4002 and MP4004, the observed treatment effect was smaller than that of previous trials (MP4001 and an earlier study using monotherapy products). Also, efficacy for ocular symptoms was less pronounced than for nasal symptoms. The sponsor therefore decided

to increase the sample size for this study to 450 subjects per treatment arm (compared to 150-195 subjects for earlier studies) in order to minimise the risk of a potentially negative trial.

A total of 1801 subjects were randomised and of these 1728 (95.9%) completed the study.

As in the prior studies, all four treatments were associated with significant improvement in rTNSS from baseline. The three active treatments were all superior to placebo and the combination was significantly more effective than the two monotherapies.

Again there were multiple secondary endpoints based on nasal symptom scores including individual symptoms and iTNSS. On these endpoints, the combination was consistently superior to placebo, and usually superior to azelastine. However, for most of the secondary endpoints there was no significant difference between the combination and fluticasone.

Results for the change in iTNSS over the first four hours on Day 1 (onset of action), the difference between the combination and placebo, was statistically significant at the 30-minute time point ( $p = 0.008$ ) and remained so over the whole 4-hour period. In this study the combination was also superior to fluticasone commencing at 30 minutes ( $p = 0.037$ ) and continuing through the 4-hour period. No differences were observed between the combination and azelastine.

**Comment:** Unlike the two previous studies, the combination was shown to have a more rapid onset of action than fluticasone alone. This presumably is the result of the larger sample size and greater power of the study.

For ocular symptoms, the results for the rTOSS over the entire 2-week treatment period, in this study, the combination was superior to placebo, but was not significantly better than azelastine or fluticasone. Other secondary endpoints (individual symptoms, iTOSS) gave similar results.

The analysis of RQLQ overall score demonstrated that the combination was superior to placebo and azelastine, but not to fluticasone. The differences in LS means between the combination and the two active comparators were less than 0.50 points, indicating that the combination had no clinically significant advantage over the monotherapy products.

### 7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

The submission included a pooled analysis of the above four trials, as well as a pooled analysis of the three trials (MP4002, MP4004 and MP 4006) that used the 'in-house' versions of azelastine and fluticasone sprays. The results of the 4-trial analysis are summarised here.

**Comment:** The four studies had virtually an identical design and produced consistent results. All four trials were positive and hence the submission is not relying on the pooled data to establish overall efficacy. Pooling of the studies is therefore considered appropriate.

The pooled analysis included 3997 subjects. The four treatment groups had comparable mean rTNSS scores at baseline.

For the primary endpoint of change in rTNSS (AM+PM scores combined) over the entire 14-day treatment period, the combination product was superior to all three comparators, and the two monotherapy products were both superior to placebo. These findings are consistent with the results of the individual studies. Analysis of AM rTNSS, PM rTNSS, individual nasal symptom scores, iTNSS and postnasal drip gave similar results.

For ocular symptoms, rTOSS (AM+PM combined) over the entire 14-day treatment period, the combination product was again superior to all three comparators, and the two monotherapy products were both superior to placebo. Analysis for individual eye symptoms gave similar results.

**Comment:** In the individual studies the combination was not shown to be superior to azelastine alone for rTOSS. In the pooled analysis, the difference between the two products just reached statistical significance ( $p = 0.0481$ ). However, the absolute difference in LS-

means between the two products was only -0.30 points, which is unlikely to be clinically significant given that subjects had baseline scores of approximately 12.0.

For RQLQ overall score, the pooled analysis failed to demonstrate a significant benefit for the combination over fluticasone. The difference between the combination and azelastine was statistically but not clinically significant.

The report included analyses of rTNSS and rTOSS for various subgroups of patients according to gender, age range (12 to 17, 18 to 65 and > 65), race (white, other) and ethnicity (Hispanic, non-Hispanic). These analyses did not raise any concerns regarding lack of efficacy in any particular subgroup.

The submission also included a post-hoc, pooled analysis of responder rates across the four efficacy studies. Analysis of responder rates is recommended in the EMA guideline on allergic rhinitis. A response was defined as at least a 50% reduction from baseline in rTNSS. The proportion of patients who achieved a response was significantly greater in the combination group than in the comparator arms. For any given level of response rate, the level was achieved earlier in combination group.

#### **7.1.4. Evaluator's conclusions on clinical efficacy for allergic rhinitis**

##### **7.1.4.1. Nasal symptoms**

- The pivotal study demonstrated that the combination product is significantly superior to both azelastine and fluticasone (200 mcg per day) nasal sprays, as assessed by nasal symptom scores. The improvement in symptoms with the combination, compared to that seen with the monotherapies, was clinically significant.
- The 3 supportive studies also demonstrated superior efficacy for the combination over the active comparators on the primary endpoint of rTNSS. However, on many of the secondary endpoints, the combination was not superior to fluticasone alone.
- A pooled analysis demonstrated superiority of the combination over all three comparators on all endpoints.
- Onset of action occurred 30 to 45 minutes after initial dosing.
- The submitted studies did not address the question of whether use of a higher dose (400 mcg per day) of fluticasone alone would be more effective than the combination.

##### **7.1.4.2. Ocular symptoms**

- In the pivotal study, the combination product was consistently superior to placebo. On most of the ocular endpoints, the combination was also superior to fluticasone. However the overall data suggest that the combination is no better than azelastine nasal spray in terms of improvement in ocular symptoms.
- A similar pattern of results was observed in the 3 supportive studies and the pooled analysis.

##### **7.1.4.3. Postnasal drip**

- The pivotal study demonstrated that the combination is no better than fluticasone nasal spray in relieving postnasal drip in subjects with allergic rhinitis. Similar results were obtained in the 3 supportive studies. In the pooled analysis the combination was superior to all three comparators.

##### **7.1.4.4. Quality of life**

- The pivotal and supportive studies and the pooled analysis demonstrated that the combination provides no clinically meaningful benefit over the individual components in terms of improvement in quality of life.

**Comment:** The submitted studies have complied with the requirements of the EMA Guidelines on allergic rhinoconjunctivitis and those on fixed combination products. The studies were adequately designed and executed. More robust evidence of efficacy would have been obtained if all the studies had used marketed monotherapy comparator products.

The EMA guidelines on fixed combination products require that each substance in fixed the combination must have a “documented therapeutic contribution” to the combination. This has been adequately demonstrated for nasal symptom scores, where the combination was consistently superior to the monotherapy products. However, for ocular symptoms the combination was not superior to azelastine alone. The sponsor is seeking approval for an indication that includes “allergic rhino-conjunctivitis” and it could be argued that the indication should be restricted to allergic rhinitis. However, the azelastine and fluticasone products in Australia are not approved for the treatment of conjunctival symptoms. It would therefore not be reasonable to insist that the combination demonstrate superiority over them. As the combination was consistently superior to placebo for ocular symptoms, an indication using the term “allergic rhinoconjunctivitis” is considered acceptable.

All four efficacy studies were conducted in patients with SAR and were only two weeks in duration. It is noted that the indication approved by the FDA is restricted to SAR. The indication proposed by the sponsor for Australia is not restricted to SAR and no limit on duration of use is proposed. The EMA guideline on allergic rhinitis products state the following:

*‘Pharmacodynamically SAR and PAR are considered comparable. For approval of the SAR/PAR indication for a new product at least two adequate and well controlled phase 3 clinical trials preferably one each in SAR and PAR, are recommended. For drugs of established classes (that is where mode of action is known) this might be two SAR or two PAR studies or one study in each condition. If however, only 2 SAR studies are conducted, additional safety data for 12 months will be required to establish safety of chronic use of the product in patients with PAR.’*

The sponsor has not conducted any studies in PAR, but has conducted a 12-month safety study (MP4000 - reviewed below). Hence approval for PAR / long-term use is considered approvable based on the submitted efficacy data.

## 8. Clinical safety

### 8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

#### 8.1.1. Pivotal and supportive efficacy studies

In the 4 pivotal and supportive efficacy studies (MP4001, MP4002, MP4004 and MP4006), the following safety data were collected:

- General adverse events (AEs) were assessed by open-ended questioning.
- A focused nasal examination was conducted at each study visit.
- Vital signs were measured at each study visit.
- No laboratory testing (apart from baseline pregnancy testing) was undertaken in these studies.

### **8.1.2. Pivotal studies that assessed safety as a primary outcome**

Study MP4000 was a pivotal study that assessed safety as a primary outcome. This study is described in greater detail later in this report (section 8.2).

### **8.1.3. Other studies evaluable for safety**

#### **8.1.3.1. Clinical pharmacology studies**

Studies 3282 and 3283 were single dose studies conducted in healthy volunteers and therefore only provided very limited data.

## **8.2. Pivotal studies that assessed safety as a primary outcome**

### **8.2.1. Study MP4000**

#### **8.2.1.1. Study design, objectives, locations and dates**

This trial was a randomised, open-label study with two parallel groups. Subjects were randomised (2:1) to receive either the combination product or fluticasone propionate spray, and treatment was continued for 12 months.

The objective of the study was to evaluate the safety and tolerability of the combination product with daily, chronic use over a 1-year period in subjects with chronic allergic or vasomotor/non-allergic rhinitis.

The study was conducted in 37 sites in India. The first patient enrolled on [information redacted] and the last patient completed on [information redacted]. The study report was dated 5 October 2010.

#### **8.2.1.2. Inclusion and exclusion criteria**

The key inclusion criterion was:

*'Male and female subjects 12 to 80 years of age with an established history (greater than or equal to 1 year) of rhinitis due to perennial allergies or non-allergic rhinitis (VMR). Subjects with a seasonal allergic component were included, provided that they had significant symptoms outside the allergy seasons. The diagnosis of rhinitis, whether allergic or non-allergic, was made on the basis of a thorough evaluation. This evaluation included medical history, physical examination, rhinitis symptoms, skin testing or validated in vitro tests for specific immunoglobulin E (IgE), such as radioallergosorbent test or paper radioimmunosorbent test, and might have included nasal smears.'*

Exclusion criteria were essentially similar to those used in the efficacy studies.

#### **8.2.1.3. Study treatments**

Subjects were randomised (2:1) to receive one of the following treatments:

- The proposed fixed combination of fluticasone propionate (50 mcg per actuation) and azelastine hydrochloride (137 mcg per actuation) nasal spray – one spray in each nostril twice daily (that is 200 mcg / 548 mcg daily)
- Fluticasone propionate (50 mcg per actuation) nasal spray (using the formulation marketed in the USA by Roxane Laboratories) - two sprays in each nostril once daily (that is 200 mcg daily).

#### **8.2.1.4. Safety variables and outcomes**

Subjects attended the clinic at screening, randomisation and then after 1, 3, 6, 9 and 12 months. Telephone contact was for every month the subjects did not attend the clinic. The main safety variables examined were:

- AEs assessed by open-ended questioning
- A focused nasal examination
- Measurement of vital signs (temperature, blood pressure, pulse and respiratory rate)
- Laboratory testing (haematology, chemistry and urinalysis). HPA axis function was assessed by measuring morning plasma cortisol in a subpopulation of subjects
- Eye examination by an ophthalmologist, including slit lamp examination and measurement of intraocular pressure.

The timing of these assessments was shown in the study schedule. A primary safety outcome measure was not specified.

#### **8.2.1.5. Randomisation and blinding methods**

Subjects were randomised (2:1) using a centralised randomisation schedule. Patients were allocated to treatment via an interactive voice response system. The study was not blinded.

#### **8.2.1.6. Analysis populations**

The safety population included all randomised subjects who received at least 1 dose of study drug, and the Intent-to-Treat (ITT) population included all randomized subjects with at least 1 post-baseline efficacy (PM rTNSS or RQLQ) observation.

#### **8.2.1.7. Sample size**

The sample size was based on ICH guideline E1A – “The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions”, which requires treatment of at least 300 subjects for 6 months and 100 subjects for 1 year. Based on an estimated attrition rate of 25% at the 6-month time point, and of 50% by the 1-year time point, 400 subjects in the MP29-02 treatment group represented an adequate sample size to ensure an adequate safety database.

#### **8.2.1.8. Statistical methods**

Descriptive statistics were used to describe the safety findings of the study.

#### **8.2.1.9. Participant flow**

A total of 612 subjects were randomised (405 to the combination and 207 to fluticasone spray). Of these, 464 (75.8%) completed the study. The numbers who withdrew, and their reasons for withdrawal, were comparable for the two groups.

#### **8.2.1.10. Major protocol violations/deviations**

The study report did not provide detailed information on protocol violations. It stated that the most common protocol deviation in both treatment groups was ‘< 75% compliance with study drug, as calculated from subject diary completion’.

#### **8.2.1.11. Baseline data**

The two treatment groups were reasonably well matched. Mean rTNSS (PM) score at baseline for the whole population was 3.84 (out of a possible 12), which reflects the fact that subjects were not required to have moderate to severe disease.

#### **8.2.1.12. Results for the safety outcomes**

The duration of treatment was comparable for the two treatment groups. The overall incidence of AEs, serious AEs (SAEs) and discontinuations due to AEs was comparable.



#### 8.2.1.12.1. Adverse Events

The overall incidence of AEs was only slightly increased in the combination arm (46.5% versus 44.4%). Treatment with the combination product was associated with an increased incidence of cough (5.0% versus 2.4%), altered taste (dysguesia – 2.7% versus 0.5%) and epistaxis (2.0% versus 0.5%). Taste perversion is listed as a common adverse reaction in the azelastine (Azep) PI.

For AEs that were considered to be treatment-related, again only altered taste, epistaxis and cough were notable increased in the combination group.

#### 8.2.1.12.2. Deaths and serious adverse events

There were no deaths in the study. All SAEs were considered unlikely to be related to the study treatments and all patients made a full recovery. Treatment was temporarily interrupted in 3 subjects.

#### 8.2.1.12.3. Discontinuations due to AEs

The overall incidence of discontinuation due to AEs was comparable, being 2.7% (n = 11) in the combination group and 2.9% (n = 6) in the fluticasone group.

**Comment:** It is noteworthy that there were 2 patients in the combination group who were discontinued due to cataracts and 3 other patients who were discontinued due to decreased cortisol levels. There were no patients discontinued for these reasons in the fluticasone monotherapy group. Study 3282 demonstrated that the combination product was associated with greater systemic absorption of fluticasone than the fluticasone monotherapy product used in this study. It is possible that the increased discontinuations due to cataract and decreased cortisol may be due to this greater systemic absorption.

#### 8.2.1.12.4. Laboratory testing

The specific tests conducted in study were:

- Haematology: haemoglobin, haematocrit, red blood cell count, mean corpuscular haemoglobin concentration, mean corpuscular volume, white blood cell count with differential, platelet count
- Biochemistry: sodium, potassium, chloride, bilirubin, ALT, AST, alkaline phosphatase, total protein, albumin, creatinine, blood urea nitrogen, creatine kinase, fasting glucose, calcium, phosphorus, uric acid
- Urinalysis: bilirubin, bacteria, blood, casts, crystals, epithelial cells, glucose, ketones, nitrites, pH, protein, red blood cells, white blood cells, specific gravity and urobilinogen.

These were measured at baseline, 6 months and 12 months.

The study report presented tabulations of changes in average values (mean plus/minus SD, median, range) and shift tables (for example number of patients changing from normal to high or low) for each of these variables. Treatment with the combination product was not associated with any notable increased incidence of laboratory abnormalities.

### Serum cortisol

Fasting serum cortisol levels were measured in a subgroup of subjects (n = 232). The mean change from baseline was similar in both treatment groups at both 6 and 12 months. These data suggest that the combination product was not associated with a greater incidence of significant reduction in serum cortisol. For example, the proportion of patients who developed a greater than 30% reduction in serum cortisol at 12 months was 23.3% in the combination arm and 28.8% in the fluticasone arm.

**Vital signs**

There were no significant differences between groups in mean values for blood pressure, pulse rate, respiratory rate or temperature.

**Focussed nasal examination**

This examination took place at each study visit. The incidence and severity of the following abnormalities were presented in tabular format in the study report: epistaxis, nasal irritation, mucosal oedema, nasal discharge, mucosal erythema, mucosal bleeding and crusting of the mucosa. There were no notable differences between groups in the incidence or severity of these findings.

**Ophthalmological examination**

The frequency of abnormalities/incidence of glaucoma and posterior capsular cataract at 6 and 12 months was comparable in the two groups.

**Comment:** This is the only study in the submission that examined long-term safety of the proposed product. In general, the product demonstrated an acceptable safety profile, with small increases in the incidence of altered taste, epistaxis and cough compared to fluticasone monotherapy.

The proposed combination has been shown to produce higher systemic fluticasone concentrations than the fluticasone monotherapy product. Despite this, there did not appear to be an increased incidence of glaucoma or cataract in the combination arm, although 2 patients had to discontinue treatment due to cataract versus 0 in the comparator arm. HPA axis function was only tested using single measurements of morning serum cortisol, an insensitive method of detecting impairment of function. The incidence of decreased morning serum cortisol was comparable in the two treatment groups. However, 3 patients in the combination arm were discontinued for decreased cortisol levels versus none in the comparator arm. As noted previously, the proposed maximum daily dose of fluticasone delivered by the combination product is 200 mcg per day, which is notably lower than the 400 mcg per day maximum approved in Australia for fluticasone propionate nasal spray. For this reason, systemic absorption of fluticasone from the combination product is not considered a major safety issue.

**8.3. Patient exposure**

In the submitted studies 1,469 subjects were treated with proposed fixed combination.

**Table 2 - Exposure to fixed combination and comparators in clinical studies.**

	Fixed Combination	Azelastine alone	Fluticasone alone	Placebo	TOTALS
Clinical pharmacology					
Study 3283	30	30	-	-	30
Study 3282	<u>29</u>	-	<u>30</u>	-	<u>30</u>
SUBTOTAL	59	30	30	0	60
Efficacy Studies					
MP4001	153	152	153	151	609
MP4002	207	208	207	210	832
MP4004	195	194	189	200	778
MP4006	<u>451</u>	<u>449</u>	<u>450</u>	<u>451</u>	<u>1801</u>
SUBTOTAL	1006	1003	999	1012	4020
Safety Study					
MP4000	404	-	207	-	611
TOTALS	1469	1033	1236	1012	4691*

\* = total number of unique individuals

In the five efficacy/safety studies the dosage regimen used was identical to that proposed for registration (1 spray in each nostril BD, for a total dose of 4 sprays per day delivering a total of 200 mcg of fluticasone and 548 mcg of azelastine). In the two clinical pharmacology studies, a single dose of 4 sprays was applied.

In the four efficacy studies, the duration of treatment was 14 days. In the safety Study MP4000 the duration of treatment was 12 months. Of the 405 subjects randomised to the combination in MP4000, 354 (87.4%) completed 6 months of treatment and 312 (77.0%) completed 12 months.

The safety findings from MP4000 have been reviewed above. The following information is from a pooled analysis of the four efficacy studies, which was included in the sponsor's summary of clinical safety and the integrated summary of safety. In these studies there were 1,006 subjects treated with the combination and 1,012 treated with placebo. For the pooled analysis, the sponsor separated the fluticasone group into subjects treated with the marketed product (n = 153) and those treated with the sponsor's own "in-house" version (n = 846). Similarly, subjects treated with azelastine were separated into those treated with the marketed product (n = 152) and those treated with the sponsor's own "in-house" version (n = 851).

#### 8.4. Adverse events

##### 8.4.1. All adverse events (irrespective of relationship to study treatment)

The incidence of all adverse events was marginally higher in the combination group (16.4%) than in the monotherapy comparator groups (13.1 – 15.1%). It was notably higher than in the placebo group (11.6%). Altered taste, epistaxis and headache were the most commonly reported AEs.

In terms of between-group differences, the most clinically relevant comparisons are those between the combination and the marketed monotherapy products. Altered taste was notably more frequent with the combination (4.1% versus 2.0% with azelastine and 0% with fluticasone). Several other AEs occurred more frequently with the combination than with the

marketed products, although all were uncommon (incidence < 0.5%), for example: dry mouth, dizziness, fatigue, sneezing, throat irritation, viral upper respiratory infection, and diarrhoea.

#### **8.4.2. Treatment-related adverse events (adverse drug reactions)**

The incidence of *treatment-related* adverse events was higher in the combination group (10.7%) than in the marketed monotherapy comparator groups (7.9 – 9.2%). It was notably higher than in the placebo group (4.8%). Altered taste was again more common, as was nasal discomfort. All the remainder were uncommon (incidence < 0.5%). The data did not include AEs that occurred more frequently in marketed products than with the combination.

#### **8.4.3. Deaths and other serious adverse events**

There were no deaths in the four studies.

There were two SAEs in the combination group. A 25 year-old female developed newly diagnosed hepatitis C, and a 23 year-old male was hospitalised for a lacerated hand. In the placebo group there was one SAE – a 40 year-old male developed a bacterial arthritis of the elbow. None of these events were considered related to study treatment. There were no SAEs in the monotherapy arms.

#### **8.4.4. Discontinuation due to adverse events**

In the combination group the incidence of AEs leading to discontinuation (1.1%) was comparable to that seen in the placebo group (1.0%) and the marketed monotherapy groups (0.7 – 1.3%). Review of the individual AEs did not suggest any particular pattern suggestive of a safety issue with the combination.

### **8.5. Laboratory tests**

Laboratory testing (haematology, biochemistry, urinalysis, ECG et cetera) was not performed during the four efficacy studies.

### **8.6. Vital signs**

Over the two-week treatment period there were no clinically significant changes in mean values for blood pressure, pulse rate, respiratory rate, temperature or body weight in any of the treatment groups.

### **8.7. Focused nasal examination**

Nasal examination took place at each study visit (screening, Day 1, Day 7 and Day 14). In the pooled analysis, the incidence and severity of the following abnormalities were presented in tabular format: epistaxis, nasal irritation, mucosal oedema, nasal discharge, mucosal erythema, mucosal bleeding and crusting of the mucosa. There were no notable differences between groups in the incidence or severity of these findings.

### **8.8. Post-marketing experience**

No post-marketing data were submitted.

### **8.9. Safety issues with the potential for major regulatory impact**

The proposed product delivers small doses of fluticasone propionate and azelastine hydrochloride directly to the nasal mucosa, and systemic exposure is therefore limited. Both agents have an established safety record. It is therefore very unlikely that the product would be associated with safety issues with the potential for major regulatory impact (that is liver or

haematological toxicity, severe skin reactions, cardiovascular toxicity or severe immunological effects). No evidence for such effects was seen in the submitted study reports.

## **8.10. Other safety issues**

### **8.10.1. Safety in special populations**

In the summary of clinical safety, the sponsor presented tabulations of adverse events by subgroups including age (12 to 18 years, 18 to 65 and > 65 years), gender and race/ethnicity. No specific safety issues were identified.

## **8.11. Evaluator's overall conclusions on clinical safety**

The overall safety profile of the combination product is acceptable. Use of the combination is associated with a small increase in the incidence of adverse events (principally altered taste) compared to use of either of the monotherapy products alone. There was no increase in the incidence of serious adverse events or discontinuations due to adverse events.

The combination product appears to produce increased systemic exposure to fluticasone, at least compared to a US-marketed fluticasone propionate monotherapy product. However, this is offset by the sponsor's proposal to use a maximum daily dose of only 200 mcg fluticasone propionate per day, which is half the maximum daily dose approved for fluticasone propionate nasal spray in Australia.

# **9. First round benefit-risk assessment**

## **9.1. First round assessment of benefits**

The benefits of the combination product in allergic rhinoconjunctivitis are:

- A reduction in the severity of nasal symptoms over and above that achieved by use of either of the monotherapy products and
- A reduction in the severity of ocular symptoms when compared to placebo.

## **9.2. First round assessment of risks**

The risks of the combination in allergic rhinitis are:

- A modest increase in the incidence of adverse effects (principally altered taste) compared to use of either of the monotherapy products.

## **9.3. First round assessment of benefit-risk balance**

The benefit-risk balance of the combination product, given the proposed usage, is favourable.

# **10. First round recommendation regarding authorisation**

It is recommended that the application for registration be approved.

## 11. Clinical questions

### 11.1. General

Please confirm that the formulation of the product proposed for registration in Australia is identical to that used in the submitted clinical trials.

### 11.2. Pharmacokinetics

It is stated in the submission that the benzalkonium chloride (BAC)-containing formulation of azelastine nasal spray was marketed in Europe until the late 1990's, when it was changed to the BAC-free formulation. It is also noted that on the ARTG, the Australian product (Azep; Aust R 104853) is described as a 'reformulation'.

Please advise whether the BAC-containing formulation was also the original formulation approved in Australia.

### 11.3. Pharmacodynamics

Not applicable.

### 11.4. Efficacy

The azelastine and fluticasone monotherapy products used in Studies MP4002, MP4004 and MP4006 appear to be "in-house" formulations developed by the sponsor. Their efficacy compared to commercially available azelastine hydrochloride and fluticasone propionate monotherapy products has not been established. Can the sponsor provide a rationale for the use of these formulations in the studies rather than commercially available monotherapy products?

### 11.5. Safety

Not applicable.

## 12. References

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