Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for fluticasone propionate and azelastine hydrochloride

Proprietary Product Name: Dymista/Dylastine

Sponsor: Meda Pharmaceuticals Pty Ltd

July 2014

TGA Health Safety Regulation

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- 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.
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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of co-variance
ARIA	Allergic Rhinitis and its Impact on Asthma (Guidelines)
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate transaminase
AUC	Area under the curve
AZE	Azelastine HCl
BAC	Benzalkonium chloride
BID	Twice daily
BLQ	Below quantification limit
BSA	Body surface area
CER	Clinical evaluation report
CI	Confidence interval
C_{max}	Maximum concentration
CYP	Cytochrome P450
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed dose combination
FLU	Fluticasone propionate
FP	Fluticasone proprionate
GCP	Good clinical practice

Abbreviation	Meaning
GIT	Gastrointestinal tract
GLP	Good laboratory practice
GMP	Good manufacturing practice
GVP	Good pharmacovigilance practices
ICH	International Conference on Harmonisation
iTNSS	Instantaneous Total Nasal Symptom Score
iTOSS	Instantaneous Total Ocular Symptom Score
LLoQ	Lower level of quantification
LOCF	Last observation carried forward
LOEL	Lowest observed effect level
LS	Least Squares
mcg	Micrograms
MP29-02	Fluticasone propionate and azelastine hydrochloride nasal spray
OTC	Over the counter
PAR	Perennial allergic rhinitis
PD	Pharmacodynamic
PI	Product information
PK	Pharmacokinetics
PSC	Pharmaceutical subcommittee
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
S2	Schedule 2 medicine
S4	Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons

Abbreviation	Meaning
SAE	Serious adverse event
SAR	Seasonal allergic rhinitis
TGA	Therapeutic Goods Administration
T_{max}	Time of maximum concentration
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
US	United States

I. Introduction to product submission

Submission details

Type of submission:	New combination of active ingredients
Decision:	Approved
Date of decision:	16 December 2013
Active ingredients:	Azelastine (as hydrochloride) and fluticasone propionate nasal spray bottle.
Product names:	Dymista, Dylastine
Sponsor's name and address:	Meda Pharmaceuticals Pty Ltd Suite 1, Level 3 110 Pacific Highway St Leonards NSW 2065
Dose form:	Nasal spray
Strength:	125/50 per spray
Container:	Bottle
Pack sizes:	4 mL (starter pack) and 17 mL.
Approved therapeutic use:	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.
Route of administration:	Intranasal
Dosage:	One spray in each nostril twice daily (morning and evening).
ARTG numbers:	203131, 203132

Product background

This AusPAR describes the application by the sponsor to register Dymista/Dylastine for the following 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.*

Azelastine hydrochloride (0.1%) is currently approved for seasonal or perennial allergic rhinitis. Presentations in the form of nasal spray, 0.05% strength, for treatment of seasonal perennial allergic rhinitis and a 0.05% presentation in the form of eye drops for conjunctivitis sponsored by Meda Pharmacetuicals are also currently approved.

Fluticasone propionate (0.05%) nasal spray is currently approved for prophylaxis or treatment of 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.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 14 January 2014.

At the time TGA considered this application, the product was approved in the United States (US) for

> *'the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.'*

It is noteworthy that it is not registered for perennial allergic rhinitis (PAR).

The product is also registered in the European Union (EU) (via decentralised procedure from January 2013.

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

Introduction

The proposed product is to be available in two presentations: 4 mL (in 10 mL amber glass bottle) and 17 mL fill (in 25 mL amber glass bottle), which are connected with a nasal pump and a nasal applicator (actuator with translucent cap). The pump delivers a nasal spray with a spray volume of 137 µL, containing 125 µg azelastine (as hydrochloride) and 50 µg fluticasone propionate.

There are pharmacopeial monographs for the drug substances azelastine hydrochloride (British and European) and fluticasone propionate (British, European and United States). There are no pharmacopeial monographs for the proposed combination drug product.

Drug substance (active ingredient)

Azelastine hydrochloride

Azelastine hydrochloride ($C_{22}H_{24}ClN_3O.HCl$, 418.37 g/mol) is a potent long acting anti-allergenic compound with particularly strong histamine H1 antagonist properties. It is manufactured by chemical synthesis and is supplied as a racemate.

It appears as a white to off-white crystalline powder. The pH of the solution is 5.5 to 7.5 and pKa is 7.2 plus/minus 0.13. It is sparingly soluble in water, soluble in ethanol and methylene chloride, and its aqueous solubility at different pH is shown below:

Azelastine hydrochloride[1] completely dissolves in the proposed product during the manufacturing process; therefore, polymorphism and particle size of this active are not considered critical for the proposed product.

Fluticasone propionate

Fluticasone propionate ($C_{25}H_{31}F_3O_5S$, 500.6 g/mol) is a synthetic tri-fluorinated glucocortico-steroid with potent anti-inflammatory activity by acting at the glucocorticoid receptor. It is a white to almost white powder.

It is practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in ethanol. Studies on polymorphism were performed, and the polymorph form of fluticasone propionate obtained by the manufacturer and used in the manufacture of the proposed nasal spray is documented. The particle size of the drug substance has been appropriately controlled in the drug substance specification to ensure its even distribution in the drug product.

Drug product

The proposed product is formulated as a white, non-sterile nasal spray suspension containing azelastine (as hydrochloride) and fluticasone propionate as the actives, and "benzalkonium chloride" and "phenylethyl alcohol" as the preservatives. The proposed product contains typical excipients for this type of product.

The key performance attribute of the proposed product is the insolubility of fluticasone propionate in water. A portion of azelastine hydrochloride precipitates and therefore the product is a suspension of both drug substances. Investigation on the particle size distribution of the suspended particles for both actives was performed and showed that the particle size does not change upon storage.

The proposed finished product specification includes acceptable controls for a nasal spray suspension, in particular Delivered Dose Uniformity, Particle Size Distribution and Droplet Size Distribution for effective dose delivery to the nasal cavity.

Acceptable data were also provided to support the initial priming (6 actuations) and repriming (at least one actuation) as stated in the labels and Product Information (PI).

Stability

Unopened product

The stability data were generated under accelerated (40°C/75% RH) and long-term (25°C/60% RH) conditions, in batches packaged in the proposed container closure system, and stored under upright and horizontal positions. Photostability study indicates that "protection from light" is not required.

- The results indicate that there was no appreciable difference between the samples stored in upright and horizontal positions.
- From both quality and sterility perspective, the stability data support the proposed shelf-life of 36 months, stored below 25°C, do not refrigerate and do not freeze for the unopened product.

[1] At the pH of proposed nasal spray (5.5-6.5), the aqueous solubility of this active is approximately 0.4-1.5% w/w, which would completely dissolve the active which is formulated in only 0.1% w/w in the proposed product.

In-use stability of opened product

From a quality and sterility perspective, the in-use stability data support the proposed in-use period of 6 months after first opening of the bottle, when stored at 25°C/60% RH.

The proposed carton and bottle labels and PIs are acceptable from a quality perspective.

Biopharmaceutics

The company provided two pharmacokinetic (PK) studies comparing the proposed combination product to the monotherapy products from the US.

As the proposed combination product is locally acting, these studies were not evaluated quality. The details of these studies were summarised for pharmacokinetic purposes for comparison of the systemic exposures of the actives in the combination product with those of the respective monotherapy products.

The pharmacokinetic studies provided are shown below:

PK study 3283

This study compared the PK parameters of the proposed combination product to the US marketed azelastine monotherapy product. The results of the maximum concentration (C_{max}) and area under the curve, both time dependent and total (AUC_{0-t} and AUC_{0-inf}) for azelastine are within the 90% Confidence Interval (CI) interval to conclude bioequivalence and span unity.

Therefore, it can be concluded that the systemic exposure of azelastine in the proposed fixed dose combination is comparable to the US marketed monotherapy azelastine nasal spray.

PK study 3282

This study compared the PK parameters of proposed combination product to the US marketed fluticasone monotherapy product. The results of C_{max} and AUC_{0-t} and AUC_{0-inf} for fluticasone are outside the 90% CI interval to conclude bioequivalence.

The point estimates for all C_{max} and AUC indicates that the systemic exposure to fluticasone propionate is about 1.6 times greater after treatment with the proposed fixed dose combination product as compared with the corresponding monotherapy product.

Given that the pharmacokinetic studies above were performed using the monotherapy azelastine product and the monotherapy fluticasone product from the US, the clinical Delegate should note that:

- The Australian and US marketed fluticasone propionate sprays are similar, but not identical, particularly in relation to the content of the some excipients, where quantitative information were not available for comparison.
- The company stated that the azelastine nasal sprays from EU and AUS are identical; therefore, the comparison of US to EU product is considered representative of the comparison of azelastine nasal sprays from US to AUS product.
    - The EU/Australian and US marketed azelastine sprays are similar, but not identical; in particular, the AUS/EU product is preservative-free, whereas the US product contains benzalkonium chloride as a preservative.

It is a clinical decision as to whether these differences are significant with regards to the current application.

Quality summary and conclusions

There are no outstanding issues from a quality or sterility perspective; hence approval can be recommended from chemistry and quality control aspects.

This is a new fixed combination product of previously approved actives, and there were no significant issues with chemistry and quality control aspect of the proposed product. Therefore, these details were not presented for consideration by the Pharmaceutical Subcommittee of the Advisory Committee on Prescription Medicines (ACPM, PSC).

The systemic exposure to fluticasone propionate is about 1.6 times greater after treatment with the proposed fixed dose combination product as compared with the corresponding monotherapy product.

III. Nonclinical findings

Introduction

Included in the submission were studies investigating the repeat dose toxicity of the combination compared to the individual compounds.

The pivotal study contained supportive toxicokinetic data. Studies were conducted under Good Laboratory Practice (GLP) conditions.

The potential for drug interaction was not specifically addressed in nonclinical studies.

The species selected, number of observations and dose administered were considered acceptable, though only one dose was administered in the pivotal studies and the target organs of toxicity were not established in this study.

Pharmacology

Azelastine has a triple mode of action: it is a long acting H1-receptor antagonist, possesses mast cell stabilizing properties and is antiphlogistic. Azelastine is a racemic mixture, the R- and S- enantiomers were equally effective at inhibiting histamine induced eyelid oedema, but the R-enantiomer was 2-fold less active at inhibiting eyeball oedema (Azep Product Information document). Fluticasone is a synthetic trifluorinated anti-inflammatory corticosteroid without significant mineralocorticoid action (Flonase monograph), its glucocorticoid action was shown to be 5 fold more potent than dexamethasone in a cloned human glucocorticoid system in vitro (Flonase Physician's desk reference). The rational for the proposed combination is to simultaneously target symptoms of allergic rhinitis mediated by histamine and also target allergic effects mediated by recruitment of inflammatory cells such lymphocytes and eosinophils, leukotriens and other cytokines or chemokines. No nonclinical efficacy studies were conducted with the proposed combination.

Pharmacokinetics

Toxicokinetics of azelastine were assessed as part of the pivotal repeat dose study in rats. Fluticasone plasma concentrations were below the lower limit of quantification (0.5 ng/mL) at all the time points, therefore no toxicokinetic data are available. The combination product was administered in the clinically proposed formulation. Azelastine was absorbed rapidly in rats administered the monoproduct (Astelin) or the combination product, no accumulation was observed with repeated dosing over a 3 month period. C_{max} and plasma AUC values were generally lower in male than in female rats. $AUC_{0-\infty}$ plasma

exposure and C_{max} in rats was lower compared to azelastine alone, this effect was less pronounced on Day 91 compared to the beginning of the study (-20% and -40 %; $AUC_{0-\infty}$ and C_{max}, respectively).

In contrast, the clinical overview reports that clinical studies did not indicate pharmacokinetic interaction between azelastine and fluticasone in humans. Half-life was comparable between sexes and the azelastine and azelastine/fluticasone combination groups and approximately 5-times the azelastine half-life reported in humans. These data suggest that the rat is an inferior model for pharmacokinetic studies of azelastine. Nevertheless, adequate systemic exposure to azelastine (but not fluticasone) was demonstrated. The lack of demonstrated fluticasone exposure is mitigated by the observation that fluticasone dominated the toxicity profile in repeat dose studies and is attributed to the insensitive analytical method rather than inadequate exposure to fluticasone. Administration of azelastine doses (on a mg/m^2 basis) far exceeding the clinically intended doses (see relative exposure table) in the pivotal repeat dose toxicity study allowed adequate assessment of toxicity induced by the combination.

Azelastine is extensively metabolised to the main metabolite desmethyl azelastine, which also exhibits H1-receptor antagonist activity (Azep Product Information document). The N-demethylation occurs mainly by Cytochrome P450 (CYP) enzymes but no single isoform was shown to be specific for azelastine metabolism at low concentrations (6 to 30 ng/mL) (Azep Product Information), even lower concentrations have been reported after administration of the maximum recommended daily dose to healthy subjects.

Direct absorption of fluticasone from the nose is minor due to low aqueous solubility and the majority of the dose is eventually swallowed (Flixonase allergy & hayfever 24 hour nasal spray Product information). When administered orally, the systemic exposure to fluticasone is < 1% due to poor absorption and presystemic metabolism. The amount of fluticasone that reaches the systemic circulation is rapidly cleared, principally by hepatic metabolism by CYP3A4. Drug interaction with azelastine via CYP3A4 are considered unlikely since no single CYP enzyme is responsible for azelastine metabolism, and fluticasone plasma levels are low (C_{max} 0.01ng/mL).

Toxicology

Toxicity studies were conducted using the clinically proposed strength and formulation.

A three month repeat dose study with the combination was conducted in rats (GLP, no recovery period), a 2 week pilot study was also conducted in rats and another 2 week study was conducted in dogs. Parallel single agent control groups were included in the studies, there were some minor differences in excipients between the single agent and combination formulations. The azelastine/fluticasone dose ratio used in these studies was the clinically proposed dose ratio (2.8). Only one dose level was tested in both species. Evaluation of reversibility is only recommended when there is severe toxicity in a nonclinical study with potential adverse clinical impact and was thus not required.[2] The duration of the pivotal study is consistent with the EU guideline on the Non-Clinical Development of Fixed Combinations in Medicinal Products.[2] The rat has been successfully used in studies investigating the repeat dose toxicity of the individual compounds. The studies were carried out by the clinically intended route in the clinically intended formulation with the clinically intended concentration at doses (on a mg/m^2 basis) that exceeded the clinically proposed dose. However, only the two week dog study used the clinical spray applicator to administer the doses.

[2] EMEA/CHMP/SWP/258498/2005.

The other studies, including the pivotal repeat dose toxicity study, used a pipette for dose administration. A difference in systemic exposure after administration of drops versus nasal spray has previously been reported. After application of 800 µg fluticasone propionate as nasal drops or nasal spray to healthy volunteers, both formulations exhibited low systemic exposure. However, bioavailability was 8 fold lower when the drops were administered.[3] This suggests that the systemic exposure caused by the combination may have been underestimated in the pivotal repeat dose study. However, given the high multiples of the clinically intended dose on a mg/m^2 basis (up to 32 times the dose proposed for human use in a 50 kg patient) this is not expected to compromise the safety assessment. Females, on average, received higher doses than males on a mg/kg (or mg/m^2) basis in the repeat dose studies since dose was not adjusted for individual body weight.

Relative systemic exposure

Exposure and dose ratios for azelastine HCl and fluticasone propionate achieved in the toxicity studies are tabulated below. Dose ratios were calculated on a mg/m^2 basis. A 0.1 mL dose per nostril was given twice daily (BID) to both rats and dogs, equal to 400/146 µg azelastine HCl/fluticasone propionate. The maximum daily human dose is 500 µg azelastine (548 µg azelastine HCl) and 200 µg fluticasone propionate.

Only the pivotal 3 month rat repeat dose toxicity study included toxicokinetic analysis. Fluticasone plasma levels were below the limit of quantification, presumably due to insensitivity of the analytical method used in the nonclinical study, the lower limit of quanitification (LLoQ) of 0.5ng/mL was above the C_{max} observed in clinical studies (less than or equal to 0.012 ng/mL, LLoQ of 0.25pg/mL).

Table 1. Relative systemic exposure in repeat-dose toxicity studies

Species	Study No. and duration		Dose mg/kg/day [mg/m^2 BSA]		Dose ratio[c]		$AUC_{0-\infty}$		Exposure ratio	
			AZE	FLU	AZE	FLU	AZE ng·h/mL	FLU ng·h/mL	AZE	FLU
Rat (SD)	2 weeks (0437RM5 7.006) [pilot]	♂	1.4 [8.4]	0.5 [3.0]	23	23	–	–	–	–
		♀	1.9 [11.4]	0.7 [4.2]	31	32	–	–	–	–
	13 weeks (0470RM5 7.001) [pivotal]	♂	0.98 [5.9]	0.36 [2.2]	16	17	28.340[b]	BLQ	7	–
		♀	1.6 [9.6]	0.58 [3.5]	26	27	41.240[b]	BLQ	10	–
Dog (beagle)	2 weeks (0437DM5 7.007)	♂	0.050 [1]	0.018 [0.36]	3	3	–	–	–	–
		♀	0.061 [1.2]	0.022 [0.44]	3	3	–	–	–	–
Human *Single dose, healthy subject* (3282, 3283)		♂ + ♀	0.011[d] [0.363]	0.004[d] [0.132]	–	–	4.217	0.098[a]	–	–

= animal:human plasma AUC0–24 h FLU: fluticasone propionate; AZE: azelastine HCl; BLQ: below quantification limit (LLoQ: 0.5 ng/mL); a more sensitive assay was used in the clinical studies (LLoQ: 0.25 pg/ml). b values determined on day 91. c conversion from mg/kg to mg/m2 body surface area (BSA) was achieved using conversion factors of 6 for rat, 20 for dog, and 33 for human. destimated for a 50 kg person.

3 Daley-Yates PT, Baker RC.Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. Br J Clin Pharmacol. 2001;51(1):103-5.

Systemic toxicity

Toxicity of the combination in rats was moderate and dominated by fluticasone propionate induced effects that have been described in previous submissions [information redacted] and was generally consistent with systemic glucocorticoid action of the drug. Decreased body weight gain was observed in males and females receiving the combination that reached statistical significance in females only at doses approximately 16 to 26-times the intended clinical dose (♂ and ♀, respectively). Comparable decreases in body weight gain were observed with the individual compounds alone. Decreases in lymphocytes are a typical steroid effect[4] and were observed in females administered 0.82 mg/kg fluticasone. Lymphocytopenia was not observed in animals receiving lower fluticasone doses such as males (0.49 mg/kg) or animals receiving the azelastine/fluticasone combination (0.36 to 0.58 mg/kg). Increases in liver enzymes (aspartate transaminase (AST) and alanine transaminase (ALT)) and serum bilirubin were observed in females treated with the combination or fluticasone alone but were not accompanied by histopathological signs of hepatotoxicity. Elevation of serum triglycerides is associated with corticosteroid treatment[5] and was observed in females treated with fluticasone alone or the combination. A statistically significant reduction in absolute spleen weight was observed in females treated with the combination or fluticasone alone. The increased toxicity observed in females compared to males is attributed to the higher relative doses administered to females.

Local toxicity

Neither the combination of azelastine hydrochloride 0.1% and fluticasone propionate 0.0365% nor the individual components alone induced signs of local toxicity in the nasal cavity or the respiratory system (larynx, nasopharynx, lungs, and trachea) of rats treated up to 3 months. Local dose ratios based on mg/m^2 nasal cavity surface area were estimated (see table below), the amount of dose swallowed was not taken into account. In dogs administration of azelastine hydrochloride 0.1% and fluticasone propionate 0.0365% was generally well tolerated. Minimal to mild acute inflammation was observed in 1/3 females receiving the combination only. It is not clear whether this finding was related to treatment, but due to the mildness of the incident and in the absence of findings in other animals it was not considered to have major clinical relevance.

Significant increases in mast cells were observed in the mesenteric lymph nodes of rats receiving the combination or fluticasone alone for 3 months. Since after intranasal application the majority of the fluticasone dose is eventually swallowed (Flixonase allergy and hayfever 24 hour nasal spray Product information document), this is possibly a result of local fluticasone action in the gastrointestinal tract (GIT.).

[4] Hayes W.A. (2008) Principles and Methods of Toxicology. Boca Raton, FL USA: CRC Press / Taylor & Francis Group.
[5] Breuer H.W. Hypertriglyceridemia: A Review of Clinical Relevance and Treatment Options: Focus on Cerivastatin. Curr Med Res Opin. 2001;17(1):60-73.

Table 2. Local dose ratios for toxicity of the nasal cavity for azelastine HCl (A) and fluticasone (F) at the lowest observed effect level (LOEL)

Study	Total daily dose (µg)		Dose/nasal cavity surface area (µg/cm^2)		Animal:human Dose Ratio	
	A	F	A	F	A	F
Rat 13 wk 0470RM57.001	400	146	38	14	13	14
Human *Single dose, healthy subject* (3282, 3283)	548	200	3	1	-	-

Nasal surface areas (both sides of the nasal cavity) of 10.4 cm^2 for rats and 181cm^2 for humans were used.[6]

Repeat dose toxicity conclusion

In summary intranasal application of azelastine hydrochloride 0.1% and fluticasone propionate 0.0365% was well tolerated locally as well as systemically. The toxicity was dominated by fluticasone induced findings. No additional new toxicity was observed with the combination compared to the individual components alone.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3[7], this is consistent with the pregnancy category of the individual components and considered appropriate.

Nonclinical summary and conclusions

- Azelastine HCl (0.1%) alone is currently approved for seasonal or perennial allergic rhinitis in the form of nasal spray, and (0.05%) for treatment of seasonal or perennial allergic conjunctivitis in the form of eye drops. Fluticasone propionate (0.05%) nasal spray is currently approved for prophylaxis or treatment of allergic rhinitis and has not been approved for the treatment of allergic conjunctivitis in Australia.
- The nonclinical package comprised three studies investigating the repeat dose toxicity of the azelastine HCl/fluticasone propionate combination in the clinically proposed strength and formulation for 2 weeks (rats, dogs) or 13 weeks (rats) and contained parallel single agent groups. The efficacy of the individual actives as well as their low systemic toxicity after intranasal application has been previously characterised in animal studies. The individual agents did not exhibit genotoxic activity in nonclinical studies provided with previous submissions. The drugs have not been approved for loose combination, but the sponsor reports loose combination in clinical practice. Taking this into account the provided data package is considered adequate.
- No studies were submitted that investigated the pharmacological action of the combination. The action of the individual compounds has been previously characterised. Azelastine has a triple mode of action: it is a long acting H1-receptor antagonist, possesses mast cell stabilizing properties and is antiphlogistic. Fluticasone

[6] Derelanko M J and HollingerM A.(Eds.) (1995) CRC Handbook of Toxicology, Boca Raton, FL: CRC Press.
[7] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

is a synthetic trifluorinated anti-inflammatory corticosteroid without significant mineralocorticoid activity.

- Pharmacokinetic interaction of azelastine and fluticasone is not expected based on the metabolism of the individual compounds. Fluticasone plasma levels were below the level of quantification with the less sensitive analytical method used in the only toxicokinetic study (LLoQ above the Cmax observed in clinical studies). A decrease in azelastine plasma levels was observed in rats when azelastine was administered in combination with fluticasone. This is addressed by clinical studies which investigated the potential pharmacokinetic interaction of azelastine and fluticasone with more sensitive analytical methods.
- Intranasal application of azelastine hydrochloride 0.1% and fluticasone propionate 0.0365% as the clinical formulation at a daily dose of 400/146 µg for 3 months was well tolerated locally (up to 14 times the clinical dose based on nasal cavity surface area) as well as systemically (at doses up to 32-times the clinical dose on a mg/m2 basis in rats, and up to 3-times in dogs. The moderate toxicity that was observed was dominated by fluticasone induced findings that were explained by systemic glucocorticoid action. No additional new toxicity was observed with the combination compared to the individual components alone. Previously, toxicology studies of longer duration than 3 months were conducted with the individual drugs alone. A similar product, fluticasone nasal drops (Flixonase Nasule drops, 800 µg/day, 0.1% fluticasone propionate) is currently approved without restriction on duration of treatment at 4-times the proposed maximum daily fluticasone dose (200 µg/day) and approximately 3-times the proposed strength of 0.0365%.
- There are no nonclinical objections to registration of the new fixed combination for allergic rhinitis. The efficacy of the azelastine HCl/fluticasone propionate nasal spray for the treatment of allergic rhino-conjunctivitis was not assessed in animal models of allergic rhinitis or allergic conjunctivitis. Neither of the currently registered individual nasal spray drug products (azelastine 0.1% nasal spray and fluticasone propionate 0.05% nasal spray) is approved for treatment of rhino-conjunctivitis, though azelastine eye drops are approved for conjunctivitis treatment. Evaluation of this new indication will rely on the clinical data.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

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 second generation (non-sedating) antihistamine, belonging to the phthalazinone class.

Clinical rationale

Allergic rhinitis/rhinoconjunctivitis is a very common disorder that affects approximately 20% of the Australian population.[8] 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). Seasonal allergic rhinitis (SAR) develops in response to allergens that only occur in certain seasons (for example pollens) whereas perennial allergic rhinitis (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[9] 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
- 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.

[8] Walls RS, Heddle RJ, Tang MLK, et al. Optimising the management of allergic rhinitis: an Australian perspective. Med J Aust 2005; 182:28-33.
[9] 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).

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 over the counter (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 (Schedule 2 (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.

Formulation

At the time of the 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.

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;[10]
- Guideline On Clinical Development Of Fixed Combination Medicinal Products;[11]
- Clinical Requirements For Locally Applied, Locally Acting Products, Containing Known Constituents.[12]

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

Contents of the clinical dossier

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

[10] European Medicines Agency. Guideline On The Clinical Development Of Medicinal Products For The Treatment Of Allergic Rhinoconjunctivitis (CHMP/EWP/2455/02); 2005.
[11] European Medicines Agency. Guideline On Clinical Development Of Fixed Combination Medicinal Products (CPMP/EWP/240/95/Rev. 1); 2009.
[12] European Medicines Agency. Clinical Requirements For Locally Applied, Locally Acting Products, Containing Known Constituents (pp 381 – 391 of Rules 1998 (3C) – 3CC29a); 1996.

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.

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 European Medicines Agency (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.[13]

> **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.

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.

Pharmacokinetics

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 3 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

[13] European Medicines Agency. Decision P/82/2011. Studies in children under 12 years of age were not conducted.

Table 3. 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.

Evaluator's conclusions on pharmacokinetics

The monotherapy product used in this study (3282) 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 azelastine monotherapy product used in Study 3283 ("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.

Pharmacodynamics

No new clinical pharmacodynamic data were included in the submission.

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[14] 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.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies

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 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[15] 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[15] 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.

The submission included a pooled analysis of the above four trials, as well as a pooled analysis of the three trials (MP4002, MP4004 and MP4006) that used the 'in-house" versions of azelastine and fluticasone sprays.

These studies are discussed in the Clinical Evaluation Report (CER) extract (Attachment 2)

Evaluator's conclusions on efficacy

Nasal symptoms

The pivotal study demonstrated that the combination product is significantly superior to both azelastineand fluticasone (200 mcg per day) nasal sprays, as assessed by nasal

[14] 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.
[15] 137mcg of azelastine HCl completely dissolved in solution providing 125mcg of azelastine.

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 reflective total nasal symptom score (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.

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.

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.

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 the fixed 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 Food and Drug Administration (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 states 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). Hence approval for PAR/long-term use is considered approvable based on the submitted efficacy data.

Safety

Studies providing safety data

The following studies provided evaluable safety data and are discussed further in the CER extract (Attachment 2).

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.

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 in the CER extract (Attachment 2).

Other studies evaluable for safety

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

Patient exposure

As shown in the table below, in the submitted studies 1,469 subjects were treated with proposed fixed combination.

Table 4. Exposure to fixed combination and comparators in clinical studies.

	Fixed Combination	Azelastine alone	Fluticasone alone	Placebo	TOTALS
Clinical pharmacology Study 3283 Study 3282 SUBTOTAL	 30 29 59	 30 - 30	 - 30 30	 - - 0	 30 30 60
Efficacy Studies					
MP4001 MP4002 MP4004 MP4006 SUBTOTAL	153 207 195 451 1006	152 208 194 449 1003	153 207 189 450 999	151 210 200 451 1012	609 832 778 1801 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 BID, 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 in the CER extract (Attachment 2). 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).

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.

Evaluator's conclusions on 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.

First round benefit-risk assessment

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.

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.

First round assessment of benefit-risk balance

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

First round recommendation regarding authorisation

It is recommended that the application for registration be approved.

Clinical questions

General

Please confirm that the formulation of the product proposed for registration in Australia is identical to that used in the submitted clinical trials.[16]

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

[16] A response to this question is included in the "Sponsor's response".

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.

Pharmacodynamics

Not applicable.

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?

Safety

Not applicable.

V. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan for this application.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator states that this submission relates to a new fixed combination product containing azelastine (as hydrochloride) 125 µg per actuation and fluticasone propionate 50 µg per actuation as a nasal spray suspension.

The proposed product is to be made available in two presentations: 4 mL (in 10 mL amber glass bottle) and 17 mL fill (in 25 mL amber glass bottle), which are connected with a nasal pump and a nasal applicator (actuator with translucent cap). The pump delivers a nasal spray with a spray volume of 137 µL, containing 125 µg azelastine (as hydrochloride) and 50 µg fluticasone propionate.

The evaluator also states that, *'the systemic exposure to fluticasone propionate is about 1.6 times greater after treatment with the proposed fixed dose combination product as compared with the corresponding monotherapy product.'*

Nonclinical

The evaluator states that, *'the nonclinical package comprised three studies investigating the repeat dose toxicity of the azelastine HCl/fluticasone propionate combination in the*

clinically proposed strength and formulation for 2 weeks (rats, dogs) or 13 weeks (rats) and contained parallel single agent groups.'

The efficacy and safety of the individual actives have been previously characterised. No genotoxicity has been exhibited by the individual actives.

Though no studies have been submitted that examined the pharmacological action of the combination, the evaluator states that this is well characterised in relation to the individual actives.

The evaluator mentions that, *'pharmacokinetic interaction of azelastine and fluticasone is not expected based on the metabolism of the individual compounds.'*

Intranasal application of azelastine hydrochloride 0.1% and fluticasone propionate 0.0365% as the clinical formulation at a daily dose of 400/146 µg for 3 months was well tolerated locally (up to 14 times the clinical dose based on nasal cavity surface area) as well as systemically (at doses up to 32 times the clinical dose on a mg/m^2 basis in rats, and up to 3 times in dogs).

No additional new toxicity was observed with the combination compared to the individual components alone.

Some PI amendments are recommended. The evaluator recommends approval.

Clinical

Pharmacokinetics

Two studies are submitted. These studies examined the effect of the fixed combination nasal spray on the systemic pharmacokinetics of fluticasone and azelastine respectively.

Study 3282

Study 3282 showed that co-administration of azelastine hydrochloride with fluticasone propionate (via 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. The evaluator states that, '*it could therefore be reasonably concluded that co-administration of azelastine does not affect systemic PK of fluticasone.'*

Study 3283

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 pharmacokinetics of azelastine.

The monotherapy azelastine product used in this study is not identical to the Australian registered product, Azep and is the US registered product (Astelin). The main difference is that the latter formulation contains benzalkonium chloride. The evaluator requests the sponsor to comment on the relationship of these formulations and their impact on safety. That is, how does the US formulation relate to the Australian formulation so that similar safety profile is implied? This needs to be addressed in the pre-ACPM response.

Pharmacodynamics

No data are submitted.

Dose ranging studies

No studies are submitted. However, the evaluator mentions that, *'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.'*

Efficacy studies

Four studies (MP4001, MP4002, MP4004 and MP4006) are discussed.

Pivotal study (MP 4001)

The evaluator states that MP4001 is the pivotal study which compared the proposed formulation with commercial azelastine (Astelin) and fluticasone propionate nasal spray. This was a randomised double blind placebo controlled study in patients with SAR.

Those 12 years and over with a 2 year history of SAR during the Texas Mountain Cedar pollen season as well as a positive skin prick test to this antigen were eligible to enrol. Exclusion criteria were comprehensive and complied with the EMA Guidelines on allergic rhinitis.

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 µg per actuation) and azelastine hydrochloride (137 µg per actuation) nasal spray – one spray in each nostril twice daily
- fluticasone propionate (50 µg per actuation) nasal spray (using a formulation marketed in the USA) - one spray in each nostril twice daily
- azelastine hydrochloride (137 µg 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 evaluator considers the comparator products acceptable as they are registered in the USA where there is a similar regulatory process (for registration) to Australia.

The primary efficacy outcome was the change from baseline to Day 14 in the 12 hour reflective total nasal symptom score (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 total ocular symptom score (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.

The sample size calculations are discussed in the CER. The evaluator mentions that the numbers were adequate for the stated comparisons. Of note: 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.

153 subjects were randomised to the proposed fixed dose combination (FDC), 152 to azelastine, 151 to fluticasone and 153 to the placebo group. 5.9 to 8.6% were in the age group 12 to less than 18 years. The mean daily reflective TNSS ranged from 18.1 to 18.8 between groups. The mean duration of the history of SAR was 18.1 to 19.0 years.

In reference to efficacy results the evaluator mentions that, *'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)'*.

The following results are reported:

Table 5. Change from baseline in AM and PM combined reflective TNSS

	n	Mean[a]	LS Mean[b]	STD	Paired t test p value[c]	source	ANOVA P value[d]	95% CI
FDC	153	-5.46	-5.31	5.084	<0.001	FDC versus P	<0.001	-4.03, -2.19
Astelin	152	-3.00	-3.25	4.155	<0.001	FDC versus A	<0.001	-2.98, -1.14
Fluticasone	151	-3.81	-3.84	4.762	<0.001	FDC versus F	0.003	-2.44, -0.50
Placebo	150	-1.91	-2.20	4.163	<0.001			

[a] Total number intent to treat (ITT) available data;
[b] Least square mean obtained from analysis of variance model for baseline or analysis of covariance model for overall.
[c] p-value for within subject change was based on paired t test.
[d] p-value for between group comparison;
[e] Baseline includes TNSS scores over the 7 day lead in period including Day 1 AM. Overall includes scores from Day 1 to Day 14 AM. FDC-Proposed fixed dose combination.

The evaluator states that though there was a significant placebo effect, the magnitude observed with the FDC was clinically significant.

The secondary efficacy endpoints relating to nasal, ocular symptoms, rhino-conjunctivitis quality of life questionnaire (RQLQ) scores showed similar results to the primary efficacy endpoints; however, some of these endpoints did not show statistically significant superiority of FDC versus fluticasone.

Other efficacy studies

There were 3 other efficacy studies (MP4002, MMP4004 and MP4006) which were similar in design to the pivotal study, MP4001. The azelastine and fluticasone monotherapy products used were "in house" formulations with no evidence of comparable efficacy to marketed formulation. Thus, the evaluator did not consider them pivotal studies.

All studies included 4 treatment groups as shown below:

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

Study MP 4002

The design and objectives were similar to MP4001. The study was conducted in those with SAR and those with documented sensitivity to a local spring pollen. The subjects were also to have moderate to severe rhinitis.

The evaluator mentions that, *'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: 207 to the proposed FDC, 207 to fluticasone and 208 to azelastine. The baseline characteristics were similar between groups. The mean duration of SAR was approximately 21 years.

The evaluator mentions that, *'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'.*

Secondary efficacy endpoints: The evaluator also mentions that, *'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'*.

MP4004

The design and methods were similar to MP4002 except that the subjects had a documented hypersensitivity to a local autumn antigen and the study was conducted during the North American autumn season.

The evaluator mentions that, '*the statistical analysis plan differed from MP4002 in that reflective total ocular symptom score (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; 195 subjects to the proposed FDC, 194 subjects to azelastine and 189 subjects to fluticasone. The baseline characteristics were similar between groups.

Regarding the results of the primary efficacy endpoint the evaluator mentions that, *'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'*.

In relation to the multiple secondary endpoints based on nasal symptom scores (individual symptoms and iTNSS), the proposed FDC was consistently superior to placebo and azelastine. However, for majority of these endpoints, there was no statistically significant difference between the FDC and fluticasone.

The results of the change in iTNSS over the first 4 hours (Day 1) showed statistically significant difference favouring the FDC over placebo, supporting the claim of rapid onset of action of the FDC. However, this was not evident in the comparison of the FDC versus fluticasone.

Ocular symptom endpoints, RQLQ scores showed that the FDC was superior to placebo. There was no clinically significant difference between the FDC and azelastine or fluticasone.

Study MP4006

This study was also similar in design to the previous studies. In addition, the subjects were also to have hypersensitivity to a prevailing individual seasonal pollen documented by positive skin prick testing within the last year.

This study included larger numbers than the previous studies in order to increase the power of the study.

A total of 1801 subjects were randomised, 451 to Dymista, 449 to azelastine, 450 to fluticasone and 451 to placebo. The relevant characteristics were similar between groups.

In relation to the primary efficacy endpoint, the three active treatments were all superior to placebo and the combination was significantly more effective than the two monotherapies.

The secondary efficacy endpoints reflected the findings of the previous studies.

In relation to the onset of action, the evaluator mentions that, *'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'*.

Pooled analysis

The evaluator discussed the pooled analysis of the 4 studies and states that, *'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'*.

Ocular symptoms showed statistical superiority of the proposed FDC over individual actives. The difference, however, was not clinically significant in relation to the comparison of FDC versus azelastine (rTOSS showed an absolute difference of -0.30).

For RQLQ overall score, the pooled analysis failed to demonstrate a significant benefit for the combination over fluticasone.

Overall conclusions on efficacy

The pivotal study (MP4001) demonstrated superior efficacy of the FDC versus azelastine and fluticasone in relation to nasal symptom scores. The pooled analysis of all studies supported this result. In relation to ocular symptoms the FDC was consistently superior to placebo. Most ocular endpoints also showed statistical superiority versus fluticasone. The evaluator states that, '*the overall data suggest that the combination is no better than azelastine nasal spray in terms of improvement in ocular symptoms.'* Pooled analysis reflected the finding of the pivotal study.

In relation to quality of life endpoints, the evaluator mentions that the pivotal study and the pooled analysis did not show a clinically meaningful difference favouring the FDC over the individual components.

The evaluator also discussed the EMA Guidelines on allergic rhinoconjunctivitis and the guidelines on fixed combination products. The submitted studies have complied with these EMA Guidelines. However, the evaluator states that, '*more robust evidence of efficacy would have been obtained if all the studies had used marketed monotherapy comparator products'*; (this was not the case in the supporting studies).

Whilst the submission requests the registration of the proposed FDC for PAR, no studies on PAR are submitted. The evaluator quotes the EU Guideline in relation to this: '*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 evaluator considers that the proposed FDC for PAR is approvable as the sponsor has provided a 12 month safety study, MP4000.

Safety

The evaluator discusses the long term safety study MP4000, a randomised open label study where subjects were randomised (2:1) to receive the FDC or fluticasone for 12 months. Those of the ages of 12 to 80 years with an established history (greater than or equal to 1 year) of rhinitis due to perennial allergies or non-allergic rhinitis were eligible to enrol. Exclusion criteria were essentially similar to those used in the efficacy studies.

The study treatments (2:1 randomisation) were as follows:

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

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

A total of 611 subjects were included, 404 subjects in the FDC group and 207 subjects in the fluticasone propionate group. The mean TNSS total score was 3.84; the evaluator states that this, '*reflects the fact that subjects were not required to have moderate to severe disease'*.

The evaluator mentions that, *'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'*.

There were no deaths in the treatment groups; SAEs were similar between groups; the events appeared not to be related to study treatment.

Discontinuations due to AEs: The evaluator mentions that the incidence was similar between groups. However, there were 2 subjects with cataract and 3 subjects with reduced cortisol levels who discontinued in the FDC group. The evaluator states that these events may be related to increased absorption of fluticasone from FDC than from the monocomponent product.

Laboratory investigations did not reveal any trends.

The incidence of glaucoma and posterior capsular cataract at 6 and 12 months were similar between groups.

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.

The results suggest that the combination product was not associated with a greater incidence of significant reduction in serum cortisol. The evaluator states, however, that this is an insensitive measure of hypothalamic pituitary adrenal function.

In the submitted studies 1469 subjects were exposed to the FDC. In the 4 efficacy studies 1006 subjects were exposed for 14 days.

The incidence of all AEs were higher (16.4%) than the monotherapy comparator groups (13.1 -15.1%). Altered taste, epistaxis and headache were the most commonly reported AEs.

There were no deaths; SAEs were not related to study treatments.

Percentage discontinuations were similar between groups. The evaluator states that these events did not suggest any safety concerns with FDC.

Overall the evaluator states that the safety profile of the FDC is acceptable. The evaluator stated that, '*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'*.

Clinical evaluator's recommendation

Overall, the risk benefit profile was found to be favourable.

Regarding the PI some amendments are recommended. Of note: there is modification of the indications-The evaluator recommends that the indication should be,

> *Symptomatic treatment of moderate to severe allergic rhinitis and rhino-conjunctivitis in adults and children 12 years and older, where treatment with an intranasal steroid alone has been inadequate.*

This is mainly because the ARIA guidelines recommend that for patients with moderate to severe persistent disease intranasal steroids should be the preferred treatment. The addition of an antihistamine in subjects who are not controlled would be appropriate.

The evaluator also has requested clarification of some issues. The sponsor has confirmed that the formulation used in the trials is that which is to be marketed.

The use of unregistered monocomponent comparators (in the supporting studies) was as per FDA recommendation, to minimise pharmacological differences between the products.

Delegate's considerations

In essence, the sponsor has responded to the modified indication proposed by the evaluator stating that '*the Australian eTherapeutic Guidelines that recommend use of a combination of an antihistamine and an intranasal glucocorticoid for the first line treatment of moderate to severe allergic rhinitis'*.

- The Delegate agrees with the clinical evaluator that the risk benefit profile is acceptable to approve Dymista for the treatment of allergic rhinoconjunctivitis whether it is seasonal or perennial. The long term safety study addresses the safety issues relating to the use long term.
- The indication proposed by the sponsor, *'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'* is acceptable as it addresses the Australian eTherapeutic Guidelines. Whilst it is

acknowledged that these Guidelines quoted by the sponsor and the evaluator are not adopted, the data set submitted supports the requested indication.

Proposed action

The Delegate had no reason to say, at this time, that the application for (the product) should not be approved for registration.

Request for ACPM advice

- Does the Committee agree that there are adequate data to register for SAR?
- Does the Committee agree that PAR could be registered based on the data on SAR and the 12 month safety study?
- Does the Committee agree with the proposed indication or should it be confined to a second line indication as recommended by the evaluator or approved for first line treatment?
- Does the Committee have any further advice regarding this submission?

Response from sponsor

The sponsor noted that the Delegate's preliminary assessment is to approve for registration Dymista and Dylastine (as additional trade name).

The sponsor supported the Delegate's final comment and agreed that the indication proposed by the sponsor *'Symptomatic treatment of moderate to severe allergic rhinitis and rhinoconjunctivitis in adults and children 12 years and older where use of a combination (intranasal antihistamine and glucocorticoid) is appropriate'* and is in the sponsors opinion acceptable as the data set submitted supports the requested indication and it addresses the Australian eTherapeutic Guidelines on Allergic Rhinitis.

SAR and PAR

The sponsor agrees with both the Delegate and clinical evaluator that the risk benefit profile is acceptable to approve Dymista for treatment of allergic rhinitis and rhinoconjunctivitis whether it is seasonal or perennial. The sponsor noted that their decision was supported by the fact that the dossier met the requirements of EMA guidelines on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis (CHMP/EWP/2455/02, London, 21 October 2004). This guidance document was adopted by the TGA effective 28 July 2005 and states that pharmacodynamically SAR and PAR are considered comparable; and if only 2 SAR studies are conducted, additional safety data for 12 months are sufficient to establish safety of chronic use of the product in patients with PAR.

MEDA performed 4 SAR studies and a long-term 12-month study (MP4000). The 4 SAR studies consistently showed superiority of the combination over both monoproducts. The long-term study provided 12-month safety as well as supportive efficacy data for PAR. In the study patients were asked to take fluticasone propionate, two sprays in each nostril once daily; or to take the combination, one spray in each nostril twice daily, as recommended in the Product Information. The efficacy endpoint in MP4000 was the evening symptom score which was in the middle of the dosing interval of fluticasone nasal spray and at the end of the morning dose for the combination. The study results showed long-term statistical and clinical superiority of the combination over fluticasone nasal spray ($p<0.05$ at least until Week 28). It is expected that clinical superiority would be more pronounced, in favour of the combination, if the morning symptom score (defined as 24 h post fluticasone dose and 12 h post combination evening dose) was measured. In

addition, both monotherapy products have been approved and recommended for SAR and PAR. Therefore the simplified indication *allergic rhinitis and rhinoconjunctivitis'* (without specifying SAR and PAR) is justified in the sponsor's opinion.

First line indication

The dossier also met the requirements of EMA guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95/Rev.1, London 19 February 2009) for first line indication, as the studies included patients receiving previously neither of the monosubstances (greater than 97% of patients per study did not previously receive either of the monosubstances). Furthermore, the Australian eTherapeutic guidelines on Allergic Rhinitis recommends the first line use of a combination of intranasal corticosteroid and either oral or intranasal antihistamine for patients with persistent moderate to severe symptoms. For patients with intermittent moderate to severe symptoms it recommends intranasal corticosteroid and/or oral or intranasal antihistamine. Therefore it is important Dymista is not confined to a second line indication as this could be misleading for Australian health care professionals (HCPs) when referring to local guidelines for allergic rhinitis management.

In addition to the overall enhanced efficacy, the combination provides an earlier response to therapy and patients achieve more rapid symptom relief than treatment with intranasal corticosteroid alone. Today, most patients self-medicate with OTC medicines prior to visiting a physician. The proposed indication and availability of Dymista by prescription empowers the treating physician to assess symptoms and prior treatment history and apply their expertise in recommending the right treatment for that patient.

Overseas registration status

Amongst countries with comparable regulatory requirements and processes, the approval for Dymista was granted first in the US (in 2012) followed by 'European approval' with 28 countries involved in the European Decentralised procedure (ended January 2013). On the basis of this European approval each country involved was issued a national product license, including UK and Sweden.

Table 6. Australian proposed indication relative to indications approved in the UK & Sweden (representing Europe) and in the US.

1. Australian Proposed Indication	2. UK and Sweden Approved Indication	3. US Approved 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.	Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient.	Dymista Nasal Spray is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

As noted by the Delegate, azelastine monoproduct (Astelin) has not been approved for perennial allergic rhinitis in the US. Unlike the TGA, the FDA has not adopted EMA guidelines on rhinoconjunctivitis. As a result, Dymista nasal spray is indicated in the US for the relief of symptoms of seasonal allergic rhinitis. Although rhinoconjunctivitis is not explicitly stated in the European indication, the summary of product characteristics mentions efficacy of the combination in treatment of both nasal and ocular symptoms. In addition, the Australian eTherapeutic guidelines for allergic rhinitis recommend intranasal corticosteroids for treatment of allergic conjunctivitis if it is an associated feature.

Astelin versus Azep formulation

The sponsor commented on the relationship between the US formulation Astelin (used in clinical trials as the comparison monotherapy product containing azelastine) and the Australian formulation Azep (original and "reformulated"), as requested by the Delegate. Astelin and Azep (original formulation) are basically the same except for a few differences. The difference in the amount of ingredient Disodium phosphate (buffering agent) is associated with the used hydrate in manufacture. When calculated on the anhydrate, identical amounts yield. Furthermore, there is a slight difference in the amount of Citric acid anhydrous used; this difference is considered negligible.

Both Astelin and Azep (original formulation) contain the preservative Benzalkonium chloride (BAC). Azep (original formulation) was approved for registration in Australia in 2000 (under the name Rhinolast). In 2004 approval was received for the "reformulated" and renamed product Azep, which has been on the market since. The "reformulated" Azep differs from the original Azep only in respect to the preservative BAC as indicated in Table 7. The reformulation was sought because the preservative BAC did not add value to Azep since azelastine has antimicrobial activity by itself and removal of BAC was welcomed by patients in Europe as well as Australia who were conscientious about preservatives in general. Investigations of spray patterns demonstrated that the absence of BAC had no influence on the particle size distribution produced by the affixed pump. Therefore, the approval for the "reformulated" azelastine nasal spray in Europe and Australia was mainly based on efficacy and safety data of clinical studies with the original BAC-containing formulation. In the US, the original BAC-containing azelastine nasal spray (Astelin) is still marketed. The BAC-free formulation was never pursued in the US.

The use of BAC as a conserving excipient in nasal sprays has been established since decades and still very common. The safety of BAC in intranasal solutions was discussed in the literature in the 90's and consensus was reached based on a systematic review published in 2004. The review considered 18 studies and concluded that intranasal products containing the preservative BAC appear to be safe and well tolerated for both short and long-term clinical use. Accordingly, no relevance in clinical safety is expected between BAC-containing and BAC-free formulations. Therefore the robustness of the efficacy and safety studies for Dymista is not impacted by the use of Astelin versus marketed Azep. Other examples of intranasal corticosteroids containing BAC that are marketed in Australia are Flixonase Allergy & Hayfever 24 Hour, Avamys and Nasonex.

Table 7. Astelin, Azep original and Azep "reformulated" formulations

Ingredients	Astelin Formulation used in clinical studies (mg/actuation)	Azep original formulation (mg/actuation)	Azep current "reformulated" formulation (mg/actuation)
Azelastine hydrochloride	0.14	0.14	0.14
Citric acid - anhydrous	0.0616	0.0613	0.0613
Disodium edetate	0.07	0.07	0.07
Hypromellose	0.14	0.14	0.14
Sodium chloride	0.9618	0.9618	0.9618
Dibasic Sodium Phosphate calculated as water-free	0.3598 from 0.6804 mg USP heptahydrate	0.3598 from 0.9072 mg dodecahydrate	0.3598 from 0.9072 mg dodecahydrate
Water - purified	138.62898	138.40218	138.4196
Benzalkonium chloride	0.0175	0.0175	-

Safety

The clinical evaluator noted that treatment with the combination was associated with an increased incidence of epistaxis in the long-term study compared to the US marketed fluticasone propionate nasal spray (2.0% versus 0.5%). However, the pooled data of all 4 placebo-controlled studies including data of 4,020 patients yielded almost no difference in incidence of epistaxis between the combination and placebo, (2.2% versus 2.0%) but a higher incidence in the US marketed fluticasone propionate nasal spray group (3.9%). Thus, epistaxis often occurs in patients with allergic rhinitis and rhinoconjunctivitis, even if left untreated and the difference in incidence between treatments in the long-term study is rather a finding by chance.

The sponsor agreed with the clinical evaluator that the combination appears to produce increased systemic exposure to fluticasone (about 1.6 times greater), when compared to a US marketed fluticasone propionate monotherapy product. However, the absolute systemic bioavailability of fluticasone is still very low (with mean peak concentration of approximately 10 pg/mL) and unlikely to cause any clinically relevant systemic effects. Moreover, we proposed the maximum daily dose of 200 mcg fluticasone propionate per day that is half the maximum daily dose approved for fluticasone propionate nasal spray in Australia.

Evaluator's comments on draft PI

All comments from pharmaceutical chemistry and nonclinical evaluators have been incorporated. Comments on the clinical aspects have also been incorporated except a few points as shown in the proposed PI and explained below. Our main concern was deleting/amending some information as requested by the clinical evaluator, which in the sponsor's view is important for Australian HCPs, therefore we propose retaining it in the PI.

Comment 1

The evaluator recommended amending the sentence '*A relief of nasal allergic symptoms is observed within 15 minutes after administration*' in the fourth paragraph in Section "Pharmacology – Pharmacodynamics" that describes the pharmacodynamics of azelastine. This information is correct and taken from the Azep PI. It is clearly written that the third and fourth paragraphs in this section describe the individual component - azelastine. The statement on onset of action for the combination product is given in Section "Clinical Trials". In addition, a similar statement is also included in the European SPCs for Dymista in "Pharmacodynamic properties". Therefore, the sponsor suggested not amending this statement.

Comment 6

The evaluator recommended that all references to the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) should be deleted, as the combination product had no clinically significant benefit compared to the monotherapy products. RQLQ is an important secondary endpoint that is recommended by the EMA guidelines on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis. It is also addressed in the ARIA guideline as '*the RQLQ scores significantly impaired in patients with moderate/severe symptoms by comparison to patients with mild symptoms*.' Information about RQLQ is important for HCPs, therefore a reference to RQLQ is included in the US prescribing information and European SPCs for Dymista. Please note that we do not claim for improved quality of life compared to monoproducts, although the combination had a clinically significant benefit compared not only to placebo but also to azelastine. The statement '*The RQLQ score for Dymista 125/50 was significantly improved over placebo*…' clearly and correctly addresses the comparison to placebo. The sponsor proposed to retain this information in the PI.

Comment 8

The evaluator recommended deleting the responder rate analysis as it was a post-hoc analysis. This analysis was performed to evaluate clinical relevance of the change in symptom score as exactly recommended by the EMA guidelines on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis: '*A merely statistical significant difference of xx points on a scale might not be sufficient. An analysis in terms of responder (for example patients with a 50% reduction in symptom score) might be helpful*". Thus, although this was a post hoc analysis the criterion for responder and the analysis are pre-defined in the guideline. This analysis is also requested by the European authorities. Furthermore, the information about statistical significant difference of xx points on a scale of symptom scores may be less comprehensive for HCPs than the information about the responder rate. Therefore, the sponsor suggested retaining this information in the PI, however the sentence has been amended to reflect the data of the pivotal study as well as the pooled analysis. This is in line with the European SPCs for Dymista.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new combination of active ingredients.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Dymista nasal spray containing azelastine hydrochloride 0.1%w/w and fluticasone proprionate 0.0365% w/w to have an overall positive benefit–risk profile for the 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.

In making this recommendation the ACPM

- noted that there were no dose-ranging studies done with the combination product. The doses for each active were taken from the monotherapy studies with no attempt to show possible dose reduction.
- expressed some concern that the combination required a two times daily regimen due to the antihistamine which then provides 1.6 times the dose of fluticasone proprionate (FP).

Specific advice

The ACPM provided the following specifically requested advice:

- Does the committee agree that there are adequate data to register for seasonal allergic rhinitis (SAR)?

The ACPM advised that evidence of efficacy with nasal symptoms (over individual products) was adequate. The evidence submitted of improvement in eye symptoms over placebo was also adequate. While efficacy was clinically significant and the secondary outcomes (nasal congestion, sneezing et cetera) showed similar results not all secondary endpoints were superior to FP alone. There are no added safety risks apparent with the combination.

- Does the committee agree that perennial allergic rhinitis (PAR) could be registered based on the data on SAR and the 12 month safety study?

The ACPM advised that the 12 month study in PAR was adequate when combined with the SAR studies to show efficacy. The three active treatment arms were all superior to placebo, the combination was more effective than the two monotherapies and the secondary outcomes for the combination were better than placebo and azelastine but not to FP. The onset of action appears to be rapid. There are no added safety risks apparent with the combination. The studies complied with EMA guideline requirements and the individual products are registered for SAR and PAR.

- Does the Committee agree with the proposed indication or should it be confined to a second line indication as recommended by the evaluator or approved for first line treatment?

The ACPM advised that the lowest effective dose should always be a starting point for therapy and in general, monotherapies at the lowest dose should be trialled first. Combination products should be used only in more severe cases (as stated in the proposed indication) where added treatment becomes necessary. The therapeutic guidelines make this clear to prescribers.

Proposed conditions of registration

The ACPM specifically advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- The sponsor wished to keep the quality of life comments (compared to placebo) and the ACPM thought this reasonable.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Dymista/Dylastine 125/50 azelastine (as hydrochloride) 125 microgram and fluticasone propionate 50 microgram nasal spray bottle indicated for:

> *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.*

Specific conditions of registration applying to these goods

Periodic Safety Update Reports (PSURs) are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module Vll- Periodic Safety Update Report, Part Vll. B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration.

Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The Product Information approved for Dymista at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>. The PI for Dylastine is identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

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