

DTB CME/CPD*

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Azelastine and fluticasone nasal spray: any advantage?

Allergic rhinitis affects over 20% of the UK population. It can have a significant impact on quality of life and interferes with both attendance and performance at school and at work.¹ Intranasal corticosteroids are widely recognised as the most effective symptomatic treatment available, but oral or intranasal new generation antihistamines are usually offered as first-line treatment for intermittent symptoms.^{1,2} Patients with moderate to severe allergic rhinitis may require a combination of drugs, and many patients only achieve limited control of their symptoms.³ Dymista is described as a novel intranasal formulation combining the antihistamine azelastine hydrochloride with the corticosteroid fluticasone propionate.³ It is licensed for the relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis in adults and adolescents if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient.⁴ The manufacturer claims that compared with fluticasone or azelastine alone, Dymista is twice as effective (when placebo effect is excluded) in providing relief from both nasal and ocular symptoms, and leads to greater overall relief from nasal symptoms. It also claims that Dymista controls nasal symptoms up to 6 days faster than fluticasone.⁵ Here we consider the evidence for Dymista and whether it represents a significant advantage in the management of patients with allergic rhinitis.

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About allergic rhinitis

Allergic rhinitis is an inflammatory disorder of the nasal mucosa mediated by early- and late-phase hypersensitivity responses to environmental allergens. It is characterised by pruritus, sneezing, rhinorrhoea, and nasal congestion.⁶

What is Dymista nasal spray?

Dymista was launched as a prescription only medicine (POM) in the UK in 2013. The licensed dose is one actuation in each nostril twice daily. Each actuation delivers 137µg azelastine hydrochloride (125µg azelastine) and 50µg fluticasone propionate.⁴ The individual agents (fluticasone propionate nasal spray 50µg/actuation⁷ and azelastine hydrochloride nasal spray 140µg/actuation⁸) are available in the UK as POMs and pharmacy medicines (P).

Clinical efficacy

The submission for the licence application for Dymista included four multicentre randomised double-blind placebo- and active-controlled studies.^{3,9} These involved over 4,000 patients, aged 12 years and older, with moderate-to-severe seasonal allergic rhinitis defined by a reflective total nasal symptom score (rTNSS) of at least 8, and a nasal congestion score of at least 2 out of 3 during screening. The studies were all conducted in the US during the spring and autumn allergy seasons in 2008/2009, and were of similar design. Each study involved a 7-day single-blind placebo lead-in period followed by 14-day treatment period. In three studies, Dymista was compared with non-commercially available formulations of azelastine and fluticasone, which were reformulated and prepared in the same vehicle and delivery device as Dymista. For the fourth study, Dymista was compared with commercially available azelastine and fluticasone nasal sprays.¹⁰ Data from three studies have been published in a single paper along with a post-hoc meta-analysis.³ The fourth study has been published as a separate paper.⁹

Symptom scoring system for allergic rhinitis

The European Medicines Agency and the US Food and Drug Administration recognise that patient self-rated symptom scores are often used as primary measures of efficacy in clinical trials of patients with allergic rhinitis/rhinoconjunctivitis. A 4-point rating scale with the following definition is generally accepted (see Box).^{11,12}

Box: 4-point rating scale

0=no symptoms (*no sign/symptom evident*)
1=mild symptoms (*sign/symptom clearly present, but minimal awareness; easily tolerated*)
2=moderate symptoms (*definite awareness of sign/symptom that is bothersome but tolerable*)
3=severe symptoms (*sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping*)

In the studies, the primary endpoint was the difference between the 12-hour rTNSS score (i.e. combined morning and evening score) over the 14-day treatment period and the 12-hour rTNSS baseline score during the 7-day, single-blind, placebo lead-in period. These summed scores included four nasal symptoms: rhinorrhea, nasal congestion, nasal itching and sneezing.^{3,9} Reflective symptom scores assessed the overall degree of effectiveness over a prespecified time interval. Secondary outcome measures included the instantaneous total nasal symptom score (iTNSS) which assessed the same symptoms at the end of the dosing interval, the reflective total ocular symptom score (rTOSS) and quality-of-life measures.^{3,12} All nasal and ocular symptoms were scored by patients twice daily on each treatment day and the maximum possible rTNSS or iTNSS was 24.^{3,9}

Trial results

Three studies (3,398 subjects) randomised patients to the following groups: Dymista, azelastine 137µg, fluticasone 50µg or placebo nasal spray. Patients administered one spray per nostril twice a day. At baseline, the rTNSS of the four treatment groups were similar. In each study Dymista reduced the mean rTNSS from baseline by a statistically significantly greater margin than azelastine, fluticasone or placebo over the 14-day treatment period. The meta-analysis demonstrated statistically significantly greater nasal symptom relief with Dymista compared with either monotherapy or placebo (p<0.001), although the absolute difference between groups was small.³

Table 1: Mean total nasal symptom scores (intention-to-treat population)³

	Number of patients	Baseline rTNSS (SD)	Change from baseline (SD)
<i>Meta-analysis of data from three studies</i>			
Dymista	848	18.8 (2.9)	-5.7 (5.3)
Fluticasone	846	18.9 (2.8)	-5.1 (4.9)
Azelastine	847	18.9 (3.0)	-4.4 (4.8)
Placebo	857	19.0 (2.8)	-3.0 (4.2)

rTNSS, reflective total nasal symptom score; SD, standard deviation.

Secondary outcome measures included overall change from baseline in the iTNSS, and rTOSS. Dymista reduced the iTNSS from baseline (-5.2) to a statistically significantly greater extent than fluticasone (-4.8), azelastine (-4.1) or placebo (-2.6). It also reduced the mean ocular symptom score from baseline (-3.2) compared with fluticasone (-2.8), azelastine (-2.9) and placebo (-1.8), achieving statistical significance compared with fluticasone (p=0.003) and placebo (p<0.001), but not azelastine (p=0.196). Quality of life was assessed using the 28-item Rhinitis Quality of Life Questionnaire (RQLQ) for subjects older than 18 years. The overall baseline scores were 3.9 in the Dymista, azelastine and placebo groups and 3.8 in the fluticasone group³ (range 0 to 6).¹³ By day 14, all active treatments led to improvements in these scores (Dymista -1.6; fluticasone -1.5; azelastine -1.4) compared with placebo (-1.0, p<0.001),³ with a change in score by greater than 0.5 considered a minimally important difference.¹⁴ Several post-hoc evaluations were also conducted, including a time to response analysis¹⁰ that indicated Dymista had an advantage in producing ≥50% reduction in rTNSS over fluticasone (up to 3 days earlier) and azelastine (up to 5 days earlier).³

In the fourth study (610 patients), patients were randomised to Dymista, azelastine 137µg, fluticasone 50µg or placebo nasal spray (one spray per nostril twice a day). All three active treatment groups resulted in a statistically significant improvement in rTNSS from baseline over 14 days (-5.3 with Dymista, -3.8 with fluticasone and -3.3 with azelastine; p<0.001). The improvement in rTNSS from baseline was 28% with Dymista, 20% with fluticasone and 16% with azelastine (p<0.01 vs. placebo and either agent alone). Dymista improved the overall rTOSS compared with either fluticasone or placebo (p<0.01) but not azelastine.¹⁵ The treatment differences of Dymista versus active comparators were more apparent in this study¹⁰ and data from post-hoc analyses of this study were used as the basis for the manufacturer's promotional claims for Dymista.⁵ In the post-hoc responder analyses, more patients on Dymista achieved reductions in rTNSS at the response cutoffs (≥30, 50, 60, 75 and 90% response), and did so faster than both the active comparators and placebo. At day 14, a ≥50% reduction in rTNSS was achieved by 49%, 37%, 38% and 28% of patients using

Dymista, azelastine, fluticasone and placebo respectively; and patients using Dymista achieved this response up to 6 days faster than those using either fluticasone ($p=0.028$) or azelastine ($p=0.022$). For the response criterion of ≤ 1 point remaining in each nasal symptom score, 18% of Dymista patients had a complete/near-to-complete nasal symptom resolution versus 9%, 8% and 8% on fluticasone, azelastine and placebo, respectively. For the strictest response criterion of ≤ 1 point remaining for all symptoms (rTSS), 14% of Dymista patients achieved complete/near-to-complete elimination of all nasal and ocular symptoms compared to 9% on fluticasone, 6% on azelastine and 6% on placebo.¹⁶

Limitations of the data

The duration of the studies was short and use of a change-in-symptom score from baseline as a primary efficacy measure is difficult to interpret in the absence of defined thresholds for what is considered a clinically meaningful change. Data from post-hoc analyses of one of the studies¹⁶ formed the basis of the manufacturer's claims for superiority of Dymista⁵ and require confirmation in prospective studies. The trial data may not be generalisable to those patients seen in primary care who may present with milder symptoms than those of the trial population.³ In addition, Dymista has not been compared with the individual agents given separately nor with the concomitant use of an oral antihistamine and intranasal corticosteroid.

Unwanted effects

The proportion of subjects with a treatment-emergent adverse event was similar for the active groups in three of the studies.³ The higher proportion of treatment-related adverse events observed in the Dymista and azelastine treatment groups was due primarily to the taste of azelastine reported as dysgeusia (taste disturbance) in these patients (2.1–4.7% of Dymista-treated patients and 3.4–7.2% of azelastine-treated patients). For these three studies, changes in vital signs and nasal examination were similar in all groups.³ In the fourth study, all three treatments were reported to be well tolerated with the most common adverse event being bitter taste (2.0% with azelastine and 7.2% with Dymista).¹⁵

National and international guidance

The British Society of Allergy and Clinical Immunology recommends oral or topical antihistamines as first-line therapy for mild to moderate

intermittent and mild persistent rhinitis. Topical intranasal corticosteroids are recommended as first-line therapy for moderate to severe persistent symptoms and treatment failures with antihistamines. An antihistamine and intranasal corticosteroid are recommended for use together for moderate/severe persistent rhinitis uncontrolled with intranasal corticosteroids.¹

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines support the use of oral antihistamines over intranasal antihistamines in adults with seasonal- or perennial/persistent allergic rhinitis.¹⁷

The Scottish Medicines Consortium does not recommend the use of Dymista as it is significantly more expensive than the components administered separately.¹⁸

Cost

Table 2: Cost of drugs

	Cost for 28 days
<i>Nasal sprays</i>	
Dymista*	£17.65
Azelastine hydrochloride 140µg/spray*	£7.48
Fluticasone propionate 50µg/spray†	£8.22
Fluticasone furoate 27.5µg/spray†	£6.01
Triamcinolone acetonide 55µg/spray†	£6.89
Mometasone furoate 50µg/spray†	£6.14
Budesonide 64µg/spray†	£3.59
Beclomethasone dipropionate 50µg/spray‡	£2.54
<i>Tablets</i>	
Cetirizine 10mg daily	£0.95
Loratadine 10mg daily	£0.99

Costs based on prices in *Chemist and Druggist and Drug Tariff*.

*One spray in each nostril twice daily.

†Two sprays in each nostril once daily.

‡Two sprays in each nostril twice daily.

Conclusion

In short term studies, Dymista produced statistically significant improvements in nasal symptoms and several secondary efficacy outcomes compared with either azelastine or fluticasone alone. However, the absolute difference in symptom scores was small and thus of questionable clinical significance. In addition, it is hard to describe such small differences in meaningful terms to patients. The manufacturer's marketing claims for superiority of Dymista come from post-hoc analyses of a single study, which require confirmation in prospective studies. However, Dymista has not been compared with individual components given separately nor with concomitant use of an oral antihistamine with an intranasal corticosteroid. Therefore, we would suggest that clinicians take a cautious approach to claims based on such data. Dymista would appear to offer no significant clinical advantage over current treatment options and is more expensive than existing therapies for allergic rhinitis.

[R=randomised controlled trial; M=meta-analysis]

1. Scadding GK et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. *Clin Exp Allergy* 2008; 38: 19-42.
2. An update on the management of hay fever in adults. *DTB* 2013; 51: 30-3.
- MR 3. Carr W et al. Novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *Allergy Clin Immunol* 2012; 129: 1282-9.

4. *Dymista Nasal Spray*. Summary of product characteristics, UK. Meda Pharmaceuticals, January 2013.
5. Meda Pharmaceuticals, 2013. *Dymista* [online]. Available: <http://www.dymista.co.uk/efficacy/> [Accessed 22 January 2014].
6. Greiner AN. Allergic rhinitis. *Lancet* 2011; 378: 2112-22.

7. *Pirinase Hayfever 0.05% Nasal Spray*. Summary of product characteristics, UK. GlaxoSmithKline Consumer Healthcare, October 2012.
8. *Rhinolast Allergy 0.1% w/v Nasal Spray*. Summary of product characteristics, UK. Meda Pharmaceuticals, August 2013.
- R 9. Meltzer EO et al. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy and safety. *Allergy Asthma Proc* 2012; 33: 324-32.
10. Bernstein JA. MP29-02: a breakthrough for the treatment of allergic rhinitis. *Expert Opin Pharmacother* 2013; 14: 2102-13.
11. European Medicines Agency, 2009. *Committee for Medicinal Products for Human Use (CHMP) guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases* [online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf [Accessed 22 January 2014].
12. Food and Drug Administration, 2000. *Guidance for industry. Allergic rhinitis: clinical development programs for drug products draft guidance* [online]. Available: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071293.pdf> [Accessed 22 January 2014].
13. Bousquet PJ et al. Impact of allergic rhinitis symptoms on quality of life in primary care. *Int Arch Allergy Immunol* 2013; 160: 393-400.
14. American Thoracic Society, 2013. *Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)* [online]. Available: <http://www.thoracic.org/assemblies/srn/questionnaires/rqlq.php> [Accessed 22 January 2014].
- R 15. Hampel FC et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. *Ann Allergy Asthma Immunol* 2010; 105: 168-73.
16. Meltzer E et al. Clinically relevant effect of a new intranasal therapy (MP29-02) in allergic rhinitis assessed by responder analysis. *Int Arch Allergy Immunol* 2013; 161: 369-77.
17. Brożek JL et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision. *J Allergy Clin Immunol* 2010; 126: 466-76.
18. Scottish Medicines Consortium, 2013. *Azelastine hydrochloride plus fluticasone propionate (Dymista)* [online]. Available: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/921_13_azelastine_hydrochloride_plus_fluticasone_propionate_Dymista/azelastine_hydrochloride_plus_fluticasone_propionate_Dymista [Accessed 22 January 2014].

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Cover illustration: St. John's wort (*Hypericum perforatum*) flower and pills

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