New Medicine Recommendation

Azelastine hydrochloride and fluticasone propionate 137microgram / 50 microgram per actuation nasal spray (Dymista®)

For relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient

Recommendation: BLACK

NOT recommended for use by the NHS in Lancashire and South Cumbria.

No evidence is available demonstrating efficacy in patients who have failed a combination of corticosteroid and antihistamine.

Summary of supporting evidence:

- Dymista® nasal spray has demonstrated improved outcomes for all severities of allergic rhinitis compared to monotherapy with intranasal corticosteroids or antihistamines.
- The safety profile of Dymista® is comparable to other nasal sprays containing either corticosteroids or antihistamines, with no substantial safety concerns raised in the overall safety database of Dymista®.
- Combinations of intranasal corticosteroids and add-on oral antihistamines have demonstrated limited if any additional benefits compared to intranasal corticosteroids alone. [9] [10] [11] [12] [13]
- Dymista® is cheaper than its two individual components and administration in a single formulation reduces the “washout effect” of administering two nasal spray devices sequentially and may improve concordance.
- The British Society of Allergy and Clinical Immunology advises the use of Dymista® when symptoms remain uncontrolled on antihistamine or intranasal corticosteroid monotherapy or a combination of oral antihistamine and intranasal corticosteroid.

Details of Review

Name of medicine (generic & brand name)**:**

Azelastine hydrochloride and fluticasone propionate (Dymista®). [1]

Strength(s) and form(s):

Azelastine hydrochloride 137 micrograms (= 125 mcg azelastine) / fluticasone propionate 50 micrograms per actuation nasal spray solution.

Dose and administration:

One actuation in each nostril twice daily (morning and evening).

BNF therapeutic class / mode of action:

Antihistamine and corticosteroid (intranasal).

Licensed indication(s):

Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient. [1]

Proposed use (if different from, or in addition to, licensed indication above):

Patients who are refractory to first line nasal steroids in combination with antihistamines.

Course and cost:

Dymista® 120 dose nasal spray cost = £14.80

Annual cost of treatment = £177.60 (assuming 12 nasal sprays would need to be supplied for 12 months treatment).

Please note that 12 months of treatment will not be necessary for some patients with allergic rhinitis.

Current standard of care/comparator therapies:

Combinations of intranasal steroids and oral antihistamines annual cost.

Example regimens:

- Beclometasone nasal spray combined with cetirizine tablets (£34.62 to £55.76)
- Mometasone nasal spray combined with loratadine tablets (£18.90 to £44.55)
- Fluticasone propionate nasal spray combined with fexofenadine 120mg tablets (£57.84 to £166.74)

Prices obtained from the June 2019 Drug Tariff.

Costs based on number original packs of nasal spray which would need to be dispensed in a 12-month period and the dose of nasal spray required.

Relevant NICE guidance:

NICE Clinical Knowledge Summary: Allergic Rhinitis. [2]

- If there is persistent nasal itching and sneezing, options are to add in an oral antihistamine to be used regularly rather than 'as needed', or to prescribe a combination preparation containing an intranasal antihistamine (azelastine) and intranasal corticosteroid (fluticasone propionate) such as Dymista® spray, if monotherapy with either

an antihistamine or intranasal corticosteroid is ineffective.

- The Allergic Rhinitis and its Impact on Asthma (ARIA) guideline recommends the option of combination treatment, particularly as this may act faster than intranasal corticosteroid monotherapy, based on low- to moderate-quality evidence. It also notes that this combination is more effective for symptom reduction than the use of intranasal antihistamine monotherapy, based on low-quality evidence.
- The British Society for Allergy and Clinical Immunology guideline (BSACI) and expert consensus statement also recommend considering combination therapy second-line (prescribed as Dymista® intranasal spray) if the person is more than 12 years old with moderate or severe seasonal or persistent symptoms if monotherapy with either agent is not effective. In addition, the BSACI guideline suggests concordance with treatment may be higher when the drug regimen is simple, and it found combination therapy is more effective than using either agent alone.

Background and context

Allergic rhinitis is an inflammatory disorder of the nose which occurs when the membranes lining the nose become sensitised to allergens. This triggers the release of histamine and other inflammatory mediators which act on cells, nerve endings, and blood vessels to produce sneezing, itching, nasal discharge (rhinorrhoea), and nasal obstruction. It is a common condition that affects 20% of the UK population and is increasing in incidence. The incidence of the type and severity of allergic rhinitis is related to age. Children of school age and adolescents are most commonly affected by seasonal allergic rhinitis. Adults are more likely to have perennial allergic rhinitis.

The primary goal in the management strategy of a patient with allergic rhinitis is to control their symptoms with the most acceptable treatment. Allergic rhinitis has a significant impact on a patient's quality of life and may adversely affect a patient's work, home and social life. It is also an independent risk factor for the development of asthma, while increasing the risk of poor asthma control and exacerbation of symptoms where asthma co-exists. Treating allergic rhinitis has been associated with improved asthma control, sleep quality and exam performance. It is believed that effective management of allergic rhinitis may prevent the development of asthma. [2]

Following allergen avoidance, first-line treatment options for allergic rhinitis depend on patient symptoms/preferences and includes antihistamines (oral and intranasal) and intranasal corticosteroids.

Dymista® nasal spray is licensed as a treatment option for allergic rhinitis if monotherapy with an antihistamine or corticosteroid is inadequate.

Summary of evidence

Summary of efficacy data in proposed use:

Four efficacy and safety studies were reviewed by the German medicines regulatory agency and accepted for license within the EU via the mutual recognition process. [3]

Each study was randomised, double-blind, placebo-controlled, and parallel-group in design and conducted in patients 12 years of age and older with seasonal allergic rhinitis (SAR). The studies had a 1-week single-blind placebo run-in period followed by a double-blind treatment period of two weeks with four treatment arms that allowed comparison of Dymista® with each single ingredient comparator product and placebo. The primary efficacy endpoint for the studies were either the change from baseline in the total nasal symptom (TNSS) or the change from baseline in average morning and evening reflective total nasal symptom scores (rTNSS: sum of runny nose, sneezing, itchy nose, and nasal congestion; each scored on 0-3 scale) collected daily and averaged over two weeks of treatment.

Hampel et al study (n=610) [5]

Dymista® produced a greater reduction in rTNSS, than fluticasone, azelastine or placebo. The difference compared to Dymista® in change from baseline in the rTNSS was 2.1 [CI95% 1.2; 3.0, p<0.001] for azelastine; 1.4 [CI95% 0.5; 2.4, p=0.003] for fluticasone; and 3.1 [CI95% 2.2; 4.0, p<0.001] for placebo. [3] A later analysis of the data from this trial found that a greater proportion (49.1%) of patients using Dymista® had a 50% or greater reduction in symptom score at Day 14 compared with 38.2% (p=0.0284) of those using fluticasone and 37.4% (p= 0.0223) of those using azelastine alone. Mean rTNSS reductions were typically 2 points greater with Dymista® than either single agent from the second day and throughout the 14-day period. This corresponds to a reduction in one level of severity (e.g. from 'severe' to 'moderate') in one nasal symptom recorded in patients' diaries. [6]

Carr et al meta-analysis (n=3398 in total) [7]

Results from the further three 2-week studies were combined in a meta-analysis. The reductions reported in this meta-analysis were comparable to those observed in study 4001. In the meta-analysis Dymista® reduced the mean rTNSS from baseline by 5.7 [SD ± 5.3]. This reduction was significantly more than that achieved by fluticasone, (5.1 [SD ± 4.9], P<0.001), azelastine (4.4 [SD ± 4.8], P<0.001), or placebo (3.0 [SD ± 4.2], P<0.001). The authors noted that the benefit was observed from the first day of assessment, with improvement in each individual nasal symptom, even in the patients with the most severe disease. Dymista® achieved response consistently days earlier and showed greater efficacy in patients with moderate-to-severe rhinitis than fluticasone and azelastine.

Price et al long-term study (n=612) [8]

In total, 612 chronic rhinitis patients (perennial allergic rhinitis [PAR], n=424; nonallergic rhinitis, n=188) aged 12 years or older were enrolled into this open-label, parallel-group study and randomised to Dymista® (1 spray/nostril twice daily) or fluticasone propionate nasal spray (2 sprays/nostril four times daily) for 52 weeks. Efficacy was assessed by change from baseline in reported reflective total nasal symptom score (rTNSS), time to first achieve 100% rTNSS reduction from baseline, and percentage of symptom-free days in the total and PAR populations posthoc.

Dymista® reduced patients' rTNSS from baseline significantly more than fluticasone propionate, from Day 1 up to and including week 28 (-2.88 vs -2.53; P=.0048), with treatment difference maintained for 52 weeks. Fluctuation in significance after week 28 might be explained, at least in part, by decreasing sample size. By Day 1 almost twice as many Dymista® patients were symptom free. After 1 month, 71.1% of Dymista® patients experienced 100% rTNSS reduction (60.3% for fluticasone propionate) and did on a median of 9 days faster (P=.0024). Over 52 weeks Dymista® patients experienced 8.4% more symptom-free days (P=.0005). These results were mirrored in the PAR subpopulation.

Summary of safety data:

The clinical development program for Dymista® included a total of 4634 subjects. Of these, 1411 patients were exposed to Dymista®, and long-term safety was studied over 52 weeks in 405 of these patients. The submitted data support the safety of Dymista® nasal spray in patients 12 years of age and older. There were no deaths in the clinical program. Serious adverse events were few, did not appear to be related to Dymista®, and did not suggest a new safety signal in additional to the safety data for intranasal azelastine and fluticasone propionate. The discontinuations due to adverse events also did not suggest a new safety signal for Dymista®. [4] Common adverse events in Dymista® treated patients were dysgeusia, headache, and epistaxis. The FDA concluded that these are typical adverse events seen in allergic rhinitis studies using nasal spray products containing antihistamines or corticosteroids. Focused nasal examinations were conducted in all clinical studies because local nasal toxicities such as nasal septal perforation, nasal mucosal ulceration, and epistaxis are safety concerns of interest for nasal spray products. In the clinical program for Dymista® there were no septal perforations seen. There was one report of nasal ulceration in a patient on placebo treatment. There were few cases of epistaxis, but they were generally mild in severity. [4] Overall in the 12-month safety study, less than 3% of subjects in either group discontinued the study due to an adverse event. None of these events were severe or serious. [8]

Ophthalmologic examination was done in the Dymista® clinical studies. Events of interest, such as increased intraocular pressure and cataracts, were rare and similar across treatment arms. Hypothalamic-pituitary-adrenal (HPA) axis effect was not formally assessed for Dymista® in a dedicated study. The totality of the information provided by the manufacturer does not suggest a clinically relevant HPA-axis effect for Dymista®. In addition, the manufacturer included serum cortisol measurements in a subset of patients in 12-month safety study. Results for Dymista® and fluticasone were similar in the study and did not indicate clinically significant changes. [4]

The SPC for Dymista® contains the following list of adverse events [6]:

	Very common (≥1/10)	***Common*** (≥1/100 to <1/10)	***Uncommon*** (≥1/1,000 to <1/100)	***Rare*** (≥1/10,000 to <1/1,000)	***Very rare*** (<1/10,000)	***Not known***
Immune system disorders					Hypersensitivity including anaphylactic reactions, angioedema (oedema of the face or tongue and skin rash), bronchospasm	
Nervous system disorder		Headache, Dysgeusia (unpleasant taste), unpleasant smell			Dizziness, somnolence (drowsiness, sleepiness)	
Eye disorders					Glaucoma, increased intraocular pressure, cataract	Vision, blurred
Respiratory, thoracic and mediastinal disorders	Epistaxis		Nasal discomfort (including nasal irritation, stinging, itching), sneezing, nasal dryness, cough, dry throat, throat irritation		Nasal septal perforation, mucosal erosion	
Gastrointestinal disorders				Dry mouth	Nausea	
Skin and subcutaneous tissue disorders					Rash, pruritus, urticaria	
General disorders and administration site conditions					Fatigue (weariness, exhaustion), weakness	

Dymista® Nasal Spray is not recommended for use in children below 12 years of age as safety and efficacy has not been established in this age group.

Dymista® is contraindicated in patients with hypersensitivities to any of its active ingredients or excipients and must be used in caution in patients with severe hepatic impairment. Systemic

effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. If there is any reason to believe that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to Dymista® Nasal Spray. Close monitoring is warranted in patients with a change in vision or with a history of increased ocular pressure, glaucoma and/or cataracts. [6]

Strengths and limitations of the evidence:

Strengths

- Dymista® nasal spray has consistently demonstrated improved outcomes for all severities of allergic rhinitis compared to intranasal corticosteroids and antihistamines.
- The safety profile of Dymista® is comparable to other nasal sprays containing corticosteroids and antihistamines, with no substantial safety concerns raised in the overall safety database of Dymista®.
- Combinations of intranasal corticosteroids and add-on oral antihistamines have demonstrated limited if any additional benefits compared to intranasal corticosteroids alone. [9] [10] [11] [12] [13]
- Dymista® is cheaper than its two individual components and administration in a single formulation reduces the "washout effect" of administering two nasal spray devices sequentially and may improve concordance.
- The British Society of Allergy and Clinical Immunology advises the use of Dymista® when symptoms remain uncontrolled on antihistamine or intranasal corticosteroid monotherapy or a combination of oral antihistamine and intranasal corticosteroid. [14]

Limitations

- No studies have directly compared Dymista® with combination monotherapies of intranasal corticosteroid and intranasal/oral antihistamines.
- Dymista® is more expensive than intranasal corticosteroids combined with oral antihistamines.

Summary of evidence on cost effectiveness:

None applicable.

Prescribing and risk management issues:

In general, the dose of intranasal fluticasone formulations should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained.

The Dymista® formulation contains benzalkonium as a preservative which may have a drying and irritant effect (also rarely hypersensitivity).

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Dymista® nasal spray (120-unit dose)	**1 spray into each nostril twice daily**	**£14.80**	**£177.60**
Beclometasone 50 mcg/dose nasal spray (200-unit dose)	1-2 sprays into each nostril twice daily	£3.02	£24.16 to £45.30
Fluticasone propionate 50 mcg/dose nasal spray (150-unit dose)	1-2 sprays into each nostril once or twice daily	£7.26	£36.30 to £145.20
Fluticasone Furoate 27.5 mcg/dose nasal spray (120-unit dose)	1-2 sprays into each nostril daily	£6.44	£45.08 to £83.72
Mometasone 50 mcg/dose nasal spray (140-unit dose)	1-4 sprays into each nostril daily	£1.71	£10.26 to £35.91
Cetirizine 10 mg tablets	One tablet daily	£0.86	£10.46
Loratadine 10 mg tablets	One tablet daily	£0.71	£8.64
Fexofenadine 120 mg tablets	One tablet daily	£1.77	£21.54
Costs based on drug tariff costs June 2019. This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:

Dymista® is the only nasal spray combining an intranasal corticosteroid and antihistamine. It allows patients to be treated using one formulation and is the only treatment that has demonstrated better efficacy than intranasal corticosteroid monotherapy. Dymista® offers a treatment option in allergic rhinitis for patients whose symptoms are not controlled by an intranasal corticosteroid, oral antihistamine or combination of the two.

Financial implications of the intervention:

Epact prescribing data from April 2018 to March 2019 showed that approximately 230,000 items of intranasal corticosteroid were prescribed across the Lancashire and South Cumbria at a total cost of approximately £1.1 million.

The referring clinicians who submitted a request to review Dymista® nasal spray indicated that only 30-40 patients within their trust would require Dymista® nasal spray. This would equate to approximately 120-160 patients across the provider trusts of Lancashire and South Cumbria.

Assuming 160 patients were switched from the maximum dose of mometasone nasal spray (lowest cost intranasal steroid spray) the additional cost of treating these patients would be

(£177.60 - £35.91) x 160 = **£ 22,670.40**

The table below shows the approximate cost if 5% of intranasal corticosteroid items were switched to Dymista nasal spray items.

BNFChemicalSubstance	Prescriber Items	Prescriber Act Cost	5% of items (Proposed Dymista usage)	95% of items (remaining monotherapy intranasal steroid usage)	5% items multiplied by the drug tariff cost of Dymista	Actual cost per item	Cost of monotherapy intranasal steroid (based on actual cost per item)	Total cost (Cost of 5% Dymista use + 95% monotherapy intranasal steroid)	Cost difference to supply 5 % Dymista items
Mometasone Furoate	83621	£163,160.72	4181	79440	£61,879.54	1.951193161	£155,002.69	£216,882.23	£53,721.50
Beclometasone Dipropionate	56960	£146,231.97	2848	54112	£42,150.40	2.567274692	£138,920.37	£181,070.77	£34,838.80
Fluticasone Propionate (Nsl)	43591	£520,320.72	2180	41411	£32,257.34	11.9364255	£494,304.69	£526,562.03	£6,241.30
Fluticasone Furoate	38620	£246,755.36	1931	36689	£28,578.80	6.389315383	£234,417.59	£262,996.39	£16,241.03
Triamcinolone Acetonide	5510	£41,435.85	276	5235	£4,077.40	7.520118694	£39,364.06	£43,441.46	£2,005.61
Budesonide	2621	£12,433.90	131	2490	£1,939.54	4.743953959	£11,812.21	£13,751.75	£1,317.84
								Total cost difference	£114,366.09

The total additional cost from April 2018 to March 2019 would have been approximately **£114,000.**

Service Impact Issues Identified:

Provision of Dymista® nasal spray is not anticipated to cause any service impact issues.

Equality and Inclusion Issues Identified:

No equality/inclusion issues have been identified

Cross Border Issues Identified:

The Pan Mersey APC and Greater Manchester Medicines Management Group (GMMMG) both recommend the use of Dymista® nasal spray.

Pan Mersey recommend the use of Dymista® nasal spray following inadequate symptom control using intranasal monotherapy with azelastine/corticosteroids where the addition of the other agent is being considered.

GMMMG recommends Dymista® nasal spray as a third line treatment option if an intranasal antihistamine or corticosteroid is not considered sufficient.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

References

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[4] US Food and Drugs Administration, "Summary Review Dymista Nasal Spray," 1 May 2012. [Online]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202236Orig1s000SumR.pdf. [Accessed 18 June 2019].

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[14] Scadding GK et al, "BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (revised edition)," *Clinical and Experimental Allergy,* vol. 47, pp. 856-889, 2017.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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