Coventry & Warwickshire Area Prescribing Committee

Drug Positioning Statement	DPS093
Fluticasone Propionate/Azelastine (Dymista®)	**December 2018**

VERDICT

The Coventry & Warwickshire Area Prescribing Committee recommends prescription of the combination nasal spray fluticasone propionate/azelastine, Dymista®, for the relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis where clinically appropriate and in line with local guidance, CG041 - Primary Care Allergic Rhinitis Treatment Pathway.

Specialist Drugs Status: Fluticasone propionate/Azelastine combination is not a specialist drug and can be initiated in primary care.

SUMMARY NOTES

Indication: 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].

Pharmacological action: Dymista Nasal Spray contains azelastine hydrochloride and fluticasone propionate,
Fluticasone propionate is a synthetic trifluorinated corticosteroid that possesses a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action. *Azelastine hydrochloride is* a phthalazinone derivative is classified as a potent long-acting anti-allergic compound with selective H_1-antagonist, mast cell stabilizing and anti-inflammatory properties.

A relief of nasal allergic symptoms is observed within 15 minutes after administration[1].

Presentation: Nasal spray, suspension. Each g of suspension contains 1000 micrograms azelastine hydrochloride and 365 micrograms fluticasone propionate. One actuation (0.14 g) delivers 137 micrograms azelastine hydrochloride (= 125 micrograms azelastine) and 50 micrograms fluticasone propionate[1].

Dose: Adults and adolescents (12 years and older): One actuation in each nostril twice daily (morning and evening).

Cost comparison for allergic rhinitis[2,3]: Cost of nasal spray at stated number of doses and cost per 28 days
(N.B. these doses are for general comparison and do not imply therapeutic equivalence)

Form	Dose	Sprays/Unit	Cost/ Unit	Cost per 28 days
Dymista® nasal spray	1 spray twice daily	120 doses	£14.80	£13.81
Beconase nasal spray	2 sprays twice daily	200 doses	£2.63	£2.95
Mometasone nasal spray	2 sprays once daily	140 doses	£1.75	£1.40
Fluticasone propionate nasal spray	2 sprays once daily	150 doses	£11.01	£8.22
Fluticasone furoate (Avamys®) nasal spray	2 sprays once daily	120 doses	£6.44	£6.01
Azelastine nasal spray	1 spray (0.14ml) twice daily	22ml	£10.50	£7.49

DRUG PROFILE

Clinical Effectiveness
610 moderate-to-severe seasonal allergic rhinitis (SAR) patients (≥12 years old) were randomized into a double-blind, placebo-controlled, 14-day, parallel- group trial to compare azelastine hydrochloride (AZE) /fluticasone propionate (FP)] combination with FP, AZE and placebo in SAR patients. The change from baseline in the reflective total nasal symptom score (rTNSS) over 14 days was the primary outcome. Further post hoc endpoints included the sum of nasal and ocular symptoms (rT7SS), efficacy by disease severity and by predominant nasal symptom, and a set of responder analyses. Fluticasone/azelastine most effectively reduced rT7SS (relative greater improvement: 52% to FP; 56% to AZE) and both nasal and ocular symptoms irrespective of severity; response was faster than the active comparators. FP/AZE alone was superior to placebo at the ≥60% (or higher) threshold. One in 2 FPE/AZE patients achieved a ≥50% rTNSS reduction and 1 in 6 achieved complete/near-to-complete response[4].

A randomized, 2-week, multicenter, double-blind trial of 151 patients showed that a combination of AZE and FP in combination (but in separate nasal sprays) showed an improvement of TNSS of 27.1% with fluticasone nasal spray, 24.8% with azelastine nasal spray, and 37.9% with the 2 agents in combination (P<.05 vs either agent alone). All 3 treatments were well tolerated[5].

DRUG PROFILE cont'd

A meta -analysis of 3 further multicenter trials of 3398 patients (≥12 years old) with moderate-to-severe SAR, compared AZE/FP with similar formulations that contained either one of the active drugs or placebo. Each trial was conducted for 14 days during different allergy seasons. The primary efficacy variable was the sum of the morning and evening change from baseline in reflective total nasal symptom score (range, 0-24) over the treatment period. Outcomes for the meta-analysis included efficacy according to disease severity and time to response in relevant responder criteria. In the meta-analysis MP29-02 reduced the mean reflective total nasal symptom score from baseline (-5.7 [SD, 5.3]) more than FP (-5.1 [SD, 4.9], P < .001), azelastine (-4.4 [SD, 4.8], P < .001), or placebo (-3.0 [SD, 4.2], P < .001). This 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. FP/AZE achieved response consistently days earlier and showed greater efficacy in patients with moderate-to-severe rhinitis than FP and azelastine. Secondary outcomes reported in the trials included changes in the ocular scores and Quality of life measures [6,7].

A German multicenter, prospective, noninterventional study of 1781 AR patients on FP/AZE (with acute AR symptoms and visual analog scale [VAS] score >50 m,) were reassessed after 14 days. Patients assessed symptom control using a VAS from 0 (not at all bothersome) to 100 mm (very bothersome) in the morning before FP/AZE use, on days 0, 1, 3, and 7 and after 14 days. Patients' perceived levels of disease control were assessed on day 3. The Youden index determined patient-reported VAS score cutoffs on day 3 for "well controlled" and "partly controlled." FP/AZE reduced the VAS score 54.1mm (sd=24.6)). One in every two patients felt their symptoms were well controlled at day 3[8].

Safety

Adverse effects: Commonly, dysgeusia (2.1-7.2%), a substance-specific unpleasant taste, may be experienced after administration (often due to incorrect method of application, namely tilting the head too far backwards during administration)[1]. Other adverse effects in trials include headache (0.5-2.6%), , epistaxis (1.0-3.9%) and nasal discomfort (0.5- 1.3%).The formulation contains benzalkonium as a preservative which may have a drying and irritant effect (also rarely hypersensitivity); other nasal sprays for rhinitis also contain this. There is a possible risk of adrenal suppression associated with nasal sprays containing corticosteroids but BSACI guidelines consider fluticasone low risk in this context. In the one year study, fasting morning serum cortisol was unchanged after 12 months[7]

Cautions: During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects

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 and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).
Dymista® Nasal Spray undergoes extensive first-pass metabolism, therefore the systemic exposure of intranasal fluticasone propionate in patients with severe liver disease is likely to be increased. This may result in a higher frequency of systemic adverse events.

Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression.
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. Higher doses than the recommended one have not been tested for Dymista®. As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently.

Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses. Since growing up is also given in adolescents it is recommended that the growth of adolescents receiving prolonged treatment with nasal corticosteroids is regularly monitored, too. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is maintained.
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.
Close monitoring is warranted in patients with a change in vision or with a history of increased ocular pressure, glaucoma and/or cataracts.

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.

In patients who have tuberculosis, any type of untreated infection, or have had a recent surgical operation or injury to the nose or mouth, the possible benefits of the treatment with Dymista® Nasal Spray should be weighed against possible risk.
Infections of the nasal airways should be treated with antibacterial or antimycotical therapy, but do not constitute a specific contraindication to treatment with Dymista® Nasal Spray.

Dymista® contains benzalkonium chloride. It may cause irritation of the nasal mucosa and bronchospasm[1].

Elderly: No dose adjustment is required in this population.
Renal and hepatic impairment: There are no data in patients with renal and hepatic impairment.
Pregnancy: There are no or limited amount of data from the use of azelastine hydrochloride and fluticasone propionate in pregnant women. Therefore, Dymista® Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Lactation: Dymista® Nasal Spray should be used during lactation only if the potential benefit justifies the potential risk to the newborns/infant [1]
Interactions: A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects. Co-treatment with other CYP 3A4 inhibitors, including cobicistat-containing products is also expected to increase the risk of systemic side effects.

DRUG PROFILE cont'd

The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side effects.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole), as there is potential for increased systemic exposure to fluticasone propionate[1]

CURRENT PLACE IN THERAPY

National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries[9]

CKS recommends antihistamines 'as-required' treatment for occasional symptoms for people with allergic conjunctivitis, children aged 2–5 years of age, and people who prefer oral treatment. For all other people, NICE CKS recommends intranasal azelastine first line and recommends the importance of maintaining good technique.

For people who want preventive treatment to control more frequent or persistent symptoms and If allergen avoidance is inadequate or not possible, the following are recommended. If nasal drops or a spray is prescribed, the importance of good technique needs to be explained.

- If the predominant symptom is nasal blockage, or nasal polyps are present**,** intranasal corticosteroid should be prescribed.
- If the predominant symptom is sneezing or nasal discharge**,** oral antihistamine (if oral treatment is preferred or allergic conjunctivitis is present) or an intranasal corticosteroid should be prescribed (if a more effective treatment is required)[9]

Scottish Medicines Consortium (SMC)[10,11]

Accepted for use within NHS Scotland for the relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient.

For patients in whom the combination of azelastine hydrochloride and fluticasone propionate nasal spray is an appropriate choice of therapy, Dymista® provides the two ingredients in a single nasal spray[9].

Primary Care of Respiratory Medicine and the British Society for Allergy and Clinical Immunology (BSACI) guidelines for allergic rhinitis[12,13]

The first line treatment recommendation in primary care for moderate/severe symptoms is with Intranasal corticosteroid +/- oral antihistamine then if treatment failure intranasal steroid/azelastine combination is recommended.

In addition, the primary care respiratory guidelines recommend that in secondary care where diagnosis is confirmed by history +/- serum specific IgE, intranasal corticosteroid/azelastine is recommended first line

Summary

- Dymista® is a combination intranasal spray containing an antihistamine (azelastine) and a corticosteroid (fluticasone) used to treat rhinitis symptoms. Administration using a head-down position is preferable, this treats the ostiomeatal complex; the 'head back' position is less effective. Regular treatment is required for full efficacy of nasal corticosteroids and maximal effect may not be seen until they have been used regularly for two weeks or more.[6]
- The British Society for Allergy and Clinical Immunology (BSACI) guidelines for allergic rhinitis recommend use as second line treatment in primary care[12].
- No trials comparing efficacy of Dymista® to oral antihistamine and intranasal corticosteroid in combination (BSACI treatment recommendation); Dymista® is more costly than prescription of oral antihistamine and intranasal beclometasone.
- Trials in patients with moderate to severe seasonal rhinitis found a greater reduction in patient- rated nasal symptom scores (primary outcome) in those using azelastine/fluticasone (28.4%) than either of the component drugs used alone (fluticasone 20.4%; azelastine 16.4%; placebo 11.2%). Ocular symptom scores (secondary outcome) were reduced similarly by 26.6%, 17.5%, 21.2% and 10.5% respectively[6].
- Quality of life scores (secondary outcome) improved with all active treatments. Differences between azelastine/fluticasone compared with either drug alone were small, but compared with placebo was considered clinically significant.[6]
- Many patients treat symptoms with over-the-counter products, including oral antihistamines, fluticasone and azelastine nasal sprays. Azelastine/ fluticasone is a Prescription-Only Medicine (POM) and may lead to additional requests for NHS prescribing rather than self-treatment.[6]

References

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