

Intranasal Azelastine

A Review of its Efficacy in the Management of Allergic Rhinitis

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Data Selection
Sources: Medical literature published in any language since 1966 on azelastine, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.
Search strategy: AdisBase, Medline and EMBASE search terms were 'azelastine' and 'allergic rhinitis'. Searches were last updated 13th May 1998.
Selection: Studies in patients with allergic rhinitis who received intranasal azelastine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.
Index terms: Azelastine, allergic rhinitis, pharmacokinetics, pharmacodynamics, therapeutic use.

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Summary

Abstract

Azelastine, a phthalazinone compound, is a second generation histamine H₁ receptor antagonist which has shown clinical efficacy in relieving the symptoms of allergic rhinitis when administered as either an oral or intranasal formulation. It is thought to improve both the early and late phase symptoms of rhinitis through a combination of antihistaminic, antiallergic and anti-inflammatory mechanisms. Symptom improvements are evident as early as 30 minutes after intranasal administration of azelastine [2 puffs per nostril (0.56mg)] and are apparent for up to 12 hours in patients with seasonal allergic rhinitis (SAR). The effect on nasal blockage is variable: in some studies objective and/or subjective assessment showed a reduction in blockage, whereas in other studies there was no improvement.

Intranasal azelastine 1 puff per nostril twice daily is generally as effective as standard doses of other antihistamine agents including intranasal levocabastine and oral cetirizine, ebastine, loratadine and terfenadine at reducing the overall symptoms of rhinitis. The relative efficacies of azelastine and intranasal corticosteroids (beclomethasone and budesonide) remain unclear. However, overall, the corticosteroids tended to improve rhinitis symptoms to a greater extent than the antihistamine.

Azelastine was well tolerated in clinical trials and postmarketing surveys. The most frequently reported adverse events were bitter taste, application site irritation and rhinitis. The incidence of sedation did not differ significantly between azelastine and placebo recipients and a preliminary report showed cardiovascular parameters were not significantly altered in patients with perennial allergic rhinitis (PAR).

Conclusion: Twice-daily intranasal azelastine offers an effective and well tolerated alternative to other antihistamine agents currently recommended for the symptomatic relief of mild to severe SAR and PAR in adults and children (aged ≥12 years in the US; aged ≥6 years in some European countries including the UK). The rapid onset, confined topical activity and reduced sedation demonstrated by the intranasal formulation of azelastine may offer an advantage over other antihistamine agents, although this has yet to be confirmed.

Rationale for the Development of Intranasal Azelastine

Antihistamine compounds have been in use for the management of allergic rhinitis since the 1940s. The clinical value of the first generation histamine H₁ receptor antagonists, however, was marred by their ability to cross the blood-brain barrier and cause, among other adverse events, sedation. The second generation histamine H₁ receptor antagonists, which include ketotifen, cetirizine, terfenadine, loratadine, ebastine and azelastine, are generally less sedative and have fewer nonspecific effects.

Azelastine is a phthalazinone derivative which binds preferentially to peripheral rather than central receptors; the drug has been used orally to manage the symptoms of bronchial and allergic asthma and allergic rhinitis. Local adminis-

**Pharmacodynamic
Properties**

tration via intranasal inhalation serves to further confine the activity of the drug and reduce possible adverse effects brought about by systemic exposure.

Sneezing caused by histamine nasal challenge was significantly reduced within 1 hour after initial application of azelastine 0.56mg (2 puffs per nostril) in patients and volunteers and it remained so for 10 to 12 hours thereafter. However, the effects of the drug on nasal blockage were varied: some studies showed improvements in either subjectively or objectively assessed nasal blockage, whereas others failed to show any improvements.

After allergen-specific nasal challenge, compared with baseline, single or repeated (twice daily for 2 weeks) administration of azelastine 1 puff per nostril significantly reduced objectively assessed nasal airway resistance (NAR) and increased nasal inspiration peak flowmeter values in patients with seasonal allergic rhinitis (SAR). The effects of azelastine compared with placebo on NAR, however, were varied. In a study which showed single-dose azelastine to have a significant effect compared with placebo, the mean time to onset of this effect was 135 minutes. Both the early (EPR) and late phase reaction (LPR) symptoms of allergen-induced rhinitis were significantly reduced (by up to 30%) in azelastine compared with placebo recipients. Azelastine significantly reduced allergen-induced sneezing within 15 minutes and was active for up to 10 hours.

In addition to its antihistamine and antiallergic effects, azelastine also has anti-inflammatory properties. It reduces EPR and LPR nasal mucosal infiltration of eosinophils and neutrophils by up to 49% after allergen-specific nasal challenge. Levels of a variety of inflammatory mediators were also reduced by azelastine, including nasal eosinophil cationic protein, myeloperoxidase, tryptase and intercellular adhesion molecule-1.

In vitro in human neutrophils, azelastine significantly and concentration-dependently inhibited arachidonic acid release and leukotriene B₄ production. In neutrophils or eosinophils from nonallergic volunteers, stimulated generation of superoxide, a reactive oxygen species, was decreased. Furthermore, azelastine significantly reduced the mobilisation of intracellular calcium in *N*-formyl-methionyl-leucyl-phenylalanine (FMLP)-stimulated neutrophils, a process that precedes superoxide generation.

Results from trials in rodent mast cell preparations suggest that azelastine may also interfere with protein kinase C activity and the release of tumour necrosis factor- α .

In animal models, azelastine has poor access to the CNS. In addition, studies in patients with SAR found that intranasal azelastine generally increased vigilance during the medication period. Intranasal but not oral azelastine reduced the circadian variation in vigilance.

**Pharmacokinetic
Properties**

Pharmacokinetic data for intranasal azelastine are scarce. Maximum plasma concentrations of azelastine were achieved approximately 2.5 hours after intranasal administration. After daily intranasal azelastine 0.56mg, mean steady-state plasma concentrations of the drug were about 0.26 μ g/L in healthy volunteers and about 0.65 μ g/L in patients; the estimated systemic exposure to the drug was 6- to 8-fold lower than that with oral azelastine 4.4mg. The systemic bioavailability after intranasal administration was approximately 40%. Azelastine is metabolised by the cytochrome P450 enzyme system to its major active metabolite desmethylazelastine. At steady state, the plasma metabolite concentration accounted for 20 to 50% of the azelastine concentration.

Therapeutic Efficacy

In adults and children aged ≥ 5 years with SAR or perennial allergic rhinitis (PAR), azelastine 1 or 2 puffs per nostril (0.28 or 0.56mg) twice daily over periods of 30 hours to ≥ 6 months, compared with baseline or placebo, significantly improved rhinitis symptoms including rhinorrhoea, itchy nose, sneezing, watery eyes, itchy eyes, ears or throat and postnasal drip. Compared with placebo, azelastine (2 puffs per nostril) significantly improved baseline rhinitis symptoms as early as 3 hours after drug administration in patients with SAR; significant improvement was apparent for up to 12 hours after initial use. Patient and physician global assessment of treatment with azelastine (1 or 2 puffs per nostril twice daily) of at least 'good' was similar and ranged from 75 to 86%.

Azelastine had varied effects on nasal blockage in clinical trials; some studies showed a significant improvement in azelastine compared with placebo recipients, whereas others found no significant effects.

In children (aged ≤ 12 years) with allergic rhinitis, azelastine 1 puff per nostril twice daily compared with placebo for up to 6 weeks significantly improved rhinitis symptoms. In a postmarketing survey in children aged 3 to 12 years, 85% of physicians evaluated the efficacy of azelastine as 'good'/'very good'. Rhinoscopic evaluation in children (aged 7 to 16 years) with PAR revealed significant improvement in nasal secretion, oedema and inflammation after 6 weeks' therapy with intranasal azelastine (0.6 mg/day); these symptoms were further improved in the 62 children who completed 6 months' treatment.

Intranasal azelastine as an adjunct to oral azelastine therapy further improves rhinitis symptoms compared with the effects of oral therapy alone in patients with SAR.

In comparative studies, azelastine 1 puff per nostril twice daily was generally as effective at reducing the overall symptoms of rhinitis as the standard doses of other antihistamine agents including intranasal levocabastine and oral cetirizine, ebastine, loratadine and terfenadine.

Symptom relief within 30 minutes of initial drug administration occurred in similar numbers of patients receiving azelastine (1 puff per nostril) or levocabastine (2 puffs per nostril); the effect was maintained for up to 8 hours after initial drug administration in both groups. Each drug improved nasal congestion by about 48% and ocular symptoms by about 66% from baseline after 1 week of twice-daily administration.

Results from studies that compared the effects of azelastine 1 puff per nostril twice daily and intranasal corticosteroids on the symptoms of rhinitis were varied, but overall, the corticosteroids appeared more effective. A significantly more rapid overall symptom relief was achieved in azelastine compared with beclomethasone recipients in 1 study, but after 2 weeks' therapy, improvements in overall symptom scores were significantly greater in the beclomethasone recipients. Both beclomethasone and budesonide were superior to azelastine at reducing the nasal symptoms of rhinitis in some studies, whereas others found no statistically significant difference between treatments. Budesonide was associated with greater improvements in nasal blockage than azelastine, although these did not reach statistical significance. In addition, patients' global assessments of 'substantial' or 'total' control of symptoms were significantly more common with budesonide (0.256mg once daily) than with azelastine (0.28mg twice daily) in a double-blind study (70.4 vs 44.7%).

Tolerability

Results from postmarketing surveys in 7682 patients aged 3 to 85 years with

allergic rhinitis who received azelastine 1 puff per nostril twice daily for up to 1 month showed the drug to be generally well tolerated. When azelastine was given alone, approximately 8% of patients reported adverse events; when it was given in combination with other antihistamines and/or topical corticosteroids the incidence of adverse events was approximately 20%. Bitter taste and rhinitis were the most frequently reported adverse events.

Where stated in clinical trials, physician and/or patient global assessment of tolerability was at least 'good' in more than 70% of patients (adults and children aged ≥ 7 years) receiving azelastine (typically 1 puff per nostril twice daily). Indeed, >90% of 35 azelastine recipients assessed tolerability as at least 'good' during a 21-month period of medication.

The most frequently reported adverse events were mild, transient bitter taste (associated with the taste of the drug) and application site irritation. Sedation did not differ significantly in azelastine or placebo recipients. Indeed, some study reports remarked on its absence and 1 trial reported an improvement in overall vigilance during a 2-week medication period.

Treatment withdrawal because of drug-related adverse events was rare (1 to 3 patients per study; $\leq 7\%$); reasons for withdrawal included mild increased nasal pruritus, nasal congestion, nausea and vomiting, dizziness and increased blood pressure.

No significant changes in PR, QS, QT or QT_c intervals were observed in patients with PAR who were randomised to receive azelastine (2 puffs per nostril) or placebo twice daily for 8 weeks. In addition, there were no changes in mean heart rate or blood pressure in any patient.

Dosage and Administration

The US prescribing recommendations specify 2 puffs per nostril of azelastine nasal spray twice daily for adults and children aged ≥ 12 years; each puff delivers approximately 0.14mg of the drug. In the UK and a number of other European countries, azelastine is approved as 1 puff per nostril twice daily for adults and children aged ≥ 6 years.

Although somnolence is rare, the US prescribing information carries a caution regarding use of the medication and driving or operating potentially dangerous machinery. Concurrent use of alcohol and/or other CNS suppressants should be avoided.

1. Rationale for the Development of Intranasal Azelastine

The use of antihistamine compounds in the management of allergic rhinitis is not new; they have been in use since the 1940s. However, the clinical value of the classical or first generation histamine H₁ receptor antagonists was marred by their ability to cross the blood-brain barrier and cause sedation (resulting from CNS depression) and a number of nonspecific events (resulting from blockade of muscarinic-cholinergic, α -adrenergic and serotonergic receptors).^[1] The newer, or second generation histamine H₁ receptor antagonists, which include

ketotifen, cetirizine, terfenadine, loratadine, ebastine and azelastine, are generally less sedative and have fewer nonspecific effects.

Azelastine is a phthalazinone derivative which, like many of the second generation H₁-receptor antagonists, binds preferentially to peripheral rather than central receptors.^[2] Local administration via intranasal inhalation serves to further confine the activity of the drug and reduce possible adverse effects brought about by systemic exposure.

Oral azelastine has been extensively used to manage the symptoms of bronchial and allergic asthma and allergic rhinitis.^[3] This review focuses

Table I. Overview of the pharmacodynamic properties of azelastine in humans (unless stated otherwise)**Antihistamine effects (after histamine nasal challenge)**Decreases objectively assessed nasal airway resistance^[4]Decreases sneezing^[4] and nasal secretions^[5]Significantly protects against a reduction in nasal volume (assessed by acoustic rhinometry)^[6]**Antiallergic effects (after allergen-specific nasal challenge)**Decreases objectively assessed nasal airway resistance^[7]Improves overall^[7,8] EPR and LPR rhinitis symptoms^[9,10] including sneezing^[4,7,11] and nasal blockage^[11]Decreases EPR and LPR nasal neutrophil and eosinophil infiltration^[9,10]**Effects on inflammatory cell mediators**Decreases ICAM-1 expression^[9,10]Decreases nasal ECP^[9,10,12,13] without affecting plasma ECP levels^[12]Decreases nasal myeloperoxidase and tryptase levels^[13]**Effects on inflammatory cells***Neutrophils*Decreases stimulated superoxide generation in whole cell suspensions^[14-18] but not cell-free lysate^[16,17]Decreases mobilisation of intracellular free calcium^[19]Decreases release of arachidonic acid^[14]Decreases the production of LTB₄^[14] and LTB₄ synthase^[20]*Eosinophils*Decreases chemotactic activity in fresh cells^[21] and EoL-1 cell cultures^[22]Decreases mobilisation of intracellular free calcium in EoL-1 cell cultures^[22]Decreases stimulated superoxide generation in whole cell suspensions^[15,18]**Central effects**Limited access to CNS (assessed using the active avoidance response model) in mice^[23]

ECP = eosinophil cationic protein; **EoL-1** = a human eosinophilic leukaemia cell line; **EPR** = early phase reaction; **ICAM-1** = intercellular adhesion molecule-1; **LPR** = late phase reaction; **LTB₄** = leukotriene B₄.

on the newer intranasal formulation of azelastine and its use in the management of seasonal (SAR) and perennial allergic rhinitis (PAR).

2. Pharmacodynamic Properties

The early pharmacodynamic data for azelastine in animals has already been documented.^[3] Therefore, this section focuses on human data, supplemented, where necessary, with animal data.

Table I gives an overview of the pharmacodynamic properties of azelastine assessed in patients, volunteers, human-derived cells and animals.

Azelastine nasal spray is administered by an inhaler that delivers approximately 0.14mg of the drug per actuation.

2.1 Antihistamine Effects

The effect of azelastine on nasal blockage is unclear, but this may be partly due to the technique used to assess the effects of the drug on this parameter. In 27 patients with SAR, rhinomanometric assessment of nasal airway resistance (NAR) revealed no significant protection from nasal histamine challenge by azelastine 1 puff per nostril, but parallel subjective evaluation showed a 50% reduction in nasal blockage ($p = 0.005$ vs placebo).^[6]

However, in another trial, objectively assessed blockage after histamine nasal challenge was significantly reduced by a higher dose of azelastine (2 puffs per nostril) compared with placebo in 31 evaluable patients with allergic rhinitis.^[4] The maximum response to histamine challenge (as a percentage of maximum response to saline chal-

lenge) was significantly reduced with azelastine compared with placebo at 1 hour [155 vs 210% (estimated from graph); $p < 0.02$] and 2 hours [150 vs 250% (estimated from graph); $p < 0.0001$] after initial administration, but there was no significant difference between the NAR values in each group after 4 hours.^[4]

In a double-blind, double-dummy trial in which healthy volunteers received intranasal azelastine 2 puffs per nostril, oral cetirizine 10mg or placebo,^[5] neither azelastine nor placebo had a significant effect on subjectively assessed histamine-induced nasal blockage, whereas cetirizine significantly reduced nasal blockage, but only at 24 hours after treatment ($p < 0.05$).^[5]

In the same study, azelastine or cetirizine, compared with placebo, significantly reduced the number of histamine-induced sneezes in volunteers at 1, 9 and 12 hours after initial drug administration ($p < 0.05$ vs placebo).^[5]

Furthermore, histamine-induced nasal secretion in volunteers was reduced by azelastine at 1 to 12 hours after application ($p < 0.05$) and by cetirizine at 9 ($p < 0.05$) and 24 hours after ingestion ($p < 0.01$; all vs placebo).^[5]

In patients with allergic rhinitis (type not defined), the number of sneezes recorded in the first 10 minutes after histamine challenge was significantly less in the azelastine than in the placebo group from 1 to 10 hours after drug administration ($p < 0.02$).^[4]

The effects of intranasal azelastine appear to be confined to the application site: the drug had no antihistaminic activity in the skin of 12 healthy volunteers who underwent histamine skin prick tests after receiving azelastine nasal spray (0.14mg per nostril twice daily) for 1 week.^[24] This suggests that there is no significant systemic distribution of the agent after intranasal administration.

2.2 Antiallergic Effects

Several trials objectively assessed the effects of azelastine 1^[6-8,11] or 2^[4] puffs per nostril on NAR after allergen-specific nasal challenge in patients with SAR.

Compared with baseline values, azelastine significantly reduced objectively assessed NAR^[8,11] and increased nasal inspiration peak flowmeter values^[8] after single^[11] or repeated (twice daily for 2 weeks)^[8] administration ($p < 0.05$). The effects of azelastine compared with placebo, however, were not clear: in 1 study the mean NAR values were significantly different ($p < 0.01$),^[7] whereas in another there was no difference between the mean maximum NAR values in placebo and azelastine treatment groups.^[4] In addition, azelastine was not significantly better than budesonide nasal spray twice daily (no further details)^[8] or N-acetyl aspartyl-glutamate 8.4mg (NAAG; inhibitor of mast cell degranulation)^[11] at reducing NAR.

In a study which did show a significant reduction in NAR in azelastine (single-dose 1 puff per nostril) compared with placebo recipients, the mean time to onset of effect (defined as a 20% difference in NAR between active drug and placebo) was 135 (range 75 to 210) minutes.^[7]

Azelastine improved baseline scores of allergen-induced symptoms of rhinitis (typically sneeze, itch, rhinorrhoea and blockage).^[7-10,25] More specifically, in patients with SAR, both the early (EPR) and late phase reaction (LPR) symptoms were reduced^[9] (by up to 30% in each phase; $p = 0.01$ for both vs placebo^[10]).

The drug significantly reduced sneezing after,^[4,11,25] or during,^[7] nasal challenge ($p < 0.05$). The number of sneezes after nasal challenge was significantly reduced 15 minutes after azelastine application in 1 study ($p < 0.05$ vs placebo).^[25] In another study, prechallenge treatment with azelastine reduced sneezing after the first 30 minutes of a 4-hour challenge in a Vienna chamber.^[7] In azelastine compared with placebo recipients, the number of sneezes after allergen nasal challenge was significantly reduced for up to 10 hours after drug administration ($p < 0.05$).^[4]

2.3 Anti-inflammatory Effects

It is widely accepted that allergic rhinitis is maintained by an inflammatory response characterised by the release of mediators, including his-

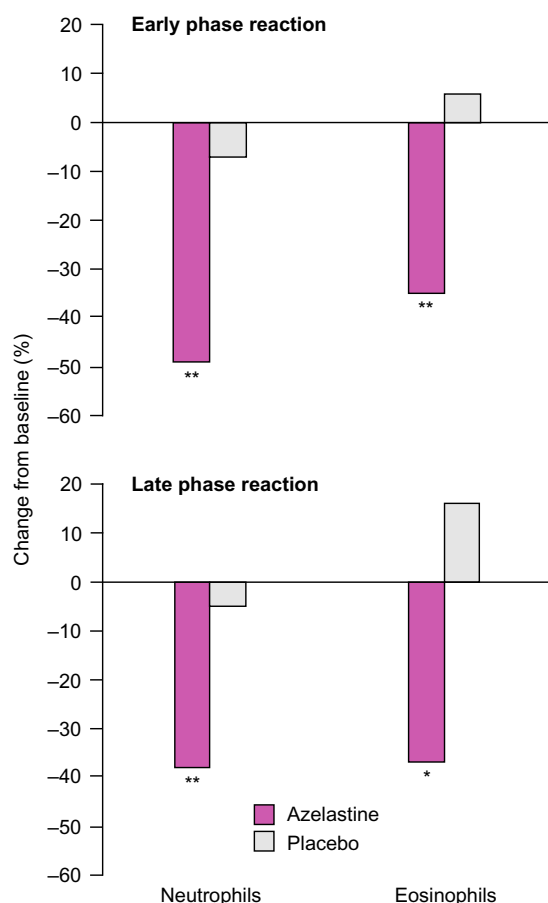


Fig. 1. Effect of azelastine on allergen-induced nasal infiltration of neutrophils and eosinophils. Single-dose azelastine 1 puff per nostril or placebo was given to 20 patients with seasonal allergic rhinitis.^[10] Nasal lavage was performed 30 minutes (early phase reaction) or 6 hours (late phase reaction) after nasal challenge. * $p < 0.05$, ** $p < 0.01$ vs placebo.

tamine, arachidonic acid derivatives and chemotactic compounds, which precede mucosal infiltration of inflammatory cells such as eosinophils and neutrophils.^[10,26]

Azelastine significantly reduced EPR and LPR nasal mucosal infiltration of eosinophils and neutrophils (by between 35 and 49% from baseline; $p < 0.05$ vs placebo^[10]) after allergen-specific nasal challenge in patients with SAR (fig. 1).^[9,10]

Whether or not the mechanism of action of azelastine in the management of allergic rhinitis includes an anti-inflammatory component remains

unclear. The following discussion, however, highlights some of the important anti-inflammatory properties exhibited by the drug.

2.3.1 Effects on Inflammatory Cell Mediators

Eosinophil cationic protein (ECP), myeloperoxidase (MPO) and tryptase are, respectively, mediators for eosinophils, neutrophils and mast cells.^[13] Several studies have investigated the effects of azelastine on these mediators.

In patients with allergic rhinitis^[12] (or nasal polyposis and thus inflammation of the nasal mucosa^[13]), azelastine 1 puff per nostril twice daily for 2^[12] or 25 weeks^[13] significantly reduced nasal levels of ECP from baseline by 57^[12] or 42%^[13] at study completion ($p < 0.05$ for both). Furthermore, compared with placebo, single-dose azelastine 1 puff per nostril reduced ECP levels both during EPR (by 12%; not significant) and LPR (by 38%; $p < 0.01$) [fig. 2]^[10]. But in another study,^[9] compared with baseline, ECP levels were reduced only during LPR ($p < 0.05$; no further details provided).

These data may explain the observed reductions in nasal mucosal infiltration of eosinophils in patients (fig. 1).

As expected, nasal but not plasma levels of ECP were reduced after intranasal azelastine, whereas both were significantly reduced after combined oral and nasal administration of the drug.^[12] This provides further evidence of the localised effect of intranasal azelastine (see section 2.1).

After 25 weeks of azelastine therapy (2 puffs per nostril twice daily) in patients with nasal inflammation resulting from polyposis, both MPO ($p = 0.0015$) and tryptase ($p = 0.0574$) levels were reduced by 41% from baseline.^[13] However, in a single-dose study in patients with SAR, levels of MPO were not significantly affected by azelastine or placebo (fig. 2).^[10]

Intercellular adhesion molecule-1 (ICAM-1) is expressed on epithelial cells only after allergen exposure.^[10] In 2 single-dose azelastine trials (1 puff per nostril), both EPR and LPR ICAM-1 expression was significantly reduced in nasal secretions ($p < 0.05$ vs placebo; fig. 2).^[9,10] Furthermore,

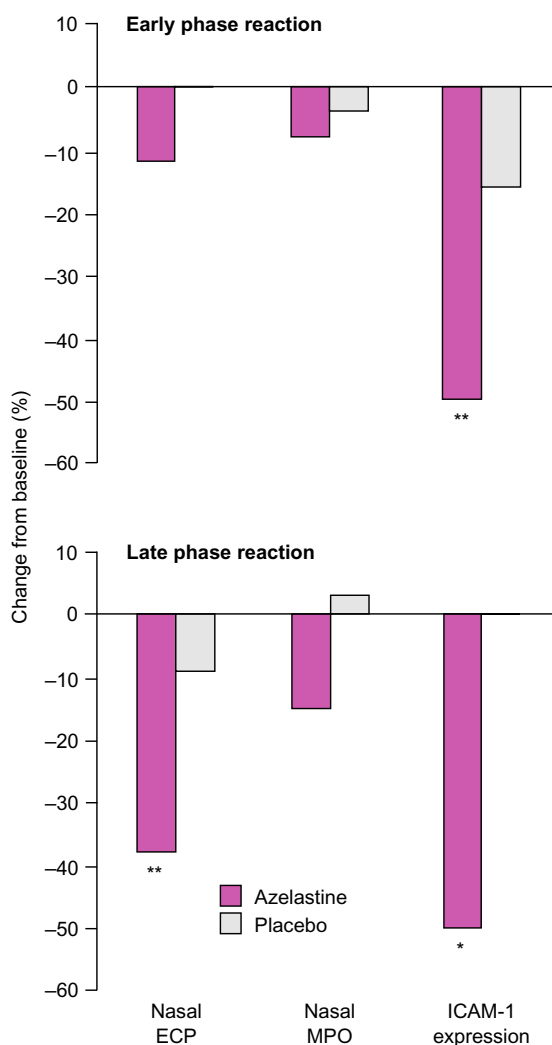


Fig. 2. Effect of single-dose azelastine 1 puff per nostril or placebo on nasal levels of eosinophil cationic protein (ECP), myeloperoxidase (MPO) and intercellular adhesion molecule-1 (ICAM-1) expression after allergen-specific nasal challenge in 20 patients with seasonal allergic rhinitis.^[10] Nasal lavage was performed 30 minutes (early phase reaction) or 6 hours (late phase reaction) after nasal challenge. * $p < 0.05$, ** $p < 0.01$ vs placebo.

ICAM-1 expression was significantly and continually reduced in 30 patients with SAR who received azelastine 1 puff per nostril twice daily for three months ($p < 0.05$ vs placebo).^[27] These latter data indicate that suppression of ICAM-1 is not a short term effect and that there is no tachyphylaxis. Thus, azelastine appears to influence the inflam-

matory process by interfering with the mediators required to initiate the response.

2.3.2 Effects on Neutrophils

It is well known that arachidonic acid is required for the production of leukotrienes, which in turn are involved in the inflammatory process.^[28,29] Leukotriene B₄ (LTB₄), for example, is a potent aggregating and chemotactic agent for inflammatory cells.^[30] Azelastine 100 $\mu\text{mol/L}$ significantly inhibited arachidonic acid release (by 87%) and LTB₄ production (by 90%; both $p < 0.01$ vs control) in human neutrophils *in vitro*; these effects were concentration-dependent over the range 20 to 100 $\mu\text{mol/L}$.^[14]

Arachidonic acid may also be required for the activation of NADPH (reduced form of nicotinamide-adenine dinucleotide phosphate) oxidase and the subsequent production of superoxide.^[31,32] Superoxide is one of a number of reactive oxygen species (ROS) produced by neutrophils in response to immunoglobulin E (IgE)-mediated allergic reactions and is thought to help initiate and sustain chronic inflammation.^[15,16]

In order to assess the effects of azelastine on ROS generation, whole cell neutrophil suspensions prepared from blood from nonallergic volunteers^[14-19] were stimulated by a variety of agents including phorbol myristate acetate (PMA; which activates intracellular protein kinase C),^[14,15,17,18] *N*-formyl-methionyl-leucyl-phenylalanine (FMLP; which stimulates a specific membrane receptor and leads to the activation of protein kinase C),^[15,19] calcium ionophore (A23187; which causes the cell membrane to transport calcium intracellularly) and zymosan (which interacts with the C₃b membrane receptor).^[15,16] Cell-free lysates were also prepared to assess the effects of azelastine on NADPH-generated superoxide,^[17,19] or xanthine-oxidase generation.^[16]

Generally, stimulated superoxide generation was decreased in a concentration-dependent manner ($p < 0.05$ ^[15]),^[16-19] where stated, over the azelastine concentration range 0.1 to 200 $\mu\text{mol/L}$. Indeed, 1 study reported significant reductions (9 to 36%) in a variety of ROS with azelastine 0.05 to 5

mg/L ($p < 0.05$).^[16] Moreover, since ROS production was reduced in whole cell but not cell-free preparations,^[16,17] it appears that azelastine prevents the generation of ROS rather than scavenging ROS already produced.

Neutrophil generation of superoxide is preceded by increased mobilisation of intracellular calcium ($[Ca^{++}]_i$).^[33] Azelastine 100 to 300 μ mol/L significantly reduced $[Ca^{++}]_i$ levels in FMLP-stimulated neutrophils ($p < 0.05$ vs control).^[19]

2.3.3 Effects on Eosinophils

Generation of superoxide stimulated by PMA or FMLP was also reduced by azelastine (3 to 100 μ mol/L) in eosinophils from nonallergic volunteers,^[15,18] although eosinophils were less sensitive to the effects of the drug than neutrophils.^[15]

Studies in human eosinophilic leukaemia (EoL-1) cell cultures (a model of eosinophil function) support the findings in fresh cell preparations and show additional anti-inflammatory effects of the drug:^[22] azelastine inhibited FMLP- and platelet aggregating factor (PAF)-induced calcium influx, reduced actin polymerisation induced by chemotactic factors (PAF, FMLP and LTB_4), and prevented the release of ECP. These results suggest that azelastine may inhibit the accumulation of eosinophils at the site of allergic inflammation and may also prevent eosinophil degranulation.

2.3.4 Effects on Mast Cells

The role of mast cells in IgE-related allergic inflammation is well established^[34] and some of the anti-inflammatory effects of azelastine on mast cell activity have been previously reported.^[3] However, subsequent reports from trials in rodent mast cell preparations have suggested that azelastine may also interfere with protein kinase C activity, and consequently cell degranulation,^[35-37] and the release of tumour necrosis factor- α , a cytokine involved in the regulation of the inflammatory response.^[38]

2.4 CNS Effects

A common problem with first generation antihistamine agents is sedation^[39] which results from

interaction of the drug with central receptors. A prerequisite for this interaction is the ability of the drug to cross the blood-brain barrier.^[40] Azelastine has been shown to have poor access to the CNS in animal models.^[23,41]

Meta-analysis of a series of studies in more than 1000 healthy volunteers or patients with SAR appraised the effects of antihistamine agents on vigilance as assessed by patients using VAS scores.^[40] In healthy volunteers (without treatment) a natural diurnal rhythm of vigilance was observed in which vigilance was maximal in the morning; there were no significant changes in morning or evening vigilance over the entire 2-week observation period. However, in patients there was a general and significant ($p < 0.05$) increase from baseline VAS scores for vigilance over the entire treatment period (2 to 4 weeks) in studies which assessed the efficacy of intranasal azelastine 1 puff per nostril twice daily, or oral azelastine (2mg), loratadine (10mg) or cetirizine (10mg) once daily (morning or evening). These data suggest that a general reduction in vigilance may be associated with the disease itself rather than with antihistamine treatment.^[40] In 1 study, vigilance significantly increased from baseline scores throughout the 2-week treatment period with both azelastine monotherapy and combined intranasal and oral therapy (i.e. nasal spray 1 puff per nostril twice daily plus placebo or azelastine 2mg tablet in the evening). However, the circadian variation (i.e. the difference between maximum and minimum vigilance) was reduced with azelastine monotherapy, whereas with combined therapy the variation in circadian rhythm was still pronounced.

Nonetheless, the US prescribing information carries a warning regarding driving and/or the use of potentially dangerous machinery while taking azelastine (section 6).^[42]

3. Pharmacokinetic Properties

Pharmacokinetic data for the intranasal formulation of azelastine are scarce; these data and those for the oral formulation are summarised in table II.

Further information pertaining to the oral formulation is available in an earlier review of azelastine.^[3]

It has been suggested that the difference between the mean steady-state plasma concentrations of the drug in patients and volunteers (0.65 vs 0.26 µg/L after intranasal 0.56mg) is the result of drug permeation through the inflamed nasal mucosa.^[43] Nevertheless, systemic exposure to the drug after daily intranasal azelastine 0.56mg (4 puffs) [recipients not defined] was estimated as approximately 6- to 8-fold lower than that with orally administered azelastine 4.4mg in volunteers.^[43,46]

Azelastine is metabolised by the cytochrome P450 enzyme system to its major active metabolite desmethylazelastine. After single-dose intranasal azelastine, plasma concentrations of this metabolite were below assay detection limits, but after intranasal dosing of the drug to steady state (no further details provided) plasma concentrations of the metabolite accounted for 20 to 50% of the azelastine concentration.^[42]

Studies using the oral formulation of azelastine found that elimination of the drug was reduced in the elderly (aged 65 to 79 years) compared with younger individuals (aged 20 to 39 years);^[48] this resulted in an approximately doubled plasma concentration in the former age group during multiple dose administration. Consequently, a 50% reduc-

tion in initial oral dosages was recommended in elderly patients.^[48] However, it is unlikely that dosage reductions will be necessary with the intranasal formulation.

Dosage reductions were not considered necessary in patients with mild to moderate hepatic dysfunction and renal insufficiency.^[49]

4. Therapeutic Efficacy

Allergic rhinitis is characterised by symptoms such as sneezing, rhinorrhoea, nasal itching and nasal congestion^[50] and may be classified as seasonal or perennial according to the source of the allergen and the duration of the condition. SAR is most commonly caused by exposure to airborne pollens and mould spores^[50] and, as the name suggests, it persists only for as long as the specific seasonal allergen is present. PAR, like SAR, is a type I hypersensitive reaction, but unlike SAR it is a chronic disorder commonly initiated and maintained by exposure to indoor allergens such as house dust mite, moulds and animal dander.^[51] The symptoms of PAR are similar to those of SAR, except that nasal inflammation and obstruction are more prevalent.

Intranasal azelastine has shown efficacy in relieving the symptoms of allergic rhinitis in both adults and children in noncomparative and comparative clinical trials. Eligible patients had at least

Table II. Pharmacokinetic data pertaining to the different formulations of azelastine (assessed in volunteers unless stated otherwise)

	Intranasal: assessed after 29 days of 4 puffs (0.56mg) per day unless stated otherwise ^[43-45]	Oral ^[46-48]
Maximum plasma concentration	0.306 µg/L	1.5-12.5 µg-eq/L ^a
Time to maximum plasma concentration	2.5h	4.2-5.2h ^a
Steady-state plasma concentration	0.26 µg/L; 0.65 µg/L (pts)	8.02 µg/L ^b
Area under the plasma concentration-time curve from time zero to infinity	3.2 µg · L/h	47.3-405.9 µg-eq · L/h ^a
Systemic bioavailability	40% ^c	81.9% ^d
Terminal elimination half-life	NR	22.2-27.6h ^a

a Assessed after single-dose azelastine 2.2 to 17.6mg.

b Assessed after 29 days of 4.4 mg/day.

c Recipients (i.e. pts/volunteers) not defined.

d Assessed after single-dose azelastine 8.8mg.

µg-eq = µg equivalents of azelastine hydrochloride (expressed in this manner because of cross-reactivity with the major metabolite desmethylazelastine); **NR** = data not reported; **pts** = patients.

a 2-year history of allergic rhinitis; SAR was confirmed by a positive skin prick test during the year prior to the start of the study or at the time of enrolment and, where reported, PAR was confirmed by radioallergosorbent test (RAST).

Clinical efficacy was determined by both patients and physicians, generally with use of patient diaries and/or visual analogue scales (VAS); improvements in both individual and total symptom scores were measured. In most studies, the primary end-point was defined as overall improvement in major symptoms (which included rhinorrhoea, itchy nose, nose blows, sneezing, watery eyes^[52-54] and sniffles^[55,56]) or total symptoms (which included major symptoms plus itchy eyes, ears or throat, cough, postnasal drip^[52] and itchy palate^[53,54] or dry nose^[55,56]). Some studies reported individual symptom improvement and/or global assessment of treatment as secondary end-points. Generally, symptom improvements were determined on a 3-point scale (0 = absent to 3 = severe).

In a number of placebo-controlled trials, orally administered chlorphenamine (chlorpheniramine maleate) 12mg twice daily was used as a positive control to validate the study (an FDA requirement) and to establish that patients' symptoms were responsive to an active treatment.^[57] However, results from chlorphenamine recipients have not been described, as patient numbers were considered too small to permit valid statistical evaluation.^[57]

Azelastine is administered by a nasal inhaler which delivers approximately 0.14mg of the drug per puff (i.e. 1 puff per nostril approximates 0.28mg; 2 puffs per nostril approximates 0.56mg) [section 6]. Throughout this section, dosage is expressed as the number of puffs applied to each nostril and number of daily applications.

4.1 Noncomparative and Placebo-Controlled Trials

Azelastine was given over periods of 30 hours to ≥ 6 months in noncomparative and placebo-controlled trials. In 1 nonblind study, 84% of 103 patients reported an onset of action within 30 min-

utes of administering the drug intranasally;^[58] the mean onset of action in this study was 17 minutes.

The efficacy of azelastine (typically 1 puff per nostril twice daily) was observed under practical conditions in a noncomparative German trial in more than 4000 patients with PAR or SAR who had been previously treated with other medication.^[59] After 4 weeks, symptom scores were markedly reduced by up to 95% (p-values not provided). In particular, the frequent occurrence of sneezing was reduced in 94% of patients. Physicians and patients assessed the efficacy of the drug to be at least 'good' in over 80% of cases.

Baseline total symptom scores were reduced by about 70% within the first month, and by about 80% at the end of a 6-month nonblind, noncomparative trial in 161 patients who completed the study (estimated from graph; no p-values provided).^[60] The incidences of individual symptoms of rhinitis were markedly reduced from baseline;^[60] stuffy nose, itchy nose, rhinorrhoea and sneezing, for example, were reported in 80, 73, 67 and 59% of patients, respectively at the start of the study and by 7, 4, 2 and 2% of patients at study completion (no p-values provided). Furthermore, 35 of 161 patients continued therapy for an additional 30 to 60 weeks: 21 patients continued therapy without a break and were almost free from symptoms by the end of the study (mean total symptom score 0.43); the remaining patients continued therapy after a break of <28 days and had a mean total symptom score of 5.27.^[60] These data indicate a greater benefit with continued long term therapy.

This is supported by evidence from another study in which continuous intranasal azelastine therapy (0.07 or 0.14mg per nostril twice daily for 3 months) was better at reducing the symptoms of rhinitis than on-demand use of the drug (i.e. patients receiving placebo, but taking intranasal azelastine as rescue).^[27] Patients with SAR who received azelastine 0.28 or 0.56 mg/day required significantly fewer supplementary doses of azelastine (rescue therapy) throughout the treatment pe-

Table III. Summary of placebo (PL)-controlled clinical trials of intranasal azelastine (AZE) in patients with seasonal allergic rhinitis^a

Reference	No. of evaluable patients [age range (y)]	Dosage (no. of puffs per nostril) [duration of administration]	Overall improvement from baseline scores (%)			Global efficacy of at least 'good' (% of patients)	
			major symptom ^b severity scores	total symptom ^b severity scores	total symptoms plus nasal stuffiness	patient assessment	physician assessment
Weiler et al. ^[56]	54 [12-58 ^c]	AZE 1 bid [2 days]	25.7	31.9	NR	75.0*	NR
	54	AZE 2 od [2 days]	43.6**	40.0*	NR*	89.0***	NR
	54	AZE 2 bid [2 days]	NR*	37.9*	NR*	83.0***	NR
	50	PL [2 days]	11.5	18.5	NR	49.0	NR
Meltzer et al. ^[53]	71 [12-59 ^c]	AZE 2 od [30h]	39.0*	44.0*	NR	73.0 ^d	NR
	76	AZE 2 bid [30h]	45.0*	40.0*	NR		NR
	75	PL [30h]	21.0 ^e	20.0 ^e	NR	65.0	NR
Ratner et al. ^[55]	62 [12-65]	AZE 2 od [2wk]	23.0	24.0*	22	86.0	73.0
	63 [12-70]	AZE 2 bid [2wk]	32.0*	30.0*	28*	82.0	84.0*
	64 [13-71]	PL [2wk]	12-13	12-13	12	77.0	66.0
Storms et al. ^[62]	60 [12-55]	AZE 2 od [2wk]	11.0	12.0	NR	80.0**	80.0**
	63 [13-69]	AZE 2 bid [2wk]	27.0***	26.0***	NR	86.0**	84.0**
	61 [12-57]	PL [2wk]	6.0	4.0	NR	59.0	54.0
LaForce et al. ^[54]	263 [12-69]	AZE 2 od [4wk]	25.0 ^e	25.0 ^e	23 ^e	75.4	66.2
		AZE 2 bid [4wk]	20.0 ^e *	20.0 ^e	18 ^e	78.5*	78.5*
		PL [4wk]	14.0 ^e	15.0 ^e	14 ^e	59.4	60.9

a All trials were double-blind, double-dummy, multicentre and positive controlled [with chlorphenamine (chlorpheniramine maleate) 12mg bid].

b Component symptoms described at the beginning of section 4.

c Age range of total study population.

d Overall score for all azelastine recipients.

e Estimated from graph.

bid = twice daily; **NR** = value not reported; **od** = once daily; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs placebo.

riod than those who received placebo ($p < 0.05$ at various times throughout the treatment).^[27]

Compared with placebo, intranasal azelastine 2 puffs per nostril once or twice daily significantly ($p < 0.05$) improved overall total and/or major symptom scores in a number of double-blind, double-dummy, randomised studies in patients with SAR (table III).

Significant reductions in overall major and total symptom scores were similar and ranged from 20 to 45% ($p < 0.05$ vs placebo) with azelastine 2 puffs per nostril twice daily (table III). Azelastine 2 puffs once daily compared with placebo also significantly ($p < 0.05$) reduced major and total symptom scores in some studies;^[52,54,55] it appeared less effective than the higher dosage of 2 puffs twice daily, but no statistically significant differences

were observed between the active treatment groups.^[53,61]

A significant improvement in major and total symptom scores was reported as early as 3 hours after the initial use of azelastine 2 puffs per nostril ($p < 0.05$ vs placebo) and was apparent up to 10 (for total symptoms) and 12 (for major symptoms) hours after initial drug administration ($p < 0.05$ vs placebo) in patients with SAR (fig. 3).^[55]

Where reported, the ranges of patient and physician global assessment of at least 'good' efficacy were 49 to 77% for placebo, 66 to 89% for once daily and 75 to 86% for twice daily azelastine 1 or 2 puffs per nostril (table III).

Table IV shows individual rhinitis symptoms which were significantly improved by azelastine 2 puffs per nostril once or twice daily over a period

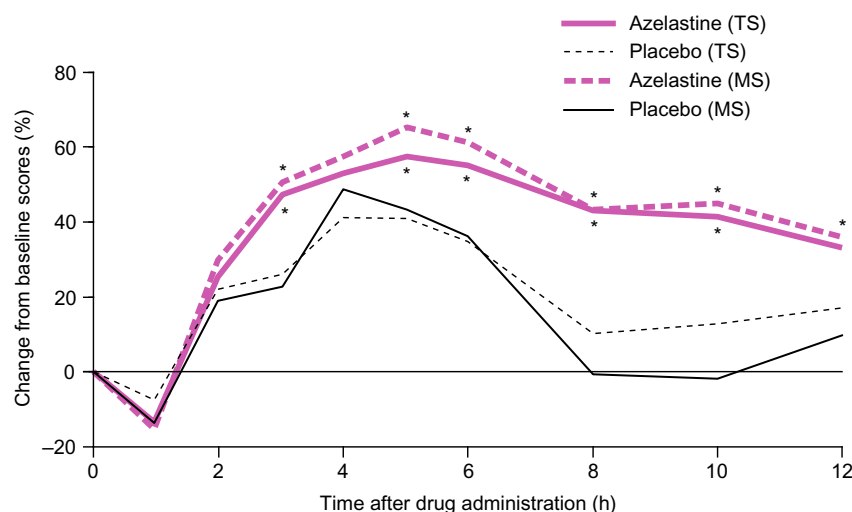


Fig. 3. Efficacy of azelastine in 20 patients with seasonal allergic rhinitis. After drug administration (azelastine 2 puffs per nostril or placebo), subjective symptom assessment was performed hourly while located in a park (hours 1 to 6), or 2-hourly at home (hours 8 to 12).^[56] Efficacy was assessed as improvement from baseline in scores of major symptoms (MS; sum of rhinorrhoea, itchy nose, sniffles, nose blows, sneezes and watery eyes) and total symptoms (TS; MS plus itchy eyes, ears and throat, dry nose and postnasal drip). * $p < 0.05$ vs placebo.

of 30 hours to 4 weeks ($p < 0.05$ vs placebo). Azelastine has shown varied effects on nasal blockage (stiffness) in clinical trials (tables III and IV): in some studies azelastine, compared with placebo, significantly improved nasal blockage,^[54,55,61] whereas in others there was no significant difference.^[52,53] Interestingly, ocular symptoms (including itchy and watery eyes) were improved with intranasal application of the drug (table IV).

In patients with PAR, significant reductions in mean scores for rhinorrhoea, sneezing, nasal obstruction, lacrimation, red eyes, and itching eyes, ears, nose and throat were observed after 3 days of treatment with azelastine 1 puff per nostril twice daily ($p < 0.001$ vs baseline) in 2 open studies ($n = 88$ ^[62] and $n = 313$ ^[63]).

4.1.1 Children with Allergic Rhinitis

Available data indicate that twice-daily azelastine 1 puff per nostril may be useful in treating nasal symptoms in children aged ≤ 12 years with allergic rhinitis^[64,65] (SAR^[66] or PAR^[66-70]).

Herman et al.^[68] assessed the effects of azelastine and placebo in 125 children aged 5 to 12 years with PAR in a randomised double-blind trial. For

each symptom assessed, and at all time points, improvements from baseline scores were significantly greater in the azelastine than placebo groups ($p < 0.05$); improvement was most rapid during the first 2 weeks of treatment. At end-point (week 6), approximate symptom improvements from baseline scores with azelastine were 70% for sneezing, 60% for nasal blockage, 70% for nasal itch and 60% for rhinorrhoea; corresponding end-point values for placebo were 15, 9, 23 and 0% (all values estimated from graph).

At the end of a second 6-week study in 125 children with PAR (ages not provided),^[67] azelastine 1 puff per nostril twice daily compared with placebo significantly improved baseline VAS scores for sneezing (29.9 vs 4.3%; $p < 0.0001$), nasal blockage (22.6 vs 1.9%; $p < 0.0002$), nasal itch (25.0 vs 7.3%; $p < 0.0001$) and rhinorrhoea (28.9 vs 1.6%; $p < 0.0001$).

Cure (not defined) rates of 26, 33 and 28%, respectively, were observed during rhinoscopic evaluation of nasal secretion, oedema and inflammation after 6 weeks of azelastine 0.56 mg/day in a subgroup of 44 children with PAR (aged 7 to 16 years;

$p < 0.001$ vs baseline for all parameters);^[71] at the end of the 6-month, nonblind, noncontrolled study, corresponding values were 77, 62 and 63%. In the same study, the baseline symptom score was reduced by about 80% in 50 of the 62 patients who completed the therapy.^[71] Investigators considered the global efficacy to be at least 'good' in 64.5% of patients. The dosage used in this study was higher than that recommended in children of this age (section 6).

Despite the high response rate (defined as $\geq 50\%$ decrease in nasal score by day 3 of therapy) in children with SAR who received placebo (43 vs 53% with azelastine), investigator global assessment of at least 'good' was significantly more common in azelastine than in placebo recipients (41 vs 15%; $p = 0.02$) in a 2-week double-blind trial.^[66]

In a postmarketing study, 211 children aged 3 to 12 years with PAR (75%) or SAR (23%) [2% had unknown diagnosis] received intranasal azelastine (generally 1 puff per nostril twice daily) for 2

(SAR) or 4 weeks (PAR).^[64] Mean total symptom scores (sum of sneezing, nasal itching, nasal congestion, rhinorrhoea, smell reduction, eye itching, lacrimation, photophobia, throat itching and coughing; scale 0 = absent to 3 = severe) were significantly reduced by 71% ($p < 0.05$ vs baseline). Overall, 85% of physicians evaluated the efficacy of azelastine as 'good' or 'very good'.^[64]

4.1.2 Nasal Spray as Adjunct Therapy to Oral Azelastine

The addition of intranasal azelastine to oral therapy has provided further symptom relief in some patients in clinical trials.

In 1 double-blind, double-dummy study in 233 patients with SAR who remained symptomatic after ≥ 7 days' treatment with twice-daily oral azelastine 0.5mg, intranasal azelastine (2 puffs per nostril twice daily) compared with placebo significantly improved total and major symptom scores for up to 6 hours after administration ($p < 0.05$).^[56]

Compared with placebo, intranasal azelastine significantly improved the individual symptoms of sniffles and itchy eyes and ears ($p < 0.05$).^[56] Overall, 64% of intranasal azelastine recipients and 59% of those receiving intranasal placebo rated their symptoms as 'improved'. The high placebo response has been observed in other studies where intranasal placebo was given^[72] and it is attributed to the lavage effect of the vehicle.

Preliminary results of a double-blind, double-dummy, randomised study in 298 patients with allergic rhinitis (type not specified) indicate that combination therapy with intranasal and oral azelastine was superior to treatment with either formulation alone.^[73] However, study details are limited and further evaluation is warranted. Nasal blockage was improved in patients receiving intranasal azelastine alone or in combination with oral azelastine; details were not provided for the effects of the oral formulation alone.^[73]

4.2 Comparisons with Other Agents

4.2.1 Antihistamine Agents

Intranasal azelastine (1 puff per nostril twice daily) has been shown to be as effective as intra-

Table IV. Secondary end-point efficacy of azelastine: assessed as reduction in individual seasonal allergic rhinitis symptoms in double-blind, multicentre studies. Azelastine was administered as 2 puffs per nostril once or twice daily over a period of 30h to 4wk

Symptom	Reference		
	LaForce et al. ^[54] (n = 263)	Meltzer et al. ^[53] (n = 222)	Storms et al. ^[62] (n = 184)
Nasal			
Itchy nose	✓	✓	✓
Rhinorrhoea	X	✓	✓
Sneezing	X	✓	✓
Nasal congestion	X	X	✓
Postnasal drip	X	✓	X
Nose blows	X	✓	X
Ocular			
Itchy eyes	✓	✓	✓
Watery eyes	✓	X	✓
Other			
Cough	✓	X	X
Itchy throat	✓	✓	✓
Itchy ears	✓	✓	✓
Itchy palate	✓	NA	NA

NA = individual symptom not assessed; X = not significantly reduced vs placebo; ✓ = significantly reduced vs placebo ($p < 0.05$).

Table V. Summary of clinical trials comparing intranasal azelastine (AZE) 1 puff per nostril with other antihistamine compounds in patients with seasonal (SAR) or perennial (PAR) allergic rhinitis

Reference	Trial design	Type and no. of evaluable patients [age range (y)]	Dosage (duration of treatment)	Improvement from baseline in total symptom scores at end of study (%)	Global efficacy assessment of at least 'good' (% of patients)		Overall clinical efficacy
					patient assessment	physician assessment	
Comparison with intranasal levocabastine (LEV)							
Mösges et al. ^[75]	mc, nb, r	SAR 119 [12-69]	AZE bid (1wk)	64 ^a	61	63.0	AZE ≡ LEV
		SAR 123 [12-65]	LEV 2 puffs per nostril bid (1wk)	63 ^a	68	70.0	
Comparisons with oral agents							
Cetirizine (CET)							
Charpin et al. ^[76]	db, dd, mc, r	SAR 129 [12-60] ^b	AZE bid (2wk)	61 ^a	69	89.0 ^c	AZE ≡ CET
Passali et al. ^[77]	db, dd, mc, r	PAR 37 [19-65] ^b	CET 10mg od (2wk)	67 ^a	68	89.0 ^c	AZE ≡ CET
			AZE bid (8wk)	77 ^{d**}		73.7	
			CET 10mg od (8wk)	65 ^{d**}		55.5	
Ebastine (EBA)							
Conde Hernandez et al. ^[78]	nb, r	SAR 29 [18-59 ^b]	AZE bid (2wk)	55	48	79.0	AZE ≡ EBA
		SAR 29	EBA 10mg od (2wk)	51	48	65.0	
Loratadine (LOR)							
Gambardella et al. ^[79]	db, dd, r	SAR 14 [18-33 ^b]	AZE bid (6wk)	80 ^{d*}		79.0	AZE ≡ LOR
		SAR 12	LOR 10mg od (6wk)	79 ^{d*}		83.0	
Miniti et al. ^[80]	db, dd, r	PAR 45 ^b	AZE bid (2wk)				AZE ≡ LOR
Mösges et al. ^[81]	db, dd, mc, r		LOR 10mg od (2wk)				AZE ≡ LOR
		SAR 125	AZE bid (2wk)		84	68	
		SAR 118	LOR 10mg od (2wk)		96	79	
Terfenadine (TER)							
Gastpar et al. ^[82] Study 1	db, dd, mc, r	SAR 80 [16-64]	AZE bid (6wk)	87 ^{**}		80.0	AZE ≡ TER
		SAR 82 [18-62]	TER 60mg bid (6wk)	85 ^{**}		80.0	
Gastpar et al. ^[82] Study 2	db, dd, mc, r	PAR 22 [18-49]	AZE bid (6wk)	90		90.9	AZE ≡ TER
		PAR 27 [17-55]	TER 60mg bid (6wk)	87		85.2	

a Investigator assessment of symptoms.

b Total study population.

c Global assessment of 'satisfied' or 'highly satisfied' with efficacy of treatment in patients.

d Values estimated from graph.

bid = twice daily; **db** = double-blind; **dd** = double-dummy; **mc** = multicentre; **nb** = nonblind; **od** = once daily; **r** = randomised; * $p < 0.05$, ** $p < 0.001$ vs baseline; ≡ indicates no statistically significant difference.

nasal levocabastine (2 puffs per nostril twice daily)^[74] and orally administered cetirizine,^[75,76] ebastine,^[77] loratadine^[78-80] (all 10mg once daily) and oral terfenadine (60mg 4 times daily)^[81] in reducing the symptoms of allergic rhinitis (table V).

Similar proportions of azelastine and levocabastine recipients (54 and 53%) experienced relief from the symptoms of SAR within 30 minutes of drug administration;^[74] symptom relief was maintained for up to 8 hours after initial drug application in both groups. After 1 week of therapy, investigator assessment of total symptom improvement from baseline was similar for azelastine (64%) and levocabastine (63%) recipients; in addition, each drug improved nasal congestion (by $\approx 48\%$) and ocular symptoms (by $\approx 66\%$).^[74] Physicians' global assessments of 'good' or 'excellent' were reported for 63% of azelastine and 70% of levocabastine recipients; corresponding patient assessments were 61 and 68%.^[74]

In double-blind, double-dummy comparative trials in patients with SAR^[75] or PAR,^[76] symptom scores were markedly reduced from baseline with both azelastine and cetirizine ($p < 0.001$ in patients with PAR; table V). Although the difference in efficacy between the 2 groups was not statistically significant in either study, azelastine appeared to improve the baseline total symptom score to a greater extent than cetirizine in patients with PAR (by 77 vs 65%).^[76] In addition, the physicians' global evaluation of efficacy in patients with PAR favoured azelastine (73.7 vs 55.5% of patients with a 'good' or better response).

When nasal and ocular symptoms were assessed separately in patients with SAR,^[75] both sets of symptom scores were similarly improved by between 60 and 65% after 2 weeks' therapy with either azelastine or cetirizine. In patients with PAR,^[76] azelastine was significantly better than cetirizine at reducing the individual scores for cough and nasal mucosal swelling ($p < 0.05$). In addition, rhinomanometric evaluation revealed that azelastine was significantly better than cetirizine throughout the 8-week study at reducing nasal blockage ($p < 0.05$).^[76] Conversely, azelastine ap-

peared less effective than loratadine at increasing nasal flow volume in patients with SAR.^[80] Baseline flow rates were improved by about 7 and 43%, respectively, after 2 weeks' therapy; however, there was no statistically significant difference between the 2 treatment groups.

4.2.2 Corticosteroid Agents

Comparisons of intranasal azelastine (usually 1 puff per nostril twice daily) with intranasal beclomethasone (0.1 or 0.2mg twice daily) or budesonide (0.1mg twice daily or 0.256mg once daily) have shown varied results. Some studies showed no significant difference in efficacy between the treatment groups, while others showed the corticosteroids to be superior to azelastine (tables VI and VII). Overall, corticosteroids showed a trend towards better improvements in nasal symptoms than azelastine.

Beclomethasone

A significantly more rapid overall symptom relief was achieved in azelastine than in beclomethasone recipients ($p < 0.003$ after 1 day).^[82] However, after 2 weeks' therapy, beclomethasone 0.2mg twice daily improved overall symptom scores significantly more than azelastine 0.56mg twice daily in patients with SAR ($p < 0.05$).^[82] However, in 2 other studies in patients with PAR^[83] or SAR,^[84] which used azelastine 0.28mg twice daily, there was no significant difference in the 2 treatment groups after 5 or 6 weeks of therapy (table VI).

In 1 study, compared with the placebo value, there appeared to be a greater reduction in the total symptom score with beclomethasone than with azelastine at the end of the study (60 vs 30%).^[84] In another study,^[83] compared with placebo, both azelastine and beclomethasone significantly reduced a number of rhinitis symptoms; the number was greater with azelastine than with beclomethasone. Objective assessment of NAR by anterior rhinomanometry indicated no significant effects in azelastine recipients in this study.^[83] However, in beclomethasone recipients, there was an increase in the second set of NAR values, which indicates a worsening of the condition.

Table VI. Summary of clinical trials comparing intranasal azelastine (AZE) 1 puff per nostril (unless otherwise stated) with intranasal beclomethasone (BEC) in patients with seasonal (SAR) or perennial (PAR) allergic rhinitis

Reference	Trial design	Type and no. of evaluable patients	Dosage (duration of treatment)	Improvement from placebo (unless stated otherwise) in total symptom score at end of study (%)	Overall clinical efficacy
Davies et al. ^[84]	db, dd, mc, r	PAR 45	AZE bid (6wk)	NR	AZE = BEC
		PAR 22	PL (6wk)	NR	
		PAR 45	BEC 0.2mg bid (6wk)	NR	
		PAR 18	PL (6wk)	NR	
Newson Smith et al. ^[83]	db, dd, mc, r	SAR 83	AZE ^a bid (2wk)	NR ^{b*}	BEC ^{†**} > AZE* > PL
		SAR 83	BEC 0.2mg bid (2wk)	NR ^{b**}	
		SAR 77	PL (2wk)	NR	
Pelucchi et al. ^[85]	db, r	SAR 10	AZE bid (5wk)	30 ^c	AZE = BEC
		SAR 13	BEC 0.1mg bid (5wk)	60 ^{c*}	BEC > PL
		SAR 13	PL (5wk)		AZE > PL ^d

a Two puffs per nostril.

b Improvement from baseline.

c Estimated from graph.

d The number of individual nasal symptoms in azelastine recipients was lower than that in placebo recipients during week 4 ($p < 0.05$) but not week 5.bid = twice daily; db = double-blind; dd = double-dummy; mc = multicentre; NR = value not reported; PL = placebo; r = randomised; = indicates not significantly different; > indicates more effective than; * $p < 0.05$, ** $p \leq 0.001$ vs placebo; † $p < 0.05$ vs azelastine.

In a third study, when reductions in nasal stuffiness were assessed by patients using VAS scores, there was no significant difference between beclomethasone and azelastine groups; however, compared with placebo, both azelastine ($p < 0.01$) and beclomethasone ($p < 0.001$) significantly reduced nasal stuffiness. Physicians reported a significant difference between nasal stuffiness in beclomethasone and placebo recipients ($p < 0.001$) but not azelastine and placebo recipients (comparison between azelastine and beclomethasone not reported). Further investigation of the relative efficacies of these agents is clearly warranted.

Budesonide

Two nonblind studies concluded that the effects of azelastine and budesonide were not significantly different,^[85,86] whereas a double-blind trial reported budesonide to be significantly superior to azelastine.^[87] The double-blind study used budesonide 0.256mg once daily as opposed to the more commonly used 0.1mg twice daily. In this study, the number of patients reporting a global assessment of 'substantial' or 'total control' of symptoms

was significantly greater in budesonide (70.4%) than in azelastine (44.7%; $p < 0.05$) or placebo recipients (26.5%; $p < 0.001$) after 6 weeks' therapy (table VII).^[87]

In the nonblind studies, subjective assessments of nasal blockage were similar in both treatment groups after 2^[86] or 6^[85] weeks' therapy: improvements ranged from 47 to 59%. Objective assessment (using anterior rhinomanometry) after 6 weeks' treatment showed nasal blockage to be decreased by 77% from baseline in azelastine recipients and by 97% in those receiving budesonide.^[85] However, despite the greater improvement with budesonide, the difference between treatment groups did not reach statistical significance.

In a Spanish study in children (aged 5 to 17 years), the onset of therapeutic effect within 15 to 30 minutes of initial drug administration was more frequent in azelastine than in budesonide recipients (67 vs 35%; no p -values provided).^[69] In this study children with PAR received either azelastine 1 puff per nostril twice daily ($n = 27$) or budesonide 0.2 mg/nostril once daily ($n = 19$) in a single-blind

randomised 15-day trial. Except for the reduction in sneezing, in which budesonide was superior (no further details), the efficacy of each drug was similar for all other symptoms assessed.

5. Tolerability

Postmarketing surveys included a total of 7682 patients (aged 3 to 85 years) treated with azelastine (1 puff per nostril twice daily) for 2 or 4 weeks.^[88] The most common adverse events occurring in 4002 patients treated for 4 weeks are summarised in figure 4: rhinitis, bitter taste (of the drug) and application site reaction occurred in 4, 2.5 and 1.2% of patients, respectively; all other events occurred in <1% of patients. The drug was generally well tolerated, with adverse events occurring in approximately 8% of patients during 2 to 4 weeks of monotherapy. The incidence of adverse events in patients receiving concomitant antihistamines

and/or topical corticosteroids was approximately 20%.

Azelastine was generally well tolerated in clinical trials of up to 6 months' duration.^[71] Indeed, long term tolerability was demonstrated in a study in which >90% of 35 patients reported tolerability of at least 'good' over a 21-month period of medication.^[60]

Where stated, physician and/or patient global assessment of the tolerability of azelastine (typically 1 puff per nostril twice daily), was considered to be at least 'good' in more than 70% of patients (aged ≥7 years).^[71,76,77,81,85] The most frequently reported adverse events were taste disturbance^[52,53,61,62,82,85] and application site irritation.^[56,74,77,83] Taste disturbance was often mild and transient^[52,56] and was associated with the taste of the drug itself rather than a systemic effect (i.e. dysgeusia).^[52,53,55,61]

Table VII. Summary of clinical trials comparing intranasal azelastine (AZE) 1 puff per nostril with intranasal budesonide (BUD) in patients with seasonal (SAR) or perennial (PAR) allergic rhinitis

Reference	Trial design	Type and no. of evaluable patients	Dosage (duration of treatment)	Improvement from baseline in total symptom score at end of study (%)	Improvement from baseline in nasal blockage (%)	Physician global assessment of at least 'good' (% of patients)	Overall clinical efficacy
Dorow et al. ^[87]	nb	SAR and/or PAR 18	AZE od (2wk)	63.0 ^a	47.0 ^b	66.7	AZE ≡ BUD
		SAR and/or PAR 18	BUD 0.1mg bid (2wk)	64.0 ^a	53.0 ^b	72.2	
Gastpar et al. ^[86]	mc, nb, r	PAR 93	AZE bid (6wk)	79.0	57.0 ^b 77.0 ^c	77.6	AZE ≡ BUD
		PAR 88	BUD 0.1mg bid (6wk)	74.0	59.0 ^b 97.0 ^c	73.9	
Stern et al. ^[88]	db, r	PAR 195	AZE bid (6wk)	-0.97 ^d	-0.35 ^e	44.7 ^f	BUD > AZE ≡ PL
			BUD 0.256mg od (6wk)	-2.05 ^d	-0.70 ^{e§}	70.4 ^{f*†}	
			PL (6wk)	-0.79 ^d	-0.25 ^e	26.5 ^f	

a Estimated from graph.

b Subjective assessment of individual symptom.

c Objective assessment using anterior rhinomanometry.

d Mean change from baseline in combined nasal symptom score (sum of blockage, sneezing and secretion scores; scale 0 to 3).

e Mean change from baseline score (0 to 3).

f Patient's overall assessment of 'substantial' or 'total control'.

bid = twice daily; **db** = double-blind; **mc** = multicentre; **nb** = nonblind; **od** = once daily **PL** = placebo; **r** = randomised; **≡** indicates not significantly different; **>** indicates more effective than; * $p \leq 0.001$ vs placebo; † $p < 0.05$ vs azelastine; § significantly different vs azelastine (p-value not provided).

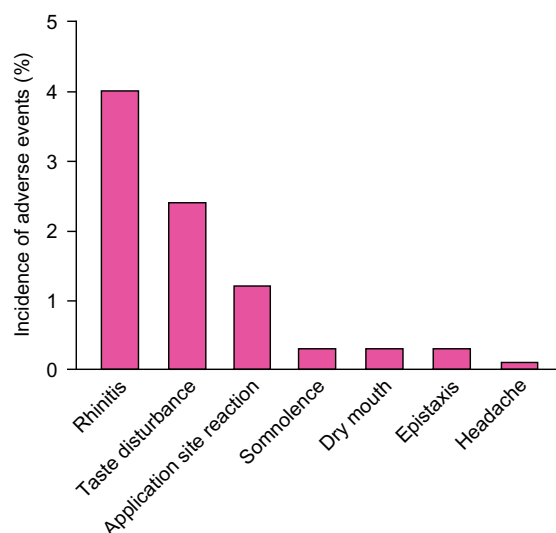


Fig. 4. Incidence of adverse events in azelastine recipients. Events were reported in postmarketing surveys including 4002 patients with allergic rhinitis aged 3 to 85 years who received intranasal azelastine 1 puff per nostril twice daily for 4 weeks.^[89]

In 62 children treated with azelastine 0.56 mg/day for 6 months, the most frequently reported adverse events were sneezing (16%), nasal itching and bitter taste (11% each), and dry nose (9.6%).^[71] Tolerability was rated by the investigators as at least 'good' in 74% of patients.^[71] These data suggest that intranasal azelastine is well tolerated in children.

Treatment withdrawal because of drug-related adverse events occurred in $\leq 7\%$ of patients receiving treatment (1 to 3 patients per study).^[54,75,78,83] Reasons for withdrawal included mild increased nasal pruritus, nasal congestion, nausea and vomiting, dizziness and increased blood pressure.

In clinical trials, the overall tolerability of intranasal azelastine was not significantly different from that of oral cetirizine,^[75,76] intranasal budesonide^[85,86] or intranasal levocabastine.^[74]

Sedation did not appear to be a major concern with the use of intranasal azelastine: where reported, it occurred slightly, but not significantly, more frequently in azelastine than placebo recipients^[52,53,56,61] and less frequently in azelastine than in ebastine^[77] or cetirizine^[76] ($p = 0.03$ ^[75]) recipients.

Indeed, some study reports remarked on the lack of sedation,^[82,89,90] and in 1 trial overall vigilance was improved during the 2-week medication period.^[80]

Case reports of serious cardiovascular adverse events in patients receiving treatment with a variety of second generation histamine H_1 receptor antagonists have caused concern regarding the use of this class of agent^[91] (reviewed by Wiseman and Faulds^[92]). Results from a double-blind trial revealed no significant changes in PR, QS, QT or QT_c intervals in patients with PAR who were randomised to receive azelastine 2 puffs per nostril twice daily ($n = 65$) or placebo ($n = 35$) for 8 weeks.^[93] Age (12 to 18 years vs >18 years) had no significant effects on the parameters measured. Furthermore, there were no changes in mean heart rate or blood pressure in any patient.

6. Dosage and Administration

Azelastine nasal spray is supplied as a 1 mg/ml solution of azelastine hydrochloride in a metered dose pump spray bottle. Each actuation delivers approximately 0.14ml solution (i.e. 0.14mg of azelastine).^[42,94] The US^[42] prescribing recommendations specify 2 puffs per nostril twice daily for adults and children aged ≥ 12 years. However, in the UK and a number of other European countries, azelastine is approved as 1 puff per nostril twice daily for adults and children aged ≥ 6 years.^[95]

Because some patients in clinical trials have reported somnolence, the US prescribing information carries a caution regarding use of the medication and driving or operating potentially dangerous machinery.^[42] In addition, concurrent use of alcohol and/or other CNS suppressants should be avoided to reduce the possibility of impairment of alertness and CNS function.

There were no specific interactions between intranasal azelastine and orally administered erythromycin or ketoconazole.^[42]

7. Place of Intranasal Azelastine in the Management of Allergic Rhinitis

Allergic rhinitis is the most commonly expressed form of atopy and is reported to occur in up to 20% of the population.^[51] Although the symptoms of allergic rhinitis may be described as benign, the condition is included in the top 10 causes of chronic disability.^[51] Morbidity arises not only from the symptoms of rhinitis, but also from associated complications such as sinusitis, asthma and upper respiratory tract infections.^[96]

The aetiology and pathophysiology of allergic rhinitis are well known and have been detailed elsewhere.^[51,97,98] The variety of causes and symptoms of allergic rhinitis provides several potential treatment targets. This is reflected in the number of different pharmacological agents available for the management of this disorder including antihistamines, corticosteroids, mast cell stabilisers and decongestants.

In the management of allergic rhinitis, pharmacotherapy and immunotherapy are recommended after attempts to achieve environmental control of the allergen (i.e. removal/avoidance of plants, pets, feather duvets, etc.).^[91,99] Environmental allergen control is not always appropriate, particularly in the case of pollen-specific SAR.

With respect to pharmacotherapy, the current International Consensus on the Management of Rhinitis in adults recommends the use of topical corticosteroids as first-line therapy for PAR and moderate SAR (with predominant nasal symptoms).^[91] However, antihistamine agents are a widely used second-line treatment option.

The antihistamine azelastine has proved to be an effective agent for the treatment of allergic rhinitis.^[3] The intranasal formulation was developed in an attempt to provide local symptom control and to reduce systemic exposure to the drug. Clinical studies have shown that intranasal azelastine is effective at reducing the symptoms of SAR and PAR in adults and children, including those aged ≤ 12 years (section 4). The drug demonstrated a rapid onset (efficacy is evident within 30 minutes of ad-

ministration) and long duration of action (10 to 12 hours).

Although studies showed varied results, corticosteroids generally appeared to reduce the symptoms of rhinitis better than azelastine. However, azelastine had a more rapid onset of symptom relief than beclomethasone and this is perhaps preferable for patients who require prompt relief over a short period. Comparative studies indicate that azelastine 1 puff per nostril twice daily is as effective as standard doses of other second generation antihistamines including oral cetirizine, ebastine, terfenadine and loratadine. Importantly, azelastine has similar efficacy to intranasal levocabastine, which is currently the only other intranasal antihistamine available.

In *in vitro* and *in vivo* studies, azelastine inhibited a variety of inflammatory mediators and cells involved in both the EPR and the LPR of allergy (section 2.3), which suggested that, like corticosteroids, azelastine may be effective at reducing nasal mucosal inflammation and thus decreasing nasal blockage. However, in the clinical setting (section 4.2.2), the effect of the drug on nasal blockage varied when compared with the effects of corticosteroids and requires further investigation.

Traditionally, antihistamines have been associated with CNS-related adverse events, particularly sedation, because of their lipophilic nature and ability to cross the blood-brain barrier. *In vivo* studies in rodents indicate a lack of central distribution of intranasal azelastine (section 2.4). In clinical trials, somnolence occurred with similar incidence in placebo and azelastine recipients; indeed a lack of sedation was demonstrated in children aged ≤ 12 years.^[90] In the trials reviewed, there were no significant differences between the tolerability of intranasal azelastine and that of intranasal levocabastine; however, somnolence and fatigue have been reported as two of the most commonly occurring adverse events with intranasal levocabastine.^[100]

No serious cardiovascular adverse events were associated with twice-daily use of intranasal

azelastine either in clinical trials or in postmarketing surveys in more than 7500 patients.

In summary, intranasal azelastine may be advocated as a useful alternative to other oral and intranasal antihistamines for the rapid symptomatic relief of SAR and PAR in adults and children (aged ≥ 6 years in the UK and some other European countries; ≥ 12 years in the US). The rapid onset, localised activity and reduced potential for sedation conferred by intranasal azelastine may prove an advantage over other antihistamine agents, although confirmation is required.

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