

Glaucoma: brinzolamide/brimonidine combination eye drops

Evidence summary

Published: 17 March 2015

[nice.org.uk/guidance/esnm56](https://www.nice.org.uk/guidance/esnm56)

Key points from the evidence

The content of this evidence summary was up-to-date in March 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

In 2 randomised controlled trials in people with glaucoma, brinzolamide/brimonidine combination eye drops were statistically significantly superior to either constituent drug administered alone as monotherapy in reducing intraocular pressure at 3 months. The combination eye drops were non-inferior to brinzolamide plus brimonidine administered concomitantly. Most reported adverse events were mild to moderate and localised, but these were higher in number with the combination eye drops compared with the individual constituent drugs.

There are no published studies comparing brinzolamide/brimonidine combination eye drops with other drug treatments for managing glaucoma and ocular hypertension. Brinzolamide/brimonidine may be an alternative treatment option for some people, for whom prostaglandin analogues and beta-blockers are unsuitable.

Regulatory status: Brinzolamide/brimonidine eye drops ([Simbrinza](#)) received a European marketing authorisation in July 2014 and were launched in the UK in September 2014.

<p>Effectiveness</p> <ul style="list-style-type: none"> • In a superiority study in people with glaucoma (n=560), at 3 months the mean change from baseline in diurnal intraocular pressure was statistically significantly lower in the group treated with brinzolamide/brimonidine combination eye drops compared with the groups treated with brinzolamide and brimonidine monotherapy (both p<0.0001). • In a non-inferiority study in people with glaucoma (n=890), at 3 months brinzolamide/brimonidine was non-inferior to brinzolamide plus brimonidine administered concomitantly for mean change from baseline in diurnal intraocular pressure. • There are no published data comparing brinzolamide/brimonidine combination eye drops with other drug treatments used for managing glaucoma and ocular hypertension. 	<p>Safety</p> <ul style="list-style-type: none"> • Across both studies, there were few serious adverse events. • In clinical studies, ocular adverse effects with the combination appear to be marginally additive compared with the constituent drugs. • The summary of product characteristics states that, in clinical trials of brinzolamide/brimonidine combination eye drops used twice-daily, the most common adverse effects were ocular reactions, such as hyperaemia (increased blood flow) and allergic type reactions (6–7%) and also dysgeusia (bitter taste; 3%). • There are no safety data for use of the combination eye drops beyond 6 months, but longer term data are available for brinzolamide and brimonidine monotherapies. These show that adverse effects are usually transient and do not usually lead to treatment discontinuation. Serious adverse effects are either uncommon or rare.
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Patient factors	Resource implications
<ul style="list-style-type: none"> • Across both studies, the overall discontinuation rates for the brinzolamide/brimonidine combination eye drops, brinzolamide plus brimonidine, and brinzolamide and brimonidine as monotherapies were 11.0%, 13.3%, 0.5% and 8.6% respectively. Most of these were for non-serious, treatment-related adverse effects. • Combination therapy offers an alternative treatment option with a simpler administration regimen for people who need more than 1 agent, and may help with adherence and reduce exposure to preservatives. • Since brinzolamide/brimonidine combination eye drops contain benzalkonium chloride preservative, they cannot be used by people who are allergic to this preservative. • Brinzolamide/brimonidine combination eye drops may be an alternative treatment option for some people, for whom prostaglandin analogues and beta-blockers are unsuitable. 	<ul style="list-style-type: none"> • Brinzolamide/brimonidine combination eye drops cost the same as the constituent products combined (£9.23 per 5 ml: 28-day treatment). • Brinzolamide/brimonidine combination eye drops are cheaper than most other combination products for glaucoma and ocular hypertension although they are not the cheapest option for products containing preservative (range £2.28 to £13.95 per 28-day treatment).

Update

This ESNM has been updated as one of the costs listed under Resource implications was incorrect in the original version.

Introduction and current guidance

Glaucoma describes a group of eye disorders in which progressive damage to the optic nerve leads to impaired vision and, in some people, blindness.

The most common form of glaucoma is chronic open angle glaucoma (primary open angle glaucoma), in which drainage of the eye's aqueous humour is impaired and leads to an increase in intraocular pressure. This may damage the optic nerve and the nerve fibres from the retina. The condition is often asymptomatic, but the person may present with significant loss of visual field. People with ocular hypertension are at increased risk of developing chronic open angle glaucoma. Chronic open angle glaucoma may be suspected, regardless of intraocular pressure, in people with suggested possible glaucomatous damage to the optic disc or visual field changes.

NICE's guideline on [glaucoma](#) and the European Glaucoma Society's report on [terminology and guidelines for glaucoma](#) emphasise the importance of person-centred care. NICE's guideline on [glaucoma](#) recommends setting a target intraocular pressure that is low enough to stop or reduce disease progression or onset and avoid disability from sight loss. Monitoring and treatment should be individualised to the needs of the person and rate of disease progression.

Drugs that reduce intraocular pressure by different mechanisms are used to manage ocular hypertension and glaucoma. The [European Glaucoma Society's guidelines](#) state that the least amount of medication to achieve the therapeutic response should be a consistent treatment goal, minimising inconvenience, adverse effects and cost. NICE's guideline on [glaucoma](#) recommends using a topical beta-blocker or a prostaglandin analogue as the first-line treatment option for ocular hypertension or suspected chronic open angle glaucoma. A prostaglandin analogue should be offered to people with mild or moderate chronic open angle glaucoma. To stop or reduce disease progression or onset, it may be necessary to combine first-line drugs or add others, such as sympathomimetics, or carbonic anhydrase inhibitors, to control intraocular pressure.

[Full text of introduction and current guidance.](#)

Product overview

Brinzolamide/brimonidine combination eye drops ([Simbrinza](#)) are licensed for treating chronic open angle glaucoma or ocular hypertension in adults for whom monotherapy did not sufficiently reduce intraocular pressure. The drops contain a fixed dose combination of brinzolamide 1%, a carbonic anhydrase inhibitor, and brimonidine 0.2%, an alpha 2 agonist (sympathomimetic) drug. The recommended dose is 1 drop into the affected eye(s) twice daily.

Brinzolamide/brimonidine eye drops are the first combination treatment for glaucoma and ocular hypertension that do not contain the beta-blocker timolol 0.5%, therefore its contraindications and adverse effect profile are different from other combination products.

[Full text of product overview.](#)

Evidence review

- This evidence summary is based on 2 phase III studies that evaluated the efficacy and safety of brinzolamide/brimonidine combination eye drops using twice daily administration. One study was a superiority study, which compared brinzolamide/brimonidine eye drops with the individual constituent monotherapies, and the other was a non-inferiority study, which compared the combination with the 2 constituents used concomitantly. Both studies were double-blind [randomised controlled trials](#) in people with chronic open angle glaucoma or ocular hypertension, who were treated for 6 months. Participants were already using 2 or more intraocular pressure lowering medications or did not have sufficient improvement with monotherapy.
- In the superiority study ([Aung et al. 2014](#)), at 3 months the mean reduction from baseline in diurnal intraocular pressure in the brinzolamide/brimonidine combination group was 7.9 mmHg. The combination statistically significantly reduced intraocular pressure compared with brinzolamide alone (mean difference 1.4 mmHg) and brimonidine (mean difference - 1.5 mmHg) alone ($p < 0.0001$ for both). The results seen at week 2 and month 6 were similar to those seen at 3 months.
- In the non-inferiority study ([Gandolfi et al. 2014](#)), at 3 months the mean reduction from baseline in diurnal intraocular pressure in the brinzolamide/brimonidine combination group was 8.5 mmHg. The combination was non-inferior to brinzolamide plus brimonidine administered concomitantly (mean difference 0.1 mmHg, 95% confidence intervals [CI] - 0.5 mmHg to 0.2 mmHg, within the ± 1.5 mmHg pre-specified CIs for showing non-inferiority). The results were similar at other time points.
- Across both studies, the mean intraocular pressure reduction for the combination eye drops was around 8 mmHg which, according to the [European product assessment report](#), is [clinically important](#). The mean percentage reduction in intraocular pressure was between 23 and 37%.
- The [summary of product characteristics](#) states that the combination product has the same contraindications, adverse effects and interactions as the individual constituent drugs.

- Generally, adverse effects were mild to moderate ocular events. The [European product assessment report](#) states that in the superiority study ([Aung et al. 2014](#)) 2 people who were using brinzolamide/brimonidine combination eye drops developed corneal erosion.
- In the superiority study ([Aung et al. 2014](#)), ocular adverse events, such as ocular hyperaemia (5.7%), eye pain (5.7%) and transient blurred vision (4.7%), were higher in the brinzolamide/brimonidine combination group compared with the brinzolamide group (0.5%, 1.6% and 0.5% respectively) and the brimonidine group (4.6%, 0% and 1.1% respectively). No p values were reported.
- In the non-inferiority study ([Gandolfi et al. 2014](#)), the incidence of adverse events with brinzolamide/brimonidine combination eye drops was similar to the incidence seen with brinzolamide plus brimonidine administered concomitantly. No p values were reported.
- In the studies no data were given comparing the effects of the brinzolamide/brimonidine combination in different grades of disease severity. A further limitation was that intraocular pressure was measured at 2 specific time points over a 24-hour period; therefore, intraocular pressure control throughout the full day cannot be inferred.

[Full text of evidence review.](#)

Context

Several combination eye drops are licensed in the UK for use in treating glaucoma but, with the exception of brinzolamide/brimonidine eye drops, all other combinations include timolol, a beta-blocker. Brinzolamide/brimonidine combination eye drops cost £9.23 for 28-days treatment for 1 eye, the same price as the constituent products combined. Brinzolamide/brimonidine combination eye drops are cheaper than most other combination eye drops, particularly preservative-free eye drops, but are not the cheapest combination product (range £2.28 to £28.59).

[Full text of context.](#)

Estimated impact for the NHS

It is not known how brinzolamide/brimonidine combination eye drops compare with other topical combination products for glaucoma because no direct comparison studies are available. The adverse effect profile of brinzolamide/brimonidine may be different from other topical glaucoma drugs. Therefore, brinzolamide/brimonidine combination eye drops may be an alternative treatment option for some people for whom prostaglandin analogues and beta-blockers are

unsuitable and whose condition is uncontrolled on 1 therapy alone. [European Glaucoma Society guidelines](#) suggest that combination products should be offered only once a person has had a partial response to 1 of the constituents. Local decision-makers will need to take into account the efficacy, safety, cost and individual user factors when considering using brinzolamide/brimonidine combination eye drops for managing intraocular hypertension and chronic open angle glaucoma.

[Full text of estimated impact for the NHS.](#)

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

Glaucoma is a group of eye disorders in which progressive damage to the optic nerve leads to impaired vision and, in some people, blindness. Glaucoma may have a secondary cause, such as a drug or condition that causes the intraocular pressure to rise and damage the optic nerve, or the cause may be unknown ([NICE clinical knowledge summary: glaucoma](#)).

The most common form of glaucoma is chronic open angle glaucoma, also known as primary open angle glaucoma. This happens when drainage of the eye's aqueous humour through the trabecular meshwork tissue is impaired, leading to increased intraocular pressure. This may damage the optic nerve and the nerve fibres from the retina. The prevalence and incidence of the condition increase with age. It is often asymptomatic, but people may present with significant loss of visual field ([British national formulary, January 2015](#); [NICE clinical knowledge summary: glaucoma](#)).

NICE's guideline on [glaucoma](#) defines ocular hypertension as consistently or recurrently elevated intraocular pressure (greater than 21 mmHg) with no signs of glaucoma. People with ocular hypertension are at increased risk of developing chronic open angle glaucoma. Suspected glaucoma is when, regardless of the level of the intraocular pressure, the optic nerve head (optic disc) or visual field show changes that suggest possible glaucomatous damage.

The guideline recommends that people with ocular hypertension or suspected chronic open angle glaucoma need regular eye examinations to detect any progression of visual damage. The NICE guideline and [NICE pathway on glaucoma](#) provide further information on monitoring and treatment thresholds.

In ocular hypertension and suspected chronic open angle glaucoma, the decision to start treatment is based on the estimated risk of [conversion](#) to chronic open angle glaucoma using age, intraocular pressure and central corneal thickness. Treatment options for chronic open angle glaucoma depend on its severity. NICE's [quality standard on glaucoma](#) defines best clinical practice in this area.

NICE recommends that healthcare professionals should use their clinical judgement to estimate a target intraocular pressure low enough to stop or reduce disease progression or onset, and avoid disability from sight loss. The [target intraocular pressure](#) (target IOP) and ongoing treatment plan may change over time according to the risk of conversion to chronic open angle glaucoma or disease progression. NICE's [full guideline on glaucoma](#) suggests that reduction of intraocular pressure is a valid 'surrogate outcome' for treatment success.

For people with glaucoma who need treatment, drugs that reduce intraocular pressure by different mechanisms are available. The NICE guideline states that the first-line option for treating ocular hypertension or suspected chronic open angle glaucoma in people under 60 years with an untreated intraocular pressure of more than 25 to 32 mmHg and central corneal thickness of 555 to 590 micrometres is usually a topical beta-blocker, such as timolol, betaxol, carteolol or levobunolol. A [prostaglandin analogue](#) (bimatoprost, latanoprost, tafluprost or travoprost) may be used if a beta-blocker is contraindicated or unsuitable. For people at higher risk of developing glaucoma, for example with an untreated intraocular pressure of more than 21 mmHg and central corneal thickness less than 555 micrometres, a topical prostaglandin analogue is recommended.

Alternative pharmacological treatments (prostaglandin analogues, beta-blockers, carbonic anhydrase inhibitors, sympathomimetics, or in some cases, preservative-free preparations) should be offered to people for whom certain medicines are not suitable because of intolerance, or whose intraocular pressure has not reduced sufficiently to prevent the risk of sight loss. Although monotherapy is preferred, to simplify the administration regimen, minimise the risk of adverse effects and reduce costs, more than 1 drug may be needed concurrently to achieve target IOP, according to the European Glaucoma Society's [terminology and guidelines for glaucoma](#).

A prostaglandin analogue should be used to treat people with newly diagnosed early or moderate chronic open angle glaucoma who are at risk of significant visual loss. If treatment does not reduce intraocular pressure sufficiently, adherence to treatment and eye drop instillation technique should

be checked. If this is satisfactory, alternative drug treatment may be offered, with more than 1 agent if necessary. Other options are laser trabeculoplasty and surgery with drug treatment. People with advanced chronic open angle glaucoma should be offered surgery with drug treatment, according to the NICE guideline on [glaucoma](#).

For more information on alternative treatments see the NICE pathway on [glaucoma](#) and [clinical knowledge summary for glaucoma](#).

Product overview

Drug action

Brinzolamide/brimonidine combination eye drops ([Simbrinza](#)) contain 2 active substances with different mechanisms of action. Both reduce intraocular pressure by suppressing the formation of aqueous humour from the ciliary process in the eye. Brinzolamide is a carbonic anhydrase inhibitor and reduces intraocular pressure by a direct antagonist activity whereas brimonidine is an alpha 2 agonist (sympathomimetic) and acts by enzyme inhibition. Benzalkonium chloride is included in the solution as a preservative. The drops are rapidly absorbed into the eye after topical administration.

Licensed therapeutic indication

Brinzolamide/brimonidine combination eye drops ([Simbrinza](#)) received a European marketing authorisation in July 2014 for treating chronic open angle glaucoma or ocular hypertension in adults in whom monotherapy has not sufficiently reduced intraocular pressure. The eye drops were launched in the UK in September 2014.

The combination product has the same contraindications, adverse effects and interactions as the individual constituent drugs. The eye drops cannot be used by people who are allergic to benzalkonium chloride preservative. Preservative-free brinzolamide/brimonidine combination eye drops are not available.

Course and cost

Brinzolamide 1%/brimonidine 0.2% eye drops are available in 5 ml containers. The recommended dose is 1 drop into the affected eye(s) twice daily.

Brinzolamide/brimonidine combination eye drops cost £9.23 per 5 ml bottle ([MIMS](#), February 2015).

Evidence review

This evidence summary is based on 2 phase III studies that evaluated the efficacy and safety of brinzolamide/brimonidine combination eye drops using twice daily dosing. According to the [European product assessment report \(EPAR\)](#) both studies were [randomised controlled trials \(RCTs\)](#) with a 6-month treatment period in people with chronic open angle glaucoma or ocular hypertension. The design of the 2 studies is similar and they are described together.

The first study ([Aung et al. 2014](#)) aimed to demonstrate the superiority of the brinzolamide/brimonidine combination eye drops compared with eye drops of each of the individual constituents. A second, larger study ([Gandolfi et al. 2014](#)) aimed to demonstrate non-inferiority of the brinzolamide/brimonidine combination eye drops to the individual constituents administered concomitantly. Information from the studies has been supplemented and clarified using the [EPAR](#) for brinzolamide/brimonidine combination eye drops and results for these 2 studies ([Aung et al. 2014](#) and [Gandolfi et al. 2014](#)) reported on the clinical trials registry ([NCT0131077](#) and [NCT01309204](#) respectively).

RCTs evaluating the safety and efficacy of brinzolamide/brimonidine combination eye drops compared with brinzolamide or brimonidine monotherapy([Aung et al. 2014](#))and with brinzolamide plus brimonidine therapy([Gandolfi et al. 2014](#))

- Design: worldwide, multicentre, [randomised](#), double-[blind](#) and parallel group studies with active controls ([Aung et al. 2014](#), n=560; [Gandolfi et al. 2014](#), n=890).
- Population: the studies enrolled adults (mean age 64 years) who had previously been diagnosed and treated for ocular hypertension or chronic open angle glaucoma, whose condition was insufficiently controlled on monotherapy or who were receiving multiple intraocular pressure-lowering medications. People with any other ocular pathology were excluded. The baseline demographic characteristics were similar across the treatment groups in both studies. Just over half of the participants were 65 years or older (53%) and female (56%), and 76% had a diagnosis of open angle glaucoma.
- Follow-up: both studies consisted of 7 visits undertaken during 2 sequential phases: the screening and eligibility phase, which included a screening visit and 2 eligibility visits, and a treatment phase, which included 4 on-therapy visits conducted at week 2, week 6, month 3 and month 6, or early exit (clinicaltrials.gov identifiers [NCT0131077](#) and [NCT01309204](#)).
- Intervention and comparator: according to the [EPAR](#), after washout of any intraocular pressure-lowering medication, people who met all inclusion and exclusion criteria at both

eligibility visits, and who had consistently raised intraocular pressure, were randomised to 1 of 3 study drug groups in the superiority study ([Aung et al. 2014](#)):

- brinzolamide 1%/brimonidine 0.2% combination eye drops, or
 - brinzolamide 1% eye drops, or
 - brimonidine 0.2% eye drops.
- Using the same criteria, participants in the non-inferiority study ([Gandolfi et al. 2014](#)) were randomised to 1 of 2 study groups:
 - brinzolamide 1%/ brimonidine 0.2% combination eye drops, or
 - brinzolamide 1% eye drops plus brimonidine 0.2% eye drops.
 - Study medications were provided in identical, masked bottles to maintain blinding. Although not stated explicitly, the methods imply that allocation was concealed in both studies. Participants self-administered 1 drop into both eyes twice daily at 9 am and 9 pm for 6 months, except on study visit days when study personnel administered the drops after obtaining safety and efficacy measurements. For each participant, one eye was chosen as the study eye, and only data for the study eye were used for the efficacy analysis ([Aung et al. 2014](#) and [Gandolfi et al. 2014](#).)
 - Outcomes: the primary efficacy outcome in both studies was mean diurnal intraocular pressure change from baseline at month 3. This was calculated using the change in intraocular pressure from baseline averaged over the 9 am, 11 am and 4 pm time points at month 3 in [Aung et al. \(2014\)](#) and the 9 am and 11 am time points at month 3 in [Gandolfi et al. \(2014\)](#). In [Gandolfi et al. \(2014\)](#), the non-inferiority of brinzolamide/brimonidine combination relative to brinzolamide plus brimonidine was assessed by examining the confidence intervals (CI) for the month 3 visit and the non-inferiority margin was defined as ± 1.5 mmHg. Supportive secondary efficacy outcomes in both studies included mean diurnal intraocular pressure change from baseline at week 2 and month 6, and mean changes in intraocular pressure from baseline at each study visit and time point, and percentage of participants with intraocular pressure below 18 mmHg at each study visit and time point. Safety assessments included monitoring of blood pressure, pulse rate, best-corrected visual acuity and ocular signs, and recording of all adverse events.

Table 1 Summary of brinzolamide/brimonidine combination eye drops compared with brinzolamide or brimonidine (Aung et al. 2014)

	Brinzolamide/ brimonidine combination	Brinzolamide	Brimonidine	Analysis
Randomised	n=193	n=192	n=175	
Efficacy ^a	n=193	n=191	n=175	
Primary outcome: LS mean diurnal IOP change from baseline at month 3, mmHg ^b	7.9	6.5	6.4	Brinzolamide/ brimonidine combination versus brinzolamide LS mean difference: -1.4 mmHg; (p<0.0001) and versus brimonidine LS mean difference: -1.5 mmHg (p<0.0001)
Selected secondary outcomes:				
LS mean diurnal IOP change from baseline at week 2, mmHg	7.6	6.1	6.0	Brinzolamide/ brimonidine combination versus brinzolamide LS mean difference: -1.5 mmHg; (p≤0.0001) and versus brimonidine LS mean difference: -1.6 mmHg, (p≤0.0001)
LS mean diurnal IOP change from baseline at month 6, mmHg	7.8	6.7	6.4	Brinzolamide/ brimonidine combination versus brinzolamide LS mean difference: -1.1 mmHg; (p≤0.0001) and versus brimonidine LS mean difference: -1.4 mmHg, (p≤0.0001)

Mean percentage reduction in IOP from baseline	Range 26.7% to 36.0%	Range 22.4% to 27.9%	Range 20.6% to 31.3%	Brinzolamide/ brimonidine combination versus brinzolamide LS mean difference: 2.7% to 9.5% and versus brimonidine LS mean difference: 4.8% to 7.6% (no statistical analysis reported)
Safety ^c	n=193	n=192	n=175	
Participants reporting serious adverse events	2.6% (5/193)	1.0% (2/191)	1.7% (3/175)	No statistical analysis reported
Patients with ≥1 adverse event	28.5% (55/193)	11.5% (22/191)	22.9% (40/175)	No statistical analysis reported
Frequently reported adverse events ^d	36.3% (70/193)	7.3% (14/191)	17.1% (30/175)	No statistical analysis reported

Abbreviations: IOP, intraocular pressure; ITT, intention-to-treat; LS, least squares; p, p value.

^a Efficacy analyses were based on the ITT population, which included all randomised participants who received study medication and had at least 1 scheduled on-therapy study visit.

^b Standard errors not reported.

^c Safety analyses included all randomised participants who were exposed to the study medication.

^d Adverse events with 3% incidence or more in any group (ocular hyperaemia [increase in blood flow], eye pain, dysgeusia [taste dysfunction], blurred vision, dry mouth, and somnolence, conjunctivitis and eye pruritus).

Table 2 Summary of brinzolamide/brimonidine combination eye drops compared with brinzolamide plus brimonidine (Gandolfi et al. 2014)

	Brinzolamide/ brimonidine combination	Brinzolamide plus brimonidine	Analysis
Randomised	n=451	n=439	
Efficacy^a	n=420	n=411	
Primary outcome: LS mean diurnal IOP change from baseline at month 3, mmHg (SE)	8.5 (±0.16)	8.3 (±0.16)	Mean treatment difference: 0.1, 95% CI 0.5 to 0.2 (non-inferior because the upper limit of the 95% CI is within the pre-specified limit of ±1.5)
Selected secondary outcomes:			
LS mean diurnal IOP change from baseline at week 2, mmHg ^b	8.4	8.4	Mean treatment difference: 0.0, 95% CI 0.4 to 0.3
LS mean diurnal IOP change from baseline at month 6, mmHg ^b	8.1	8.2	Mean treatment difference: 0.1, 95% CI 0.3 to 0.4
Mean percentage reduction in IOP from baseline	Range 27.0% to 37.6%	Range 28.2% to 37.4%	No statistical analysis reported
Percentage of patients with IOP < 18 mmHg across study visits	68.9% to 71.6%	65.8% to 71.6%	No statistical analysis reported
Safety^c	n=452	n=436	
Participants reporting non-fatal serious adverse events	2.4% (11/452)	1.6% (7/436)	No statistical analysis reported
Discontinuation due to treatment-related adverse event	10.0% (45/452)	11.7% (51/436)	No statistical analysis reported

Frequently reported adverse events ^d	17.0% (77/452)	22.2% (97/436)	No statistical analysis reported
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Abbreviations: CI, [confidence interval](#); IOP, intraocular pressure; ITT, intention-to-treat; LS, least squares; p, p value; SE, standard error.

^a Efficacy analyses were based on the per protocol population, which included all randomised participants who received study medication and had at least 1 scheduled on-therapy study visit.

^b Standard errors not reported.

^c Safety analyses included all randomised participants who received the study medication.

^d Adverse events with 3% incidence or more in any group (ocular hyperaemia, allergic conjunctivitis, dry mouth, dysgeusia, blurred vision and somnolence).

Clinical effectiveness

The superiority study ([Aung et al. 2014](#)) found that brinzolamide/brimonidine combination eye drops were statistically significantly superior to both of the individual constituent drugs in reducing mean diurnal intraocular pressure after 3 months (the primary outcome: see table 1). The mean reduction from baseline in the brinzolamide/brimonidine combination group was 7.9 mmHg, compared with 6.4 mmHg and 6.5 mmHg in the brinzolamide and brimonidine groups respectively. The mean effect size was 1.4 mmHg compared with brinzolamide and 1.5 mmHg compared with brimonidine. Similar results were obtained at month 6. For the same outcome, [Gandolfi et al. \(2014\)](#) found that the upper limits of the 95% CIs were less than 1.5 mmHg, showing that the combination eye drops were non-inferior to brinzolamide plus brimonidine administered concomitantly. Similar results were seen at other time points. Across both studies, the mean intraocular pressure reduction for the combination eye drops was around 8 mmHg which, according to the EPAR, is [clinically important](#).

Across the 2 studies, the secondary outcome of mean percentage intraocular pressure reduction was 23% to 37% in the combination eye drop groups, according to the EPAR. As a general principle, NICE's [full guideline on glaucoma](#) advocates aiming for a 25% to 30% reduction from the untreated intraocular pressure in chronic open angle glaucoma. In the superiority study ([Aung et al. 2014](#)), the changes in mean percentage intraocular pressure from baseline were, according to the EPAR, statistically significant in the brinzolamide/brimonidine combination eye drops group compared with both of the individual constituent groups (p values not reported). In the non-inferiority study ([Gandolfi et al. 2014](#)), the changes in mean percentage intraocular pressure from baseline were similar between treatment groups at each study visit and time point (statistical analysis not reported).

In [Aung et al. \(2014\)](#), the percentage of participants who achieved an intraocular pressure less than 18 mmHg was greater in the brinzolamide/brimonidine combination eye drops group than the individual constituent groups at most study visits. The difference between the groups was smaller at month 6 than at month 3 (data and statistical analysis not reported). In [Gandolfi et al. \(2014\)](#), the percentage of participants with intraocular pressure less than 18 mmHg was similar in both treatment groups. At the time of peak morning efficacy (11 am), the percentage of participants with intraocular pressure less than 18 mmHg across study visits was 68.9% to 71.6% in the combination eye drops group and 65.8% to 71.6% in the brinzolamide plus brimonidine group (p values not reported). These results show that two-thirds of participants had an intraocular pressure below the notional 21 mmHg threshold advocated in NICE's [full guideline on glaucoma](#), as a general principal, for most cases of ocular hypertension.

Safety and tolerability

The [EPAR](#) states that the phase III safety and efficacy trials ([Aung et al. 2014](#); [Gandolfi et al. 2014](#)) included 645 people treated with brinzolamide/brimonidine combination eye drops. Most adverse drug reactions were local ocular side effects with a known causal association with one or more of the individual constituents. According to the [EPAR](#), ocular adverse effects with the combination appear to be additive compared with the constituent drugs, but slightly lower than the concomitant administration of brinzolamide plus brimonidine.

There were few serious adverse events across both studies and the investigators considered most these to be unrelated to the study medication. In [Aung et al. \(2014\)](#), 3 people across all groups withdrew because of serious adverse events (2 because of cancers and 1 because of macular degeneration). In the non-inferiority study ([Gandolfi et al. 2014](#)), serious adverse events were seen in approximately 2% of people in both groups (1 person died of myocardial infarction in the combination eye drops group but this was unrelated to the study drug). In addition, the [EPAR](#) highlighted that 2 people who used the combination eye drops developed corneal erosion but this resolved after treatment. These incidents were also classified as serious adverse events.

The [EPAR](#) states that the overall discontinuation rates for the brinzolamide/brimonidine combination, brinzolamide plus brimonidine and brimonidine alone were 11.0%, 13.3% and 8.6% respectively in the 2 studies combined. Most of the discontinuations were because of non-serious, treatment-related adverse effects. Generally, fewer topical adverse reactions were seen with brinzolamide monotherapy than with brimonidine-containing treatments and there were few treatment-related discontinuations (0.5%) in the brinzolamide study arm ([Aung et al. 2014](#)).

The brinzolamide/brimonidine combination eye drops contain less benzalkonium chloride preservative than the concomitant administration of the 2 individual constituents. In principle, according to the [EPAR](#), reduced daily preservative exposure should result in fewer allergic adverse effects. In the non-inferiority study ([Gandolfi et al. 2014](#)), incidence of ocular allergy was similar across both treatment groups (1.1% in the combination group compared with 1.4% in the brinzolamide plus brimonidine group, no statistical analysis reported).

According to the [summary of product characteristics](#), in clinical trials using twice-daily brinzolamide/brimonidine combination eye drops, the most common adverse reactions were ocular hyperaemia and ocular allergic type reactions (approximately 6–7% of people) and dysgeusia (bitter taste after administration: approximately 3% of people).

In the superiority study ([Aung et al. 2014](#)), there were more common ocular adverse effects in the brinzolamide/brimonidine combination eye drops group than the brinzolamide and brimonidine monotherapy groups. For example, ocular hyperaemia, (5.7%, 0.5% and 4.6% brinzolamide/brimonidine combination eye drops, brinzolamide and brimonidine monotherapy groups respectively), eye pain (5.7%, 1.6% and 0% respectively) and transient blurred vision (4.7%, 0.5% and 1.1% respectively). However, no statistical analyses were provided. In the non-inferiority study ([Gandolfi et al. 2014](#)), adverse effects were comparable between the 2 treatment arms.

The [summary of product characteristics](#) gives further information on contraindications, potential interactions and adverse effects of brinzolamide/brimonidine combination eye drops.

Evidence strengths and limitations

In 2 phase III RCTs, fixed dose combination brinzolamide/brimonidine combination eye drops were shown to be statistically significantly superior to the individual constituents and non-inferior to brinzolamide plus brimonidine administered concomitantly.

The European Medicines Agency guidance on the [points to consider on switching between superiority and non-inferiority](#) advises that, although in a superiority study the [intention-to-treat](#) analysis is the analysis of choice (as in [Aung et al. 2014](#)), in a non-inferiority study the intention-to-treat and per-protocol analyses have equal value and their use should lead to similar conclusions for a robust interpretation of the results. In the non-inferiority study ([Gandolfi et al. 2014](#)), the reported non-inferiority analyses were done in the per-protocol population and the authors stated that findings were confirmed by the analysis of the intention-to-treat population, although no data were provided to support this. The investigators for both studies reported that secondary outcomes were supportive of the primary end point. However, no statistical analysis was

reported for some outcomes, for example, the mean percentage reduction in intraocular pressure from baseline.

Reduction in intraocular pressure from baseline is a disease-oriented or surrogate outcome. Surrogate outcomes should generally be avoided when possible because their relationship to clinical outcomes is often uncertain. However, when NICE considered published studies in the evidence review for the full guideline on [glaucoma](#), it included studies that reported the relative risk of chronic open angle glaucoma progressing or developing for each mmHg reduction in intraocular pressure. From published studies in people who had ocular hypertension or already had chronic open angle glaucoma, the Guideline Development Group (GDG) found that reduction of intraocular pressure reduced the absolute risk of conversion to or progression of glaucoma. After establishing credible links between intraocular pressure reduction and disease progression, the GDG accepted a reduction in intraocular pressure as a valid surrogate outcome measure.

According to the [EPAR](#), the study design was appropriate for the study objectives and was conducted in an appropriate population and at an appropriate dose for European clinical practice. Although it is not stated explicitly in both studies, [allocation concealment](#) is implied in the methods, therefore avoiding an important potential source of [bias](#).

The [EPAR](#) states that, in both studies, randomisation was stratified at baseline into participants with lower intraocular pressure (24 to 27 mmHg) and those with higher intraocular pressure (28 to 36 mmHg). However, the studies were not sufficiently [powered](#) to evaluate the comparative efficacy of brinzolamide/brimonidine combination eye drops in these 2 different groups. Similarly, the baseline population across both studies included people with ocular hypertension or chronic open angle glaucoma and no data were provided comparing the effect size in different grades of disease severity. A further limitation pointed out by the investigators in both studies was that intraocular pressure was not measured over a 24-hour period; therefore, intraocular pressure reductions later in the day or during the night cannot be inferred.

In the superiority study ([Aung et al. 2014](#)), the effects of the fixed dose brinzolamide/brimonidine combination eye drops were not completely additive compared with the effects of the individual constituents and the authors suggested that this may be because of the overlapping mechanisms of action of brinzolamide and brimonidine. However, discontinuations in the combination group were slightly higher than in the monotherapy treatment arms, which suggests that the adverse effects may be marginally additive.

The numerous exclusion criteria of the studies are reflected in the contraindications and special warnings and precautions for use in the [summary of product characteristics](#). For example,

brinzolamide/brimonidine combination eye drops have not been studied in people with severe renal impairment or narrow angle glaucoma, or people receiving monoamine oxidase inhibitor therapy or antidepressants that affect noradrenergic transmission, such as tricyclic antidepressants and mianserin.

The studies lasted 6 months and there are no long-term published data for brinzolamide/brimonidine combination eye drops. The GDG for the NICE guideline on glaucoma specified that assessment of clinical effectiveness needed a minimum of 6 months follow-up. The primary outcome in both studies was assessed at month 3 and this may be a limitation of the data. It was acknowledged in the [EPAR](#) that there were long-term safety data for the constituent therapies and that the long-term safety of the combination eye drops would be assessed post-marketing.

It is not known how brinzolamide/brimonidine combination eye drops compare with other glaucoma therapies, for example, beta-blockers or prostaglandin analogues, either as monotherapies or in combination products. According to the [EPAR](#), brinzolamide/brimonidine combination eye drops achieve similar reductions in intraocular pressure as prostaglandin analogues and beta-blockers. However, extrapolating data from different populations using different interventions may not be valid when considering implications for clinical practice.

There are several completed unpublished studies registered on the U.S. National Institutes of Health clinical trials database which look at brinzolamide/brimonidine combination eye drops in combination with other therapies: [NCT01937299](#) and [NCT01937312](#). However, these are for 3 times daily dosing of brinzolamide/brimonidine combination eye drops which is not licensed in the UK.

Context

Alternative treatments

The NICE guideline on [glaucoma](#) recommends that, when treatment is started for mild to moderate chronic open angle glaucoma, suspected glaucoma or ocular hypertension, topical glaucoma medications are the first choice. There are 5 main classes of drugs: prostaglandin analogues, beta-blockers, carbonic anhydrase inhibitors, sympathomimetics and miotics. All these medications are licensed to treat chronic open angle glaucoma by reducing intraocular pressure. Currently prostaglandin analogues and beta-blockers are licensed for first- and second-line use, the others are licensed for second-line use only.

Brinzolamide and brimonidine are available as licensed individual constituent drugs for use alone and in combination with other treatments for managing chronic open angle glaucoma and ocular hypertension.

Apart from brinzolamide/brimonidine, all fixed combination eye drops contain the beta-blocker timolol 0.5%. Combinations are available with prostaglandin analogues (bimatoprost, latanoprost and travoprost) for once-daily use, and with brimonidine an alpha 2 agonist (sympathomimetic) and the carbonic anhydrase inhibitors, brinzolamide and dorzolamide, for twice-daily use ([British national formulary](#) January 2015).

The NICE guideline on [glaucoma](#) recommends that people with ocular hypertension or suspected open angle glaucoma who are at high risk of conversion to, or have established chronic open angle glaucoma and who are allergic to preservatives, should be offered preservative-free topical glaucoma treatments. Brinzolamide/brimonidine combination eye drops are not available as a preservative-free preparation.

Costs of alternative treatments

Constituent drugs and alternative fixed dose combinations ^a	Frequency of use ^a	Cost per 28-day treatment ^a (excluding VAT)
Brimonidine 0.2% eye drops	1 drop into affected eye(s) twice daily	£2.26 ^b
Brinzolamide 1% eye drops	1 drop into affected eye(s) twice daily	£6.92 ^b
Bimatoprost 0.03%/timolol 0.5% eye drops	1 drop into affected eye(s) daily	£13.95 ^b
Bimatoprost 0.03%/timolol 0.5% preservative-free eye drops	1 drop into affected eye(s) daily	£17.50 ^c
Brinzolamide 1%/brimonidine 0.2% eye drops	1 drop into affected eye(s) twice daily	£9.23 ^b
Brimonidine 0.2%/timolol 0.5% eye drops	1 drop into affected eye(s) twice daily	£10.00 ^b
Brinzolamide 1%/timolol 0.5% eye drops	1 drop into affected eye(s) twice daily	£11.05 ^b

Dorzolamide 2%/timolol 0.5% eye drops	1 drop into affected eye(s) twice daily	£2.72 ^b
Dorzolamide 2%/timolol 0.5% preservative-free eye drops	1 drop into affected eye(s) twice daily	£28.59 ^b
Latanoprost 0.005%/timolol 0.5% eye drops	1 drop into affected eye(s) daily	£3.87 ^b
Travoprost 0.0004%/timolol 0.5% eye drops	1 drop into affected eye(s) daily	£13.95 ^b
<p>^a Doses taken from the summaries of product characteristics. The doses shown do not imply therapeutic equivalence. Prices quoted are the lowest NHS costs based on unit cost per eye.</p> <p>^b Costs taken from Drug Tariff, February 2015.</p> <p>^c Costs taken from MIMS, February 2015.</p>		

Estimated impact for the NHS

Likely place in therapy

The NICE guideline on [glaucoma](#), and the [European Glaucoma Society guidelines](#) emphasise the importance of person-centred care. In particular, treatment should be individualised to the need of the person and rate of progression. The [European Glaucoma Society guidelines](#) state that the least amount of medication to achieve the therapeutic response should be a consistent treatment goal, minimising inconvenience, adverse effects and cost.

Both NICE and the [European Glaucoma Society](#) recommend prostaglandin analogues and beta-blockers as first-line treatment options for managing mild to moderate chronic open angle glaucoma, suspected glaucoma and ocular hypertension, depending on individual factors. After checking adherence and eye drop instillation technique, NICE [guidance](#) recommends offering another drug treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) if intraocular pressure has not been reduced sufficiently to prevent disease progression. More than 1 agent may be needed concurrently to achieve target intraocular pressure. However, NICE and [European Glaucoma Society guidelines](#) suggest trying monotherapy with a different agent before adding a second drug.

When compared with prescribing the separate constituent drugs, fixed combination preparations offer a simple and convenient administration regimen, less daily exposure to preservative and may result in some cost savings for people who pay prescription charges. However, fixed combinations

do not allow titration of the individual constituents both in terms of concentration and timing of administration, and this may be a limitation for some people.

Brinzolamide/brimonidine is the only combination treatment for glaucoma that does not contain a beta-blocker; therefore its contraindications and adverse effect profile are different from other combination products. Brinzolamide/brimonidine combination eye drops may be an alternative treatment option for some people with glaucoma or ocular hypertension for whom prostaglandin analogues and beta-blockers are unsuitable and whose condition is insufficiently controlled on 1 intraocular pressure-lowering medication. [European Glaucoma Society guidelines](#) suggest that combination products should be offered only once a person has been treated with 1 of the constituents and has had a partial response. The addition of the second drug (either singularly or in combination) may then be indicated.

As well as efficacy, safety and individual user factors, local decision-makers will need to take cost into account when considering the likely place in therapy of brinzolamide/brimonidine combination eye drops for managing intraocular hypertension and chronic open angle glaucoma. Brinzolamide/brimonidine combination eye drops are comparable in price to the individual constituent products combined. They are less costly than most combination eye drops containing preservative (see table above for comparative treatment costs).

Estimated usage

The [NHS prescription cost analysis for England 2013](#) reports that approximately 8.6 million community prescriptions for treating glaucoma were dispensed in 2012 at a cost of approximately £90 million (net ingredient cost).

The manufacturer of brinzolamide/brimonidine combination eye drops estimates that 4000 to 5000 people may start treatment with this product over a 12-month period (personal communication, Alcon Laboratories (UK) Ltd October 2014).

Relevance to NICE guidance programmes

Brinzolamide/brimonidine combination eye drops were not considered appropriate for a NICE technology appraisal and are not currently planned into any other NICE work programme.

NICE has issued a guideline on [glaucoma](#) (CG85). This was published April 2009 and will be reviewed in June 2015.

Additional NICE products include:

- NICE pathway on [glaucoma](#) [last updated September 2014]
- NICE [quality standard on glaucoma \(QS7\)](#) (2011)

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Celia Fenerty is a consultant ophthalmologist employed by the NHS with a specialist interest in glaucoma and Royal College of Ophthalmologists expert adviser to the MRHA. She was provided with overnight accommodation for an educational meeting sponsored by Spectrum Thea (meeting content not promotional).

Richard Sheard is a consultant ophthalmologist employed by the NHS and had no relevant interests to declare.

Fiona Spencer is a consultant ophthalmologist employed by the NHS. She was provided with travel and accommodation expenses for attendance at educational events by Alcon, Allergan, Merck Sharpe and Dohme and Spectrum Thea, and has received honoraria from Alcon, Allergan and Pfizer for speaking at educational events.

Changes after publication

June 2015: Minor maintenance

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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ISBN: 978-1-4731-1068-7