National Institute for Health and Care Excellence

Health Technology Evaluation

Netarsudil-latanoprost for previously treated primary open-angle glaucoma or ocular hypertension [ID1363]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Santen	Yes - there is a high unmet need for new interventions to treat primary-open angle glaucoma and ocular hypertension by targeting the trabecular meshwork, as the prevalence of these conditions is increasing worldwide.	Thank you for your comment. Following the consultation on this proposed appraisal this topic will proceed within the NICE work programme as a single technology appraisal (STA).
	The Royal College of Ophthalmo-logists	Appropriate subject & scope	Thank you for your comment. No action needed.
	Fight for Sight	This is appropriate.	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
Wording	Santen	Current wording: "To appraise the clinical and cost effectiveness of netarsudil-latanoprost within its marketing authorisation for treating open-angle glaucoma or ocular hypertension." Suggested wording: "To appraise the clinical and cost-effectiveness of netarsudil-latanoprost within its marketing authorisation for treating primary open-angle glaucoma or ocular hypertension." Rationale To reflect the wording of the marketing authorisation.	Thank you for your comment. The wording in the scope has been amended to reflect the marketing authorisation.
	The Royal College of Ophthalmo-logists	Yes [wording of the remit reflects the issues of clinical and cost effectiveness about this technology]	Thank you for your comment. No action needed.
	Fight for Sight	The wording and the remit look complete.	Thank you for your comment. No action needed.
Timing issues	Santen	As noted in the draft scope, there are more than approximately 560,000 adults in England with primary open-angle glaucoma, with the overall risk increasing substantially with increasing intraocular pressure and age. Furthermore, it is estimated that there could be over 1 million adults in England with ocular hypertension. These statistics demonstrate that even though there are many interventions available to treat these conditions, there still remains a high unmet need for a product that can reduce the prevalence of these conditions in England.	Thank you for your comment. No action needed.

Section	Stakeholder	Comments [sic]	Action
		Elevated intraocular pressure is a major risk factor for developing primary-open angle glaucoma. Netarsudil-latanoprost offers a unique opportunity to treat trabecular meshwork dysfunction and thereby reduce elevated intraocular pressure inside the eye. Reducing pressure inside the eye can prevent eye pain and loss of vision. In order to make this benefit available to patients, an appraisal should be conducted as soon as possible. Santen is working to gather the necessary information and expects to be able to provide a full submission by April 2023.	
	The Royal College of Ophthalmo-logists	Non-urgent	Thank you for your comment. No action needed.
	Fight for Sight	Glaucoma is one of the most common causes of vision loss in the UK and has a complex aetiology. Aging is an influential factor in some cases, and this is important as there is an aging population in the UK.	Thank you for your comment. No action needed.
Additional comments on the draft remit	Santen	None	Thank you for your comment. No action needed.
	The Royal College of Ophthalmo-logists	Well written, comprehensive and understandable	Thank you for your comment. No action needed.
	Fight for Sight	None	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Santen	Current wording: 1. "Primary, or chronic, open-angle glaucoma (COAG) accounts for over 70% of all glaucoma cases." 2. "Open-angle glaucoma has an estimated UK prevalence of 2% of people over the age of 40. Using the 2020 ONS population projections this would be more than approximately 560,000 people in England. The overall risk of developing open-angle glaucoma increases substantially with increasing IOP and with age." 3. "A generic prostaglandin analogue is offered to people with confirmed COAG. For people with advanced COAG, surgery with pharmacological augmentation is offered (with interim treatment with a generic prostaglandin analogue while listed for surgery)." Suggested wording: 1. "Primary, or chronic, open-angle glaucoma (POAG) accounts for over 70% of all glaucoma cases." 2. "Primary open-angle glaucoma has an estimated UK prevalence of 2% in people over the age of 40. Using the 2020 ONS population projections this would be more than approximately 560,000 people in England. The overall risk of developing primary open-angle glaucoma increases substantially with increasing IOP and with age." 3. "A generic prostaglandin analogue is offered to people with confirmed POAG. For people with advanced POAG, surgery with pharmacological augmentation is offered (with interim treatment with a generic prostaglandin analogue while listed for surgery)." Rationale To reflect the exact population within the marketing authorisation.	Thank you for your comment. The wording in the scope has been amended to reflect the marketing authorisation.

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	The Royal College of Ophthalmo-logists	Accurate	Comment noted. No action needed.
	Fight for Sight	The link for reference 4 did not open when clicked- it would just be good to know where the estimate of 660,000 came from as the report that Fight for Sight commissioned in 2020 estimated around 500,000 people in the UK suffer from Glaucoma. Otherwise, the background looks complete.	Comment noted. The link to the reference has been updated. Prevalence figures included within the scope have been calculated by applying the estimated prevalence percentages to the UK population figures provided by the Office of National Statistics.
The technology/ intervention	Santen	None.	No action needed.
	The Royal College of Ophthalmo-logists	Yes [the description of the technology is accurate]	Comment noted. No action needed.
	Fight for Sight	Good description of the product.	Comment noted. No action needed.
Population	Santen	Current wording: “People with previously treated open-angle glaucoma or ocular hypertension.”	Thank you for your comment. The wording of the scope has been

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		Suggested wording: “Adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.” Rationale To reflect the wording of the marketing authorisation	amended to algin with the marketing authorisation.
	The Royal College of Ophthalmo-logists	Yes [the population is defined appropriately]	Comment noted. No action needed.
	Fight for Sight	n/a	No action needed.
Comparators	Santen	Yes - the treatments listed are the standard treatments currently used in the NHS. As patients with primary-open angle glaucoma or ocular hypertension typically cycle through multiple treatments, it is not appropriate to consider any of the listed comparators as “best alternative care”	Thank you for your comment. No action needed.
	The Royal College of Ophthalmo-logists	Yes [these are the standard treatments currently used in the NHS with which the technology should be compared]	Comment noted. No action needed.
	Fight for Sight	As the guidance currently stands and until the it is updated, surgical and laser treatments may be worth considering.	Comment noted. The list of comparators now includes selective laser trabeculoplasty and surgery.

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Outcomes	Santen	None.	No action needed.
	The Royal College of Ophthalmo-logists	Yes [these outcome measures capture the most important health benefits of the technology]	Comment noted. No action needed.
	Fight for Sight	The outcomes mentioned look appropriate.	Comment noted. No action needed.
Equality	Santen	Glaucoma risk differs between ethnic groups. We do not anticipate that there will be sufficient evidence to support separate evaluations of the clinical effectiveness and cost-effectiveness of netarsudil-latanoprost for separate ethnic groups. We anticipate that NICE may issue guidance that allows clinicians to take into consideration differing glaucoma risk in certain groups in practice.	Thank you for your comment. NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination. The Technology Appraisal Committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. No changes to the scope required.
	The Royal College of Ophthalmo-logists	A specific look at the responses of different ethnic groups would be valuable and if not available a statement requesting such data be made available.	Thank you for your comment. The Technology Appraisal Committee will consider whether its

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			recommendations could have a different impact on people protected by the equality legislation than on the wider population.
	Fight for Sight	N/A	No action needed.
Economic analysis	Santen	None.	No action needed.
	The Royal College of Ophthalmo-logists	Yes [the economic analysis is appropriate]	Comment noted. No action needed.
	Fight for Sight	N/A	No action needed.
Other considerations	Santen	Suggested wording (no change): If the evidence allows, the following subgroups will be considered: • Adult patients with primary open-angle glaucoma for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction. • Adult patients with ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction. Rationale It is not yet clear if there is sufficient evidence to establish separate estimates of clinical effectiveness or cost-effectiveness in these subgroups.	Thank you for your comment. The scope has been updated to include subgroups if evidence allows.
Innovation	Santen	**Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how**	Thank you for your comment. The extent to

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		it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Intraocular pressure is controlled by three main mechanisms: (1) increasing aqueous humor outflow via the trabecular meshwork pathway, (2) increasing aqueous humor outflow via the uveoscleral outflow pathway, or (3) decreasing the production of aqueous humor. The trabecular meshwork is responsible for approximately 70-96% of aqueous humor outflow.3–5 For primary open-angle glaucoma, the pathology underlying increased intraocular pressure resides in the trabecular meshwork.6 Currently available treatments for primary open-angle glaucoma or ocular hypertension do not act directly on the trabecular meshwork to reduce intraocular pressure. Rho-kinase (ROCK) inhibitors are the first new class of drugs for glaucoma since the mid-1990s, and their unique mechanism of action targeting the trabecular meshwork represents an opportunity to evolve primary open-angle glaucoma and ocular hypertension treatment.7,8 ROCK signalling has been identified as an important regulator of trabecular meshwork outflow.9 The ROCK pathway is involved in cytoskeletal integrity of cells, synthesis of extracellular matrix components for aqueous humor outflow and in the permeability of endothelial cells with Schlemm's canal.10,11 Inhibition of the ROCK signalling pathway has been associated with the relaxation of the trabecular meshwork, with subsequent increase in aqueous humor outflow facility and reduced episcleral venous pressure, which leads to a reduction in intraocular pressure.12 Existing pre-clinical and clinical scientific evidence suggests that the ROCK inhibitor netarsudil lowers intraocular pressure through at least two mechanisms: by increasing trabecular outflow and by reducing episcleral venous pressure.13–17	which the technology may or may not be innovative will be considered by the Technology Appraisal Committee. No changes to the scope required.

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		Netarsudil-latanoprost is the first treatment to target the trabecular meshwork to increase aqueous humor outflow, thereby reducing pressure in the eye. Netarsudil lowers intraocular pressure by increasing the trabecular outflow which complements the increased uveoscleral outflow by latanoprost.18 Two Phase 3 trials (MERCURY 1 and MERCURY 2) demonstrated that treatment with netarsudil-latanoprost produced statistically significant and clinically relevant reductions in intraocular pressure that were statistically superior to reductions achieved by netarsudil and latanoprost monotherapy.19 Furthermore, the Phase 3 MERCURY 3 trial (expected publication date: January 2023) adds to this evidence, supporting netarsudil-latanoprost as a novel and valuable addition to primary open-angle glaucoma and ocular hypertension management.20 The addition of netarsudil-latanoprost in England will make a significant and substantial impact to the existing treatment pathways for primary open-angle glaucoma and ocular hypertension, as these have typically relied on the same classes of interventions for more than two decades.8 A treatment like netarsudil-latanoprost will provide patient's with a new and unique option to achieve their target intraocular pressure reduction. **Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** The company is not aware of major health-related benefits associated with netarsudil-latanoprost that cannot be included in the QALY calculation. **References:** 3. Goel M, Picciani RG, Lee RK, et al. Aqueous humor dynamics: a review. Open Ophthalmol J 2010. 4: 52–59.	

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		4. Koga T, Koga T, Awai M, et al. Rho-associated protein kinase inhibitor, Y-27632, induces alterations in adhesion, contraction and motility in cultured human trabecular meshwork cells. Exp Eye Res 2006. 82: 362–370. 5. Park J-H, Chung HW, Yoon EG, et al. Morphological changes in the trabecular meshwork and Schlemm's canal after treatment with topical intraocular pressure-lowering agents. Sci Rep 2021. 11: 18169. 6. Er T, Bm B & R F. Intraocular Pressure and the Mechanisms Involved in Resistance of the Aqueous Humor Flow in the Trabecular Meshwork Outflow Pathways. Prog Mol Biol Transl Sci 2015. 134: 7. Berrino E & Supuran CT. Rho-kinase inhibitors in the management of glaucoma. Expert Opin Ther Pat 2019. 29: 817–827. 8. Schehlein EM & Robin AL. Rho-Associated Kinase Inhibitors: Evolving Strategies in Glaucoma Treatment. Drugs 2019. 79: 1031–1036. 9. Moura-Coelho N, Tavares Ferreira J, Bruxelas CP, et al. Rho kinase inhibitors-a review on the physiology and clinical use in Ophthalmology. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol 2019. 257: 1101–1117. 10. Honjo M, Tanihara H, Inatani M, et al. Effects of rho-associated protein kinase inhibitor Y-27632 on intraocular pressure and outflow facility. Invest Ophthalmol Vis Sci 2001. 42: 137–144. 11. Yang C-YC, Liu Y, Lu Z, et al. Effects of Y27632 on Aqueous Humor Outflow Facility With Changes in Hydrodynamic Pattern and Morphology in Human Eyes. Invest Ophthalmol Vis Sci 2013. 54: 5859–5870. 12. Wang J, Liu X & Zhong Y. Rho/Rho-associated kinase pathway in glaucoma (Review). Int J Oncol 2013. 43: 1357–1367.	

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		13. Kazemi A, McLaren JW, Kopczynski CC, et al. The Effects of Netarsudil Ophthalmic Solution on Aqueous Humor Dynamics in a Randomized Study in Humans. J Ocul Pharmacol Ther 2018. 34: 380–386. 14. Sit AJ, Gupta D, Kazemi A, et al. Netarsudil Improves Trabecular Outflow Facility in Patients with Primary Open Angle Glaucoma or Ocular Hypertension: A Phase 2 Study. Am J Ophthalmol 2021. 226: 262–269. 15. Xu H, Thomas MT, Lee D, et al. Response to netarsudil in goniotomy-treated eyes and goniotomy-naïve eyes: a pilot study. Graefes Arch Clin Exp Ophthalmol 2022. 260: 3001–3007. 16. Zaman F, Gieser SC, Schwartz GF, et al. A multicenter, open-label study of netarsudil for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension in a real-world setting. Curr Med Res Opin 2021. 37: 1011–1020. 17. Ren R, Li G, Le TD, et al. Netarsudil Increases Outflow Facility in Human Eyes Through Multiple Mechanisms. Invest Ophthalmol Vis Sci 2016. 57: 6197–6209. 18. Netarsudil-latanoprost (Roclanda) summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/roclanda-epar-product-information_en.pdf. Last accessed: 11/01/23. 19. Asrani S, Bacharach J, Holland E, et al. Fixed-Dose Combination of Netarsudil and Latanoprost in Ocular Hypertension and Open-Angle Glaucoma: Pooled Efficacy/Safety Analysis of Phase 3 MERCURY-1 and -2. Adv Ther 2020. 37: 1620–1631.	

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		20. Safety and Efficacy Study of PG324 (Netarsudil/Latanoprost 0.02% / 0.005%) Ophthalmic Solution Compared to GANFORT® Ophthalmic Solution in Open Angle Glaucoma or Ocular Hypertension. Available at: https://clinicaltrials.gov/ct2/show/NCT03284853. Last accessed: 11/01/23.	
	The Royal College of Ophthalmo-logists	Yes – there is potential to reduce need for surgery	Comment noted. No action needed.
	Fight for Sight	This is a combination treatment, so it would be a step change in the management of the condition. Fight for Sight is supportive of providing patients with different alternatives that improves the burden of the condition for them.	Comment noted. No action needed.
Questions for consultation	Santen	**Where do you consider netarsudil-latanoprost will fit into the existing care pathway for glaucoma?** Netarsudil-latanoprost (Roclanda®) will fit into the existing pathways for primary open-angle glaucoma and ocular hypertension at the point where patients need to step up from prostaglandin analogue monotherapy onto a combination therapy to control intraocular pressure, in line with its marketing authorisation. **Would netarsudil-latanoprost be a candidate for managed access?** No. **Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** See comments under “Innovation” section.	Thank you for the comment. The positioning of the technology in the treatment pathway, as well as its clinical and cost-effectiveness, will be considered and appraised by the Technology Appraisals Committee during the appraisal. Stakeholders will be invited to submit evidence and statements and all will be considered. No

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		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. See comments under “Equality” section.	changes to the scope required.
	The Royal College of Ophthalmo-logists	None.	No action needed.
	Fight for Sight	N/A	No action needed.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

AbbVie