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Netarsudil plus latanoprost (Roclatan) for glaucoma or ocular hypertension

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LAY SUMMARY

Glaucoma describes a group of disorders characterised by sight loss. Glaucoma is generally associated with high pressure in the liquids inside the eye but it can happen when the pressure level is normal. Individuals with consistently high eye pressure are at risk of developing glaucoma. Glaucoma does not normally cause any symptoms but once eye sight is lost it cannot be recovered. Approximately one in every ten blindness registrations is due to glaucoma. There are approximately half a million people living with glaucoma in England.

Current treatment options include a number of different eye drop formulations to stop internal eye pressure raising. If the eye drops do not work and glaucoma is diagnosed, laser therapy or eye surgery can also be used to stop sight loss. Roclatan is a fixed dose combination of two drugs, netarsudil and latanoprost, which is widely used to treat eye pressure. Individually, both drugs act in different and unique ways to lower the pressure in the eye. When used in combination, both drugs have a potential to produce a stronger and more sustained effect. If licenced, Roclatan has the potential to be more effective at lowering eye pressure when compared to current treatment options.

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TARGET GROUP

Patients with glaucoma or ocular hypertension.

TECHNOLOGY

DESCRIPTION

Roclatan (PG-324) is a once-daily eye drop that combines in a fixed dose netarsudil (Rhopressa, AR-13324) with latanoprost at a rate of 0.02% to 0.005% respectively.[1]

Netarsudil inhibits both Rho Kinase (ROCK) and the Norepinephrine Transporter (NET) which increases fluid outflow and reduces fluid inflow. ROCK is a type of protein kinase that regulates actin and myosin which are proteins that are responsible for cellular contraction. In the trabecular outflow pathway of the eye, the resistance to fluid outflow that maintains normal intraocular pressure (IOP) is regulated by the contraction of trabecular meshwork (TM) cells and the production of extracellular matrix. ROCK inhibitors block TM cell contraction and reduce the production of extracellular matrix, thereby increasing fluid outflow and thus decreasing IOP.[2]

Latanoprost ophthalmic solution is a topical medication widely used for controlling the progression of glaucoma or ocular hypertension, by reducing intraocular pressure. It is a prostaglandin analogue (PGA) that works by increasing the outflow of aqueous fluid from the eyes. It is also known by the brand name of Xalatan manufactured by Pfizer.[3]

In the ongoing phase III trial (NCT02558400), netarsudil plus latanoprost ophthalmic solution is administered once a day (in the evening) in both eyes.[4]

Netarsudil plus latanoprost ophthalmic solution does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If approved, netarsudil plus latanoprost ophthalmic solution (Roclatan) would be the first glaucoma product to lower IOP through all known mechanisms: (i) increasing fluid outflow through the trabecular meshwork, the eye's primary drain, (ii) increasing fluid outflow through the uveoscleral pathway, the eye's secondary drain, (iii) reducing fluid production in the eye, and (iv) reducing episcleral venous pressure (EVP). By covering the full spectrum of known IOP-lowering mechanisms, Netarsudil plus latanoprost ophthalmic solution has the potential to provide a greater IOP-lowering effect than any currently approved glaucoma product.[1]

DEVELOPER

Aerie Pharmaceuticals

AVAILABILITY, LAUNCH or MARKETING

Aerie Pharmaceuticals plans to file a new drug application (NDA) to the US FDA for Glaucoma and Ocular hypertension in the first half of 2018.[2]

Aerie Pharmaceuticals plans the phase III Mercury 3 trial for Glaucoma and Ocular hypertension in European Union in third quarter of 2017.[2]

PATIENT GROUP

BACKGROUND

Ocular hypertension (OHT) is defined as consistently elevated intraocular pressure (IOP) - greater than 21mmHg (2 standard deviations above the population mean IOP) by Goldmann applanation tonometry (GAT) on 2 or more occasions - in one or both eyes in the absence of clinical evidence of optic nerve damage, visual field defect or other pathology that could explain high IOP.[5]

If a person has a consistently raised eye pressure, when this is measured, but no signs of glaucoma, he or she is said to have OHT. This is not glaucoma, as there is no damage to the optic nerve, but untreated OHT nevertheless leads to primary open angle glaucoma (POAG) in 10% of patients within five years.[5]

Glaucoma is a common sight threatening disease that affects the optic nerve.[6] It is classified into two major categories according to the appearance and obstruction of the drainage pathway at the iridocorneal angle (trabecular meshwork). In open angle glaucoma, despite the normal clinical appearance, the aqueous outflow is restricted, and in closed angle glaucoma tissue physically obstructs the angle. Glaucoma can also be classified according to whether it is primary (idiopathic; the most common type) or secondary - associated with detectable comorbidity. Such comorbidities include pseudoexfoliation; rubeosis associated with ocular ischaemia due to vascular occlusion or diabetes; uveitis; or after ocular surgery, such as retinal detachment surgery.[8]

If not diagnosed, monitored and treated correctly, glaucoma can result in severe loss of vision or blindness. Approximately 10% of UK blindness registrations are related to glaucoma. Vision lost due to glaucoma is not recoverable. Therefore, successful management of glaucoma requires lifelong monitoring and treatment to prevent or minimise further vision loss.[5] People with glaucoma often do not experience symptoms until the disease is advanced and there has already been considerable damage to the person's vision. Therefore, people at high risk of glaucoma need to be monitored to diagnose and treat glaucoma at an early stage.[6]

CLINICAL NEED and BURDEN OF DISEASE

The commonest type of glaucoma in the UK is primary open-angle glaucoma (chronic open angle glaucoma or COAG), affecting around 2% of people older than 40 years and rising to almost 10% in people older than 75 years in white Europeans. In England there are over a million glaucoma-related outpatient visits in the hospital eye service annually.[7] The number of individuals affected by COAG is expected to rise due to changes in population demographics. Based on these estimates 480,000 people are currently affected by COAG in England.[7]

The prevalence of COAG is higher in people of black African or black Caribbean descent and in people who have a family history of the condition. These people, as well as people living in deprived areas with poor access to services, are at highest risk of becoming blind due to glaucoma.[8]

Ocular hypertension affects 3-5% of the population over 40 years of age, but only a small proportion of these people develop glaucoma.[8]

The social and economic burden of glaucoma is likely to increase in the future because of longer life expectancy and an ageing population. In the UK, glaucoma is the second most common cause for registration of visual impairment, accounting for 9-12% of registrations in people over the age of 65 years.[8]

In the United Kingdom, the management of patients with glaucoma constitutes a major part of ophthalmologists' workload, accounting for 23% of all follow-up attendances to the UK hospital eye service.[8] Over 30% of glaucoma related NHS hospital eye service attendances are related to OHT.[6]

In 2015/16 the Hospital Episodes Statistics recorded approximately 22,500 finished consultant episodes (FCE), 22,397 admissions and 4,693 FCE bed days for glaucoma (ICD-10 code H40).[9]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline in development. Glaucoma: diagnosis and management (update) (GID-NG10017). Expected publication date November 2017
- NICE clinical guideline. Glaucoma: diagnosis and management (CG85). April 2009.

- NICE quality standard. Glaucoma in adults (QS7). March 2011.

- NICE interventional procedure guidance in development. Ab externo canaloplasty for primary open-angle glaucoma (GID-IPG10047). Expected publication date to be confirmed
- NICE interventional procedure guidance in development. Micro-invasive subconjunctival insertion of a transcleral gelatin stent for primary open-angle glaucoma (GID-IPG10041). Expected publication date to be confirmed.
- NICE interventional procedure guidance. Trabecular stent bypass microsurgery for open-angle glaucoma (IPG575). February 2017
- NICE interventional procedure guidance. Trabeculotomy ab interno for open angle glaucoma (IPG397) May 2011
- NICE interventional procedure guidance. Canaloplasty for primary open-angle glaucoma (IPG260). May 2008.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthamology (Adult). D12/S/a
- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthamology (paediatrics). D12/S/b

OTHER GUIDANCE

- Clinical Council for eye health commissioning. *Commissioning guide: Glaucoma (recommendations)*. The Royal College of Opthalmologists: June 2016
- Scottish Intercollegiate Guidelines Network. *Glaucoma referral and safe discharge: A national clinical guideline (SIGN144)*. Healthcare Improvement Scotland: March 2015

CURRENT TREATMENT OPTIONS

In the UK, there are several different treatments for glaucoma, including eye drops, laser treatment and surgery. Eye drops the main treatment options. The main types of eye drops are[10,12]:

- prostaglandin analogues, such as latanoprost, bimatoprost, tafluprost and travoprost
- beta-blockers, such as betaxolol hydrochloride, carteolol hydrochloride, levobunolol hydrochloride and timolol maleate
- carbonic anhydrase inhibitors, such as acetazolamide, brinzolamide and dorzolamide
- sympathomimetics, such as brimonidine tartrate or apraclonidine
- miotics, such as pilocarpine

EFFICACY and SAFETY

Trial	NCT02674854; phase III
Sponsor	Aerie Pharmaceuticals
Status	Complete but unpublished
Source of Information	Trial registry[11]
Location	USA
Design	Randomised, active/controlled
Participants	N= 750; aged more than 18 years old; open angle glaucoma or ocular hypertension diagnosis in both eyes; un-medicated intraocular pressure >20mmHg and <36mmHg in both eyes at 2 qualification visits; corrected visual acuity equivalent to 20/200.
Schedule	Randomised to either: • Netarsudil plus latanoprost Ophthalmic Solution, 1 drop daily (evening) both eyes; • Netarsudil (AR-13324) ophthalmic solution,1 drop daily (evening) both eyes, or • Latanoprost ophthalmic solution, 1 drop daily (evening) both eyes.
Follow-up	Active treatment for 90 days
Primary Outcomes	Intraocular pressure
Secondary Outcomes	-
Key Results	Not reported
Adverse effects (AEs)	Not reported

Expected reporting date	Not reported

Trial	NCT02558400; phase III
Sponsor	Aerie Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[4]
Location	USA
Design	Randomised, active/controlled
Participants	N= 690 (planned); aged more than 18 years old; open angle glaucoma or ocular hypertension diagnosis in both eyes; un-medicated intraocular pressure >20mmHg and <36mmHg in both eyes at 2 qualification visits; corrected visual acuity equivalent to 20/200.
Schedule	Randomised to either; • Netarsudil plus latanoprost Ophthalmic Solution, 1 drop daily (evening) both eyes; • Netarsudil (AR-13324) ophthalmic solution, 1 drop daily (evening) both eyes, or • Latanoprost ophthalmic solution, 1 drop daily (evening) both eyes.
Follow-up	Active treatment for 12 months
Primary Outcomes	Intraocular pressure
Secondary Outcomes	Number of participants with adverse events as a measure of safety and tolerability [Time Frame: 12 months] Changes in visual acuity from baseline [Time Frame: 12 months] Changes in visual field test from baseline [Time Frame: 12 months] Changes in pupil size from baseline [Time Frame: 12 months]
Key Results	Not reported
Adverse effects (AEs)	Not reported
Expected reporting date	Not reported

ESTIMATED COST and IMPACT

COST

The cost of PG-324 (netarsudil and latanoprost) is not yet known. The cost of current approved drugs are summarised in the table below.

Drug	Dose (eye drop formulation)	Unit dose[12]

Betaxolol	2.5 mg per 1 ml	NHS indicative price £13.77 (50 unit dose) or NHS indicative price £2.66 (5 ml)
Carteolol hydrochloride	10 mg per 1 ml, or 20 mg per 1 ml	NHS indicative price £7.60 (5 ml) or NHS indicative price £8.40 (5ml)
Levobunolol hydrochloride	5 mg per 1 ml	NHS indicative price £9.98 (30 unit dose)
Timolol maleate	2.5 mg per 1 ml 5 mg per 1 ml	Several providers, NHS indicative price range from £1.43 to £3.12 Several providers, NHS indicative price range from £1.25 to £3.12
Latanoprost	50 microgram per 1 ml	Several providers, NHS indicative price range from £1.40 to £12.48
Tafluprost	15 microgram per 1 ml	NHS indicative price £12.20 (30 unit dose)
Apraclonidine	5 mg per 1 ml	NHS indicative price £10.88 or £77.85 (24 unit dose)
	Dose (eye drops and other formulations)	
Acetazolamide	250mg tablets	NHS indicative price range from £28.20 to £75.36 (112 tables)
	500mg powder for solution for injection vials	NHS indicative price £14.76
	250 mg modified-release capsules	NHS indicative price £16.60
Brinzolamide	10 mg per 1 ml	Several providers, NHS indicative price from £2.11 to £6.92
Dorzolamide	20 mg per 1 ml	Several providers, NHS indicative price from £1.90 to £6.33 (5ml)
Pilocarpine	10 mg per 1 ml 40 mg per 1 ml	Several providers, NHS indicative price from £11.99 (20 unit dose) to £19.71 Several providers, NHS indicative price from £16.29 to £21.99

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☒ Clinical uncertainty or other research question identified: phase III trial for efficacy and safety not yet completed, results not yet available.

☐ None identified

INFORMATION FROM

No information was received from Aerie Pharmaceuticals.

Aerie Pharmaceuticals did not enter information about this technology onto the *UK PharmaScan* database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other

sources. *UK PharmaScan* is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use *UK PharmaScan* so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

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