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Mitomycin ophthalmic (Mitosol) for glaucoma surgery

LAY SUMMARY

Glaucoma is a serious condition caused by abnormal pressure within the eye leading to blindness. All glaucoma treatments aim to prevent further damage to sight, but any damage to vision that has already been caused by glaucoma can not be repaired. Glaucoma can be treated with eye drops, tablets, laser surgery, eye surgery or a combination of these methods.

Surgery for glaucoma creates a channel for the fluid in the eye to drain. Surgery is only usually recommended for patients who are not responding to eye drops and tablets.

During glaucoma surgery, a drug called mitomycin-c may be applied to the eye to prevent scarring and improve the success rates of glaucoma surgery. Mitosol is a new solution of mitomycin-c ophthalmic that is applied by saturated sponges to the site for 2 minutes.

It may be more straightforward to store and use than the current options for using mitomycin-c.

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**National Institute for
Health Research**

TARGET GROUP

- Glaucoma – for use during surgery for glaucoma.

TECHNOLOGY

DESCRIPTION

Mitomycin ophthalmic (Mitosol – mitomycin for solution – kit for ophthalmic use; mitomycin-c ophthalmic solution; optomycin; trabomycin) is a topical ophthalmic formulation of mitomycin, an inhibitor of DNA synthesis. Mitosol comprises a new ophthalmic formulation of mitomycin-c presented in a self-contained surgical procedure kit that includes a closed delivery system and disposal components. It is administered topically as a 0.2mg solution applied via saturated sponges to the site of glaucoma filtration surgery for 2 minutes¹. Intraoperative application of mitomycin ophthalmic at varying concentrations is used to prevent scarring and improve success rates of glaucoma filtration surgery, especially trabeculectomy surgery which is considered the “gold standard” surgery^a.

The drug (as Mitosol) is currently approved in the USA for the use as an adjunct to ab externo glaucoma surgery. Mitosol does not currently have Marketing Authorisation in the EU for any indication, however mitomycin-c is licensed and available for the treatment of certain types of cancer, either as a topical agent (for superficial bladder cancer) or for parenteral administration, and has been used “off-label” in the UK for glaucoma surgery since 1995, and more recently for other ocular surgeries including for the ocular surface^a. Mitosol is also in development for use during surgery for corneal disorders and recurrent pterygium.

INNOVATION and/or ADVANTAGES

If licensed, mitomycin ophthalmic will offer an additional treatment option for use during surgery for glaucoma patients who are unresponsive or intolerant to medical treatment or laser treatment^a. It would be the only formulation of this agent licensed for ophthalmic use and would represent the first pharmaceutical therapy specifically licensed to prevent scarring during glaucoma surgery. In addition, Mitosol has a long shelf-life and does not require refrigeration or light shielding during storage, which potentially offers an advantage over current preparations of mitomycin-c used off-label during surgery.

DEVELOPER

Mobius Therapeutics.

AVAILABILITY, LAUNCH OR MARKETING

The drug is in phase III clinical trials.

^a Expert personal communication.

PATIENT GROUP

BACKGROUND

Glaucoma is the name given to a group of eye conditions which cause optic nerve damage, giving rise to characteristic optic disc changes and visual field loss. This is caused by an imbalance of aqueous fluid production and drainage out of the eye, with the emphasis on reduced outflow^b. In its early stages, glaucoma affects peripheral vision (it can sometimes start with a paracentral scotoma)^b, but as it advances it also affects central vision and can result in severe sight impairment. Without adequate treatment, glaucoma can progress to visual disability and eventual blindness². Glaucoma is usually associated with an increase in intraocular pressure (IOP) above the normal value; however, surveys show that 20-52% of patients with glaucoma have IOP within the normal range³. Ocular hypertension is a term used to describe any situation in which IOP is greater than 21mmHg, with absence of glaucomatous defects on visual-field testing; it can be present for many years without development of glaucoma^{2,4}.

The overall risk of developing glaucoma increases with the number and strength of risk factors. It increases substantially with the level of IOP elevation and with increasing age. Other risk factors include high myopia, Black ethnicity and a family history of glaucoma in a first degree relative^{5,3}. Identifiable gene mutations are implicated but account for only about 5% of cases of adult onset glaucoma³.

Glaucoma is classified into two major categories according to the appearance and obstruction of the drainage pathway at the iridocorneal angle³. Primary open angle glaucoma is the most common type of glaucoma, accounting for over 70% of cases³ in White ethnic groups and angle closure glaucoma is more prevalent in those from Chinese ethnic groups^b.

NHS or GOVERNMENT PRIORITY AREA

- NHS England 2013/14 NHS Standard Contract for Ophthalmic Pathology Service (All Ages) D12/S(HSS)/b.
- NHS England 2013/14 NHS Standard Contract for Specialised Ophthalmology (Adult) D12/S/a.
- NHS England. 2013/14 NHS Standard Contract for Osteo-odonto-keratoprosthesis Service for Corneal Blindness D12/S(HSS)/c.

CLINICAL NEED and BURDEN OF DISEASE

Glaucoma is one of the most common ophthalmic conditions encountered in primary and secondary care⁴. The World Health Organization estimated that in 2010, glaucoma accounted for 2% of visual impairment and 8% of global blindness³. Disability adjusted life years attributable to glaucoma more than doubled between 1990 and 2010 due to the worldwide increase in the number of older people^{3,4}. Glaucoma is the leading cause of irreversible blindness in the world and the social and economic burden is likely to increase in the future because of longer life expectancy and an ageing population^{6,4}. 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 years³.

^b Expert personal communication.

In England and Wales, it is estimated that more than 500,000 people have glaucoma⁷. Approximately 10% of UK blindness registrations are attributed to glaucoma⁸. The overall prevalence of glaucoma is approximately 2% of people over the age of 40 years⁹. Direct healthcare costs of glaucoma treatment per person year by stage in the UK ranged from €457 at the earliest stage of diagnosis to €1,065 at the end stage¹⁰.

A trabeculectomy is the most common type of glaucoma surgery performed in the UK⁷, however only 5% of people with glaucoma require surgery¹¹. In 2011 it was estimated that approximately 5,300 trabeculectomy operations had been performed per year for the past 5 years¹².

In 2014-15 in England, there were 21,792 hospital admissions for glaucoma (ICD-10 H40), resulting in 4,804 bed days and 21,964 finished consultant episodes¹³.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE clinical guideline. Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension (CG85). April 2009.
- NICE quality standard. Glaucoma (QS7). March 2011.
- NICE interventional procedure guidance. Trabeculectomy ab interno for open angle glaucoma (IPG397). May 2011.
- NICE interventional procedure guidance. Trabecular stent bypass microsurgery for open glaucoma (IPD396). May 2011.
- NICE interventional procedure guidance. Canaloplasty for open angle glaucoma (IPD260). May 2008.

Other Guidance

- Scottish Intercollegiate Guidelines Network. Glaucoma referral and safe discharge. (SIGN 144). 2015¹⁴.
- Scottish Intercollegiate Guidelines Network. Antibiotic prophylaxis in surgery a national clinical guideline. (SIGN 104). 2014¹⁵.
- Canadian Agency for Drugs and technologies in Health. Injectable and topical antibiotics for the eye: clinical effectiveness (HTA). 2010¹⁶.

CURRENT TREATMENT OPTIONS

Medical, laser, and surgical options are available for managing glaucoma; these all aim to lower IOP. Typically, the patient is started on glaucoma eye drop monotherapy, with extra drops being added as required, so that two or more different types of drug can be used in cases that are difficult to control. If the maximum tolerated treatment regimen is unsuccessful, a laser intervention may be advised or the patient may proceed directly to surgery³. Current treatment options include^{3,17}:

- Topical drug therapies (eye drops):
 - Prostaglandin analogues to increase outflow – latanoprost; bimatoprost; tafluprost; travoprost.

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- Beta-adrenergic receptor blockers to decrease aqueous production – betaxolol; levobunolol; timolol; carteolol.
- Alpha-agonists to increase outflow and decrease aqueous production – apraclonidine; brimonidine.
- Carbonic anhydrase inhibitors to decrease aqueous production – brinzolamide; dorzolamide.
- Parasympathomimetic agents to increase outflow – pilocarpine.
- Oral therapy – carbonic anhydrase inhibitors. Patients may experience tingling in their fingers and toes, lethargy, and loss of appetite, making it unsuitable for long term treatment but useful for controlling acute increases in pressure or managing raised IOP in the short term while awaiting surgery³.
- Laser treatment – laser trabeculoplasty is used to improve drainage of fluid out of the eye. Cyclo diode and endocyclo diode laser of the ciliary body reduces fluid formation and can be used if standard surgery is not effective or unsuitable for the patient^c.
- Surgical treatment – trabeculectomy, which creates a guarded fistula into the wall of the eye to allow a slow egression of aqueous humour into the subconjunctival space and is currently considered the “gold standard” surgery.
- Newer surgical devices^c.
- Non-penetrating glaucoma procedures^c.

Following trabeculectomy surgery, scar tissue may sometimes block the newly created opening. Existing formulations of mitomycin-c may be used during the initial stages of surgery to prevent the conjunctiva healing onto the sclera¹⁸.

EFFICACY and SAFETY

Mitomycin ophthalmic (Mitosol) was approved for use in the USA in 2012 as an adjunctive therapy in glaucoma surgery. In the review that supported this approval, the FDA identified 22 prospective studies, of which 9 randomised-controlled and masked studies of mitomycin-c in glaucoma filtration surgery (primarily trabeculectomy) were considered to meet the criteria for adequate and well controlled trials¹⁹. The company have confirmed that they have no plans to conduct further trials, and the nine trials identified by the FDA are summarised below.

Trial	Carlson <i>et al.</i> 1995; mitomycin-c vs placebo.	Cohen <i>et al.</i> 1996; mitomycin-c vs placebo.
Sponsor	Investigator sponsored.	Investigator sponsored.
Status	Complete and published.	Complete and published.
Source of information	Publication ²⁰ .	Publication ²¹ .
Location	USA.	USA.
Design	Randomised, placebo-controlled.	Randomised, placebo-controlled.
Participants	n= 29; cataract and glaucoma requiring surgery; no known coexisting ocular disease or previous intraocular surgery.	n=71; glaucoma and cataracts requiring surgery for decreased vision, uncontrolled IOP, or to obtain better view of optic nerve; either open-angle or chronic angle closure glaucoma; no incisional intraocular surgery; no laser surgery within 2 months; no intraocular inflammation or neovascular glaucoma.

^c Expert personal communication.

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Schedule	Randomised to mitomycin-c, topical during surgery at 0.5mg/mL every 3.5 mins; or placebo, topical during surgery every 3.5 mins.	Randomised to mitomycin-c, topical during surgery at 0.5mg/mL every 2.5 mins; or placebo balanced-salt solution, topical during surgery every 2.5 mins.
Follow-up	6 to 30 months.	12 months.
Primary outcome/s	IOP at 8 and 12 months	IOP at 12 months.
Secondary outcome/s	% Laser suture lysis	-
Key results	For mitomycin-c vs placebo, respectively: IOP at 8 months, 12.3 (SE ±1.6) mmHg vs 15.2 (SE±1.5) mmHg; IOP at 12 months, 12.6 (SE±1.0) mmHg vs 16.2 (SE±1.5) mmHg; need for laser suture lysis, 43% vs 80% patients (p<0.05); mean number of laser treatments, 0.7 vs 2.0 (p<0.05); mean number of postoperative medications per patient for IOP control, 0.0 vs 1.8.	For mitomycin-c vs placebo, respectively: mean IOP reduction through to 12 months, 7.05 to 7.65 mmHg vs 2.62 to 3.83 mmHg (p=0.001 to 0.028).
Adverse effects (AEs)	-	Reported (AEs) included filtering blebs and persistent hypotony.

Trial	Costa <i>et al.</i> 1996; mitomycin-c vs placebo.	Robin <i>et al.</i> 1997; mitomycin-c vs placebo.
Sponsor	Investigator sponsored.	Investigator sponsored.
Status	Complete and published.	Complete and published.
Source of information	Publication ²² .	Publication ²³ .
Location	Brazil.	Southern India.
Design	Randomised, placebo-controlled.	Randomised, placebo-controlled.
Participants	n=28; medically uncontrolled advanced primary open angle or chronic angle closure glaucoma; planned to undergo primary trabeculectomy.	n=300; ≥21 years of age; no prior intraocular surgery; no chronic uveitis, no neovascular glaucoma; no best-corrected visual acuity <10/200 in treated eye.
Schedule	Randomised to topical mitomycin-c, at 0.2mg/mL intraoperatively for 3 mins; or topical saline solution, intraoperatively for 3mins.	Randomised to mitomycin-c 0.2mg/mL topical, during surgery for 2 mins; mitomycin-c 0.2mg/mL topical, during surgery for 4 mins; mitomycin-c 0.4 mg/mL topical, during surgery for 2 min; or placebo.
Follow-up	Up to 24 months.	12 months.
Primary outcome/s	IOP	IOP.
Secondary outcome/s	-	-
Key results	Mean IOP significantly lower in mitomycin-c group at day 1, 6 months and final visit (all p<0.05). Probability of IOP control was reportedly statistically significantly higher in mitomycin-c group compared to placebo.	Significant treatment-related difference in IOP, with decrease in IOP in all three mitomycin-c groups. Authors note that proportion of eyes achieving strict IOP control suggests possible dose relationship between mitomycin-c and IOP control.
Adverse effects (AEs)	AEs reported included short term complications associated with hypotony (more frequent in mitomycin-C group) and a high incidence (57%) of thin ischaemic blebs observed in active-treatment group.	AEs reported include cataracts, persistent choroidal effusions, hypotony and maculopathy.

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Trial	Andreanos <i>et al.</i> 1997; mitomycin-c.	Martini <i>et al.</i> 1997; mitomycin-c.
Sponsor	Investigator sponsored.	Investigator sponsored.
Status	Complete and published.	Complete and published.
Source of information	Publication ²⁴ .	Publication ²⁵ .
Location	Greece.	Italy.
Design	Randomised, controlled.	Randomised, controlled
Participants	n=46; aged 44-72 years; un-controlled primary open-angle glaucoma after previous filtering surgery failure.	n=48; undergoing surgery for controlled glaucoma; chronic open-angle glaucoma; no previous anti-glaucomatous or filtering surgery; no uncontrolled glaucoma with elevated IOP and or visual field deterioration or optic nerve damage; no other forms of glaucoma.
Schedule	Randomised to second trabeculectomy with mitomycin-c, topical at 0.4mg/mL, applied for 2-3 mins during surgery; or second trabeculectomy without mitomycin-c.	Randomised to standard trabeculectomy or trabeculectomy with intraoperative topical application of 0.1mg/ml mitomycin-c applied for 3 mins.
Follow-up	18 months.	12 months.
Primary outcome/s	IOP control, defined as IOP \leq 20 mmHg; visual acuity (VA).	IOP at 1 year, need for anti-hypertensive medicine during follow-up
Secondary outcome/s	-	-
Key results	For mitomycin-c vs no mitomycin-c group, respectively: mean postoperative IOP, 12.5 (SE \pm 3.2) mmHg vs 19.6 (SE \pm 6.1) (p<.001); good IOP control (\leq 20 mmHg), 83.3% vs 63.6%.	For mitomycin-c vs no mitomycin-c group, respectively: mean IOP at 1 year, 11.1 (SE \pm 3.1) mmHg vs 16.4 (SE \pm 6.1) mmHg (p=0.0001); need for antihypertensive medicine during follow-up, 6.6% vs 20%.
Adverse effects (AEs)	-	AEs at the 0.1mg/mL dose comprised mostly hypotony.

Trial	Rasheed 1999; mitomycin-c.	Wudunn <i>et al.</i> 2002; mitomycin-c or 5-fluorouracil.
Sponsor	Investigator sponsored.	Investigator sponsored.
Status	Complete and published.	Complete and published.
Source of information	Publication ²⁶ .	Publication ²⁷ .
Location	Egypt.	USA.
Design	Randomised, controlled.	Randomised, active-controlled.
Participants	n=25; aged 20-75 years; primary open-angle glaucoma or chronic angle-closure glaucoma; eligible for treatment with trabeculectomy.	n=103; uncontrolled intraocular pressure (IOP); eligible for primary trabeculectomy.
Schedule	Participants receive trabeculectomy with mitomycin-c, topical during surgery at 0.3-0.4mg/mL applied for 4 min in one eye and trabeculectomy alone in the other eye. Order of treatments and eye receiving mitomycin-c was randomised.	Randomised to trabeculectomy with either mitomycin-c, topical during surgery at 0.2mg/mL applied for 2 mins; or 5-fluorouracil, topical during surgery at 50 mg/mL applied for 5min.
Follow-up	12 months.	12 months.
Primary outcome/s	IOP control, defined as \leq 20 mmHg with or without medication.	Number of eyes achieving target pressures of 21, 18, 15, and 12mmHg at 6 and 12 months.
Secondary outcome/s	-	IOP; VA.

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Key results	For mitomycin-c vs no mitomycin-c group, respectively: successful IOP control, 23 eyes (92%) vs 17 eyes (68%); IOP \leq 20 mmHg without hypotensive medications, 21 eyes (84%) vs 12 eyes (48%); IOP $>$ 20 mmHg, 2 eyes (8%) vs 8 eyes (32%); postoperative laser suture lysis needed, 13 eyes (52%) vs 21 eyes (84%) ($p=0.015$); additional filters needed, 1 eye (4%) vs 7 eyes (28%) ($p=0.020$).	For mitomycin-c and 5-fluorouracil groups, respectively: IOP \leq 21mmHg, 89% vs 94%; IOP \leq 18mmHg, 87% vs 94%; IOP \leq 15mmHg, 78% vs 81%; IOP \leq 12mmHg, 65% vs 67%.
Adverse effects (AEs)		AEs reported included persistent choroidal effusions and bleb leaks. The mitomycin-c treated group reportedly had more complications, including hypotony, maculopathy and infection.

Trial	Sanders <i>et al.</i> 1999; mitomycin-c.
Sponsor	Investigator sponsored.
Status	Complete and published.
Source of information	Publication ²⁸ .
Location	USA.
Design	Randomised.
Participants	n=50; \geq 21 years of age; primary open-angle pseudoexfoliation or pigmentary glaucoma requiring trabeculectomy who had previously undergone either limbal cataract surgery or trabeculectomy; no diagnosis of neovascular, congenital, traumatic or secondary glaucoma.
Schedule	Randomised to mitomycin-c, topical during surgery at 0.2mg/mL/2mins; or mitomycin-c, topical during surgery at 0.4mg/mL/2mins.
Follow-up	12 months.
Primary outcome/s	% change in IOP.
Secondary outcome/s	-
Key results	IOP decreased from baseline in both treatment groups, but no statistically significant difference between groups were observed at any time point. The % decrease in IOP at 1 year was 46% and 55.8% in the 0.2 and 0.4mg/ml groups, respectively.
Adverse effects (AEs)	AEs included post-operative hypotony, choroidal effusions and haemorrhages, and wound leaks, and were slightly more frequent in the 0.4mg/mL group.

ESTIMATED COST and IMPACT

COST

The cost of mitomycin ophthalmic (Mitosol) in the UK is not yet known. However, Mitosol is already marketed in the USA, where a 0.2mg/vial kit for ophthalmic use costs \$359.00 per kit²⁹.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- | | |
|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> Reduced mortality/increased length of survival
<input type="checkbox"/> Other | <input checked="" type="checkbox"/> Reduced symptoms or disability
<input type="checkbox"/> No impact identified |
|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|

Impact on Health and Social Care Services

- | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> Increased use of existing services: <i>Mitosol is also used during tube surgery and preoperatively in some of the newer minimally invasive glaucoma surgery (MIGS) procedures like Xen implant^d</i> | <input checked="" type="checkbox"/> Decreased use of existing services: <i>due to its instability, current compounded mitomycin-c preparations must be refrigerated and light shielded in order to maintain a maximum shelf life of two weeks. Typically, in UK practice the prepared solution is discarded after 24 hours^d. During this time, the solution can degrade by as much as 25%³⁰. It does not require refrigeration or additional light shielding and has a shelf life of 24 months from date of sterilisation.</i> |
| <input type="checkbox"/> Re-organisation of existing services
<input type="checkbox"/> Other: | <input type="checkbox"/> Need for new services
<input type="checkbox"/> None identified |

Impact on Costs and Other Resource Use

- | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> Increased drug treatment: <i>the current cost of existing mitomycin-c preparations used for each trabeculectomy is less than £10^d. This will have a significant impact on reimbursement and will increase the cost of surgery.</i> | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs: | <input checked="" type="checkbox"/> Other reduction in costs: <i>current preparations of mitomycin-c need to be ordered by hospital pharmacy and are not available for use off the shelf whenever needed. They are reconstituted just before surgery by the hospital pharmacy or prepared in the theatre by the nursing staff. This has cost implications^d.</i> |
| <input type="checkbox"/> Other: | <input type="checkbox"/> None identified |

Other Issues

- | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| <input checked="" type="checkbox"/> Clinical uncertainty or other research question identified: <ul style="list-style-type: none"> • <i>Safety issues: mitomycin-c is classified as a hazardous drug, with documented health risks associated with its handling. Therefore the closed containment feature of Mitosol contains these hazards to the point of patient delivery.</i> • <i>In its usable liquid form, mitomycin-c is an unstable substance, degrading at a rate of 0.1%/hour²⁷. Mitosol is reconstituted at</i> | <input type="checkbox"/> None identified |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|

^d Expert personal communication.

the time of use and may result in a more standardised dose to each patient.

- *Mitomycin-c is currently used regularly in varying concentrations – from 0.01 to 0.4mg/ml, therefore a 0.2mg only concentration licensed drug (with a fixed application time, currently these range from 1-4min) may be very useful. It would not replace use of other concentrations, which may have different outcomes in certain circumstances (e.g. 0.4mg/ml is more efficacious and used for patients at high risk of scarring; however these patients have more risk of side effects including long term risk of leaking blebs and infections)^e.*

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