Aqueous Shunts and Stents for Glaucoma

Policy # 00421
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Ophthalmologic Techniques for Evaluating Glaucoma and Viscocanalostomy and Canaloplasty are addressed separately in medical policies 00089 and 00280, respectively.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider insertion of aqueous shunts approved by the U.S. Food and Drug Administration (FDA) as a method to reduce intraocular pressure (IOP) in patients with glaucoma where medical therapy has failed to adequately control intraocular pressure (IOP) to be eligible for coverage.

Based on review of available data, the Company may consider implantation of a single U.S. Food and Drug Administration (FDA)-approved microstent in conjunction with cataract surgery in patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of an aqueous shunt for all other conditions, including in patients with glaucoma when intraocular pressure (IOP) is adequately controlled by medications, to be investigational.*

Based on review of available data, the Company considers the use of a microstent for all other conditions to be investigational.*

Background/Overview
Glaucoma surgery is intended to reduce IOP when the target IOP cannot be reached with medications. Due to complications with established surgical approaches such as trabeculectomy, a variety of shunts are being evaluated as alternative surgical treatments for patients with inadequately controlled glaucoma. Microstents are also being evaluated in patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.
GLAUCOMA

Surgical procedures for glaucoma aim to reduce IOP resulting from impaired aqueous humor drainage in the trabecular meshwork and/or Schlemm's canal. In the primary (conventional) outflow pathway from the eye, aqueous humor passes through the trabecular meshwork, enters a space lined with endothelial cells (Schlemm's canal), drains into collector channels, and then into the aqueous veins. Increases in resistance in the trabecular meshwork and/or the inner wall of Schlemm's canal can disrupt the balance of aqueous humor inflow and outflow, resulting in an increase in IOP and glaucoma risk.

Treatment

Surgical intervention may be indicated in patients with glaucoma when the target IOP cannot be reached pharmacologically. Trabeculectomy (guarded filtration surgery) is the most established surgical procedure for glaucoma, allowing aqueous humor to directly enter the subconjunctival space. This procedure creates a subconjunctival reservoir, which can effectively reduce IOP, but commonly results in filtering “blebs” on the eye, and is associated with numerous complications (e.g., leaks or bleb-related endophthalmitis) and long-term failure. Other surgical procedures (not addressed in this policy) include trabecular laser ablation, deep sclerectomy, (which removes the outer wall of Schlemm’s canal and excises deep sclera and peripheral cornea), and viscocanalostomy (which unroofs and dilates Schlemm’s canal without penetrating the trabecular meshwork or anterior chamber).

The Trabectome™, an electrocautery device with irrigation and aspiration, has been used to selectively ablate the trabecular meshwork and inner wall of Schlemm’s canal without external access or creation of a subconjunctival bleb. IOP with this ab interno procedure is typically higher than the pressure achieved with standard filtering trabeculectomy. Canaloplasty involves dilation and tension of Schlemm’s canal with a suture loop between the inner wall of the canal and the trabecular meshwork. This ab externo procedure uses the iTrack™ illuminated microcatheter (iScience Interventional) to access and dilate the entire length of Schlemm’s canal and to pass the suture loop through the canal.

Aqueous shunts may also be placed in the anterior or posterior chamber to facilitate drainage of aqueous humor. Established shunts cleared by FDA include the Ahmed™ (New World Medical), Baerveldt® (Advanced Medical Optics), Molteno® (IOP), and EX-PRESS® mini-shunt (Alcon); which shunt aqueous humor between the anterior chamber and the suprachoroidal space. These devices differ by explant surface areas, shape, plate thickness, the presence or absence of a valve, and details of surgical installation. Generally, the risk of hypotony (low pressure) is reduced with aqueous shunts in comparison with trabeculectomy, but IOP outcomes are higher than after standard guarded filtration surgery. Complications of anterior chamber shunts include corneal endothelial failure and erosion of the overlying conjunctiva. The risk of postoperative infection is less than after trabeculectomy, and failure rates are similar, with about 10% of devices failing each year. The primary indication for aqueous shunts is when prior medical or surgical therapy has failed, although some ophthalmologists have advocated their use as a primary surgical intervention, particularly for selected conditions such as congenital glaucoma, trauma, chemical burn, or pemphigoid.

Aqueous stents are being developed as minimally penetrating methods to drain aqueous humor from the anterior chamber into the Schlemm canal or the suprachoroidal space. They include the iStent (Glaukos),
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which is a 1-mm long stent inserted into the end of the Schlemm canal by an internal approach through the cornea and anterior chamber; the second-generation iStent inject; the third-generation iStent supra, which is designed for ab interno implantation into the suprachoroidal space; and the CyPass (Transcend Medical) suprachoroidal stent.

Because aqueous humor outflow is pressure-dependent, pressure in the reservoir and venous system is critical for reaching the target IOP. Therefore, some devices may be unable to reduce IOP below the pressure of the distal outflow system used (eg, <15 mm Hg) and are not indicated for patients for whom very low IOP is desired (eg, those with advanced glaucoma). It has been proposed that stents such as the iStent®‡, CyPass™‡, and Hydrus Microstent may be useful in patients with early-stage glaucoma to reduce the burden of medications and problems with compliance. One area of investigation is patients with glaucoma who require cataract surgery. An advantage of ab interno shunts is that they may be inserted into the same incision and at the same time as cataract surgery. In addition, most devices do not preclude subsequent trabeculectomy if needed. It may also be possible to insert more than 1 shunt to achieve desired IOP. Therefore, health outcomes of interest are the IOP achieved, reduction in medication use, ability to convert to trabeculectomy, complications, and device durability.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration

The regulatory status of the various aqueous shunts and microstents is summarized in Table 1. The first-generation Ahmed (New World Medical), Baerveldt (Advanced Medical Optics), Krupin (Eagle Vision), and Molteno (Molteno Ophthalmic) aqueous shunts were cleared for marketing by the FDA through the 510(k) process between 1989 and 1993; modified Ahmed and Molteno devices were cleared in 2006. They are indicated for use “in patients with intractable glaucoma to reduce intraocular pressure where medical and conventional surgical treatments have failed.” The AquaFlow™‡ Collagen Glaucoma Drainage Device was approved by FDA through the premarket approval (PMA) process for the maintenance of the sub scleral space following nonpenetrating deep sclerectomy. In 2003, the EX-PRESS Mini Glaucoma Shunt was cleared for marketing by FDA through the 510(k) process. The EX-PRESS shunt is placed under a partial thickness scleral flap and transports aqueous fluid from the anterior chamber of the eye into a conjunctival filtering bleb. In 2016, the Xen® Glaucoma Treatment System (Allergan), which consists of the XEN45 Gel Stent preloaded into the XEN Injector, was cleared for marketing by FDA through the 510(k) process as an aqueous shunt for management of refractory glaucoma. FDA determined that this device was substantially equivalent to existing devices, specifically the Ahmed Glaucoma Valve and the EX-PRESS Glaucoma Filtration Device.

Table 1. Regulatory Status of Aqueous Shunts and Stents

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Type</th>
<th>FDA Status</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>AquaFlow</td>
<td>Staar Surgical</td>
<td>Drainage device</td>
<td>PMA</td>
<td>2001</td>
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<tr>
<td>Trabectome</td>
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<td>Electrocautery device</td>
<td>510(k)</td>
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<td>Aqueous glaucoma shunt</td>
<td>510(k)</td>
<td>&lt;1993</td>
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<td>Baerveldt</td>
<td>Advanced Medical</td>
<td>Aqueous glaucoma shunt</td>
<td>510(k)</td>
<td>&lt;1993</td>
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<tr>
<td>Krupin</td>
<td>Eagle Vision</td>
<td>Aqueous glaucoma shunt</td>
<td>510(k)</td>
<td>&lt;1993</td>
</tr>
<tr>
<td>Molteno</td>
<td>Molteno Ophthalmic</td>
<td>Aqueous glaucoma shunt</td>
<td>510(k)</td>
<td>&lt;1993</td>
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<tr>
<td>EX-PRESS</td>
<td>Alcon</td>
<td>Mini-glaucoma shunt</td>
<td>510(k)</td>
<td>2003</td>
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<td>XEN Gel Stent</td>
<td>AqueSys/Allergan</td>
<td>Aqueous glaucoma shunt</td>
<td>510(k)</td>
<td>2016</td>
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<td>Glaukos</td>
<td>Microstent</td>
<td>PMA</td>
<td>2012</td>
</tr>
<tr>
<td>CyPass</td>
<td>Transcend Medical</td>
<td>Suprachoroidal stent</td>
<td>PMA</td>
<td>2016</td>
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<tr>
<td>Hydrus™‡</td>
<td>Ivantis</td>
<td>Microstent</td>
<td>Not approved</td>
<td></td>
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<tr>
<td>SOLX™ Gold</td>
<td>SOLX</td>
<td>Micro-Shunt</td>
<td>Not approved</td>
<td></td>
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<tr>
<td>iStent inject™‡</td>
<td>Glaukos</td>
<td>Suprachoroidal stent</td>
<td>Not approved</td>
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</tr>
<tr>
<td>iStent supra™‡</td>
<td>Glaukos</td>
<td>Suprachoroidal stent</td>
<td>Not approved</td>
<td></td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration; PMA: premarket approval.

In 2012, the iStent Trabecular Micro-Bypass Stent (Glaukos) was approved by FDA through the PMA process for use in conjunction with cataract surgery for the reduction of IOP in adults with mild-to-moderate open-angle glaucoma currently treated with ocular hypotensive medication.

The labeling describes the following precautions:

1. The safety and effectiveness of the iStent Trabecular Micro-Bypass Stent has not been established as an alternative to the primary treatment of glaucoma with medications. The effectiveness of this device has been demonstrated only in patients with mild to moderate open-angle glaucoma who are currently treated with ocular hypotensive medication and who are undergoing concurrent cataract surgery for visually significant cataract.

2. The safety and effectiveness of the iStent Trabecular Micro-Bypass Stent has not been established in patients with the following circumstances or conditions, which were not studied in the pivotal trial:
   - In children
   - In eyes with significant prior trauma
   - In eyes with abnormal anterior segment
   - In eyes with chronic inflammation
   - In glaucoma associated with vascular disorders
   - In pseudophakic patients with glaucoma
   - In uveitic glaucoma
   - In patients with prior glaucoma surgery of any type, including argon laser trabeculoplasty
   - In patients with medicated IOP greater than 24 mm Hg
   - In patients with unmedicated IOP less than 22 mm Hg nor greater than 36 mm Hg after "washout" of medications
   - For implantation of more than a single stent
   - After complications during cataract surgery, including but not limited to, severe corneal burn, vitreous removal/vitrectomy required, corneal injuries, or complications requiring the placement of an anterior chamber intraocular lens (IOL)
   - When implantation has been without concomitant cataract surgery with IOL implantation for visually significant cataract

Note that use of the iStent has subsequently been reported for many of the circumstances or conditions listed above; most of the publications are case series.
In 2016, the CyPass Micro-Stent (Alcon Laboratories) was approved by FDA through the PMA process for use in combination with cataract surgery in adults with mild-to-moderate primary open-angle glaucoma.

The SOLX DeepLight Gold Micro-Shunt and Hydrus Microstent are currently in FDA-regulated trials. They have received regulatory approval in Europe, but have not been cleared by FDA for use in the United States.

FDA product codes: OGO, KYF.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD) for aqueous shunts and stents for glaucoma. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

AQUEOUS SHUNTS

This section reviews the evidence on aqueous shunts with FDA approval. Evidence on nonapproved devices is included in a later section.

Systematic Reviews

A 2006 Cochrane review evaluated 15 randomized or pseudo-randomized controlled trials (RCTs), with a total of 1153 participants, on the Ahmed, Baerveldt, Molteno, and Schocket shunts. Trabeculectomy was found to result in a lower mean IOP (by 3.8 mm Hg) than the Ahmed shunt at 1 year. This systematic review did not compare complications, because reviewers considered them to be too variably reported to permit comparative tabulation. There was no evidence of superiority of 1 shunt over another.

A technology assessment on commercially available aqueous shunts, including the Ahmed, Baerveldt, Krupin, and Molteno devices, for an American Academy of Ophthalmology (AAO) technology assessment was published in 2008. It indicated that the IOP will generally settle at higher levels (approximately 18 mm Hg) with aqueous shunts than after standard trabeculectomy (14-16 mm Hg) or after trabeculectomy with antifibrotic agents 5-fluorouracil or mitomycin C (8-10 mm Hg). In 1 study, mean IOPs with the Baerveldt shunt and adjunct medications were found to be equivalent to trabeculectomy with mitomycin C (13 mm Hg). Five-year success rates for the 2 procedures were found to be similar (50%). The assessment concluded that based on level 1 evidence, aqueous shunts were comparable with trabeculectomy for IOP control and duration of benefit. The risk of postoperative infection was less with aqueous shunts than after trabeculectomy. Complications of aqueous shunts were noted to include: immediate hypotony after surgery; excessive capsule fibrosis and clinical failure; erosion of the tube or plate edge; strabismus; and, very rarely, infection. The most problematic long-term consequence of anterior chamber tube placement was described as accelerated damage to the corneal endothelium.

A 2012 comparative effectiveness review on glaucoma treatments, prepared for the Agency for Healthcare Research and Quality, found that available data on the role of aqueous drainage devices in open-angle glaucoma (primary studies, systematic review) were inadequate to draw conclusions on the comparative effectiveness of these treatments versus laser and other surgical treatments.
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Baerveldt Glaucoma Shunt

Early results from the open-label, multicenter, randomized Tube Versus Trabeculectomy (TVT) study were reviewed in the 2008 AAO technology assessment and, in 2012, reported in a 5-year follow-up by Gedde et al. The study included 212 eyes of 212 patients (age range, 18-85 years), who had trabeculectomy and/or cataract extraction with intraocular lens implantation and uncontrolled glaucoma with IOP of 18 mm Hg or greater and 40 mm Hg or lower on maximally tolerated medical therapy, randomized to tube (Baerveldt shunt) or trabeculectomy. Excluding patients who had died, the study had an 82% follow-up rate at 5 years, with a similar proportion of patients in the tube and trabeculectomy groups. At 5 years, neither IOP (14.3 mm Hg in the shunt group vs 13.6 mm Hg in the trabeculectomy group) nor number of glaucoma medications (1.4 in the shunt group vs 1.2 in the trabeculectomy group) differed significantly based on intention-to-treat analysis. The cumulative probability of failure over the 5 years was lower in the shunt group (29.8%) than in the trabeculectomy group (46.9%), and the rates of reoperation were lower (9% vs 29%, respectively). The rates of loss of 2 or more lines of visual acuity were similar (46% in the shunt group vs 43% in the trabeculectomy group).

Ex-PRESS Mini Shunt

A 2014 publication described a U.S. multicenter randomized trial of trabeculectomy compared with EX-PRESS implantation in 120 patients (120 eyes). The groups were comparable at baseline, with a preoperative IOP of 25.1 mm Hg on a mean of 3.1 medications for the EX-PRESS group, compared with 26.4 mm Hg on a mean of 3.1 medications in the trabeculectomy group. Throughout 2 years of follow-up after surgery, the average IOP and number of medications were similar in the 2 groups. At 2 years, mean IOP was 14.7 mm Hg on 0.9 medications in the EX-PRESS group and 14.6 mm Hg on 0.7 medications in the trabeculectomy group. Surgical success was 90% and 87% at 1 year and 83% and 79% at 3 years in the EX-PRESS and trabeculectomy groups, respectively. Visual acuity returned to near baseline levels at 1 month after EX-PRESS implantation and 3 months after trabeculectomy (p=0.041), with a median time to return to baseline vision of 0.7 months and 2.2 months, respectively. Postoperative complications were higher after trabeculectomy (41%) than after EX-PRESS implantation (18.6%).

In 2009, de Jong reported a randomized study of the EX-PRESS mini shunt compared with standard trabeculectomy in 78 patients (80 eyes) with a diagnosis of open-angle glaucoma that could not be controlled with maximal-tolerated medical therapy. Five-year follow-up was reported in 2011. The 2 groups were similar after randomization, with the exception of difference in the mean age (62 years for the EX-PRESS group, 69 years for the trabeculectomy group). At an average 12 months’ follow-up, mean IOP had improved from 23 to 12 mm Hg in the EX-PRESS group and from 22 to 14 mm Hg in the trabeculectomy group. Both groups of patients used fewer antiglaucoma medications postoperatively than before the procedure (from 2.8 at baseline to 0.3 in the EX-PRESS group and from 3.0 at baseline to 0.6 in the trabeculectomy group). Twelve-month Kaplan-Meier success rates (defined as an IOP of >4 mm Hg and ≤18 mm Hg without use of antiglaucoma medications) were 82% for the EX-PRESS shunt and 48% for trabeculectomy. At 5 years, the success rates were not significantly different between the 2 groups. In the EX-PRESS group, IOP remained stable from year 1 (12.0 mm Hg) to year 5 (11.5 mm Hg), while in the trabeculectomy group, IOP decreased from year 3 (13.5 mm Hg) to year 5 (11.3 mm Hg). There were more complications after trabeculectomy than after EX-PRESS implantation.
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Two additional small RCTs were published in 2015 and 2016 by Wagschal et al (N=64) and Gonzalez-Rodriguez et al (N=63). Both trials corroborated the results of the earlier RCTs, reporting no differences between trabeculectomy and Ex-PRESS shunt groups on outcomes for mean IOP, success rates, number of medications used, or complication rates.

A 2015 Cochrane review evaluated the efficacy of adjunctive procedures for trabeculectomy. Three RCTs were included and compared trabeculectomy alone with trabeculectomy plus EX-PRESS Mini Shunt. These trials were rated as having high or unclear risk of bias using the Cochrane risk of bias tool. None of the RCTs reported a significant improvement for the EX-PRESS group. In pooled analysis, IOP was slightly lower in the combination group than in the trabeculectomy alone group (weighted mean difference, -1.58; 95% confidence interval [CI], -2.74 to -0.42). Pooled analysis also showed that subsequent cataract surgery was less frequent in the combination group than in trabeculectomy alone (relative risk, 0.34; 95% CI, 0.14 to 0.74). The combination group had a lower rate of some complications (eg, hyphema, needling).

**Xen Glaucoma Treatment System**

FDA documents include the clinical study evaluating the effectiveness and safety of the Xen Glaucoma Treatment System in 65 patients with refractory glaucoma. Effectiveness data were collected for 12 months and safety data for 18 months. The mean diurnal IOP was 25 mm Hg at baseline on a mean of 3.5 IOP-lowering medications. Approximately 76% of patients had a 12-month mean diurnal IOP reduction of 20% or more without increasing IOP-lowering medications. The mean IOP reduction at 12 months was -6.4 on a mean of 1.7 medications. The most common adverse events were glaucoma surgery, hypotony, IOP increase of 10 mm Hg or more, and needling procedures. FDA concluded that the Xen System was as safe and effective as predicate devices.

**Comparative Effectiveness of Shunts**

Five-year results of 2 RCTs comparing the Ahmed and Baerveldt shunts have been published. The Ahmed Baerveldt Comparison (ABC) study was a multicenter international RCT evaluating the comparative safety and efficacy of the Ahmed Glaucoma Valve FP7 and Baerveldt Glaucoma Implant BG 101-350 (1:1 ratio) in 276 adults with previous incisional eye surgery or refractory glaucoma. ABC was funded by National Eye Institute, Research to Prevent Blindness and New World Medical. Mean IOP was 14.7 mm Hg in the Ahmed group and 12.7 mm Hg in the Baerveldt group at 5 years (p=0.01). The number of glaucoma medications in use at 5 years, cumulative probability of failure at 5 years, and visual acuity at 5 years did not differ statistically significantly between the 2 groups. The number of patients with inadequately controlled IOP or reoperation for glaucoma was 46 (80%) with the Ahmed shunt and 25 (53%) with the Baerveldt shunt (p=0.003). The 5-year cumulative reoperation rate for glaucoma was 21% in the Ahmed group versus 9% in the Baerveldt group (p=0.01). Late complications were defined as those developing after 3 months. Late complications occurred in 56 (47%) patients in the Ahmed group and 67 (56%) patients in the Baerveldt group during 5 years of follow-up (p=0.08). The cumulative incidences of serious complications at 5 years were 16% and 25% in the Ahmed and Baerveldt groups, respectively (p=0.03).

The Ahmed Versus Baerveldt (AVB) study was an international, multicenter RCT enrolling 238 patients with uncontrolled glaucoma despite maximum tolerated medical therapy. AVB is funded by the Glaucoma Research Society of Canada. Patients were randomized in a 1:1 ratio to the Ahmed FP7 implant and the...
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Baerveldt 350 implant. Failure of the shunt implant was the primary outcome or was defined as any one of the following: IOP of less than 5 mm Hg or more than 18 mm Hg or less than a 20% reduction from baseline for 2 consecutive visits after 3 months; de novo glaucoma surgery required; removal of the implant; severe vision loss related to the surgery; or progression to no light perception for any reason. The cumulative failure rate was 53% in the Ahmed group and 40% in the Baerveldt group at 5 years (p=0.04). In the Ahmed and Baerveldt shunts, the mean percent reduction in IOP was 47% and 57% (p=0.001) and mean percent reduction in medication use was 44% and 61% (p=0.03), all respectively. Hypotony was reported in 5 (4%) patients in the Baerveldt group but not in the Ahmed group (p=0.02).

In summary, the comparative effectiveness of the Ahmed vs Baerveldt has been addressed in two trials, the AVB trial and the Ahmed Baerveldt Comparison ABC trial. The trials had similar results. Both of the devices lowered IOP. There was a small difference in reduction in IOP favoring Baerveldt (1.2 – 1.3 mmHg lower) and patients with Baerveldt required slightly fewer medications. The Baerveldt also had a higher rate of serious hypotony-related complications.

Section Summary: Aqueous Shunts
Evidence from RCTs exists for most of the FDA-approved aqueous shunts. Trial results are consistent that the magnitude of reduction in IOP following aqueous shunt placement is similar, or slightly inferior, to that following trabeculectomy. Shunts have fewer complications than trabeculectomy, and reduce the need for future operations. Overall, the risk-benefit ratio for shunts does not appear to differ substantially from that for trabeculectomy. The comparative effectiveness trials of the Ahmed and Baerveldt shunts showed similar overall improvement in health outcome with slightly larger reduction in IOP with Baerveldt but also higher rates of complications.

AQUEOUS MICROSTENTS WITH CATARACT SURGERY
Aqueous microstents have been used in conjunction with cataract surgery. The majority of evidence addresses a single stent as an adjunct to cataract surgery. Both the iStent and CyPass have RCTs comparing a single stent with cataract surgery to cataract surgery alone. There have also been studies of multiple implants which have all been performed with iStent devices.

iStent
Results from the iStent U.S. investigational device exemption (IDE) open-label 29 site multicenter randomized clinical trial were reported to the FDA in 2010, with 1-year results published in 2011 and 2-year results published in 2012. The objective of the trial was to measure the incremental effect on IOP from iStent implantation over that of cataract surgery alone and to determine the potential benefit of combining 2 therapeutic treatments into 1 surgical event. A total of 240 patients (mean age, 73 years) with cataracts and mild to moderate open-angle glaucoma (IOP ≤ 24 mm Hg controlled on 1-3 medications) underwent a medication washout period. Patients were randomized to undergo cataract surgery with iStent implantation or cataract surgery only if the unmedicated IOP was 22 mm Hg or higher and 36 mm Hg or lower. The mean number of medications at baseline was 1.5. The medicated IOP at baseline was 18.7 mm Hg in the stent group and 18.04 in the control group. After washout, the mean IOP was 25 mm Hg and mean visual acuity (logMAR) was 0.36. Follow-up visits were performed at 1, 3, 6, and 12 months. Results were assessed by intention-to-treat analysis with the last observation carried forward and per protocol analysis.
Of the 117 subjects randomized to iStent implantation, 111 underwent cataract surgery with stent implantation, and 106 (91%) completed the 12-month postoperative visit. Of the 123 subjects randomized to cataract surgery only, 117 underwent cataract surgery and 3 exited the study because of complications of cataract surgery. Of the remaining 114 subjects, 112 (91%) completed the 12-month visit. The proportion of eyes meeting both the primary (unmedicated IOP ≤ 21 mm Hg) and secondary outcomes (IOP reduction ≤ 20% without hypotensive medications) was higher in the treatment group than in the control group through 1-year follow-up. At 1-year follow-up, 72% of treatment eyes and 50% of control eyes achieved the primary efficacy end point. The proportion of patients achieving the secondary efficacy end point at 1 year was 66% in the treatment group versus 48% in the control group. Ocular hypotensive medications were initiated later in the postoperative period and used in a lower proportion of patients in the treatment group throughout 1-year follow-up (eg, 15% vs 35% at 12 months). The mean reduction in IOP was similar in the 2 groups, with a slightly higher level of medication used in the control group (mean, 0.4 medications) in comparison with the treatment group (0.2 medications) at 1 year.

At 2-year follow-up, there were 199 of the original 239 patients (83%) remaining in the study. The primary end point, IOP of 21 mm Hg or less without use of medication, was reached by 61% of patients in the treatment group compared to 50% of controls (p = 0.036). The secondary outcomes of IOP reduction of 20% or more without medication (53% vs 44%) and mean number of medications used (0.3 vs 0.5) were no longer significantly different between the groups at 2 years. As noted by FDA, this study was conducted in a restricted population with an unmedicated IOP of 22 mm Hg or higher and a medicated IOP of 36 mm Hg or lower. Study results suggested that microstent treatment in this specific group likely improved outcomes at 1 year compared with cataract surgery alone; however, 2-year results make it difficult to conclude with certainty that health outcomes improved.

In 2010, Fea et al reported a randomized, double-blind, trial of 36 cataract surgery patients who did or did not receive an iStent implantation (2:1 ratio). Inclusion criteria were a previous diagnosis of primary open-angle glaucoma with an IOP above 18 mm Hg at 3 separate visits and taking 1 or more hypotensive medications. Investigators were masked to the treatment condition and conducted follow-up at 24 hours, 1 week, and 1, 2, 3, 6, 9, 12, and 15 months. Prescription of hypotensive medications was performed according to preset guidelines. Primary outcomes were IOP and reduction in medication use over 15 months and IOP after a 1-month washout of ocular hypotensive agents (16 months postoperatively). At baseline, IOP averaged 17.9 mm Hg with 2.0 medications in the stent group and 17.3 mm Hg with 1.9 medications in the control group. Mean IOP at 15 months was 14.8 mm Hg with 0.4 medications in the stent group and 15.7 mm Hg with 1.3 medications in the control group. Eight (67%) of 12 patients in the stent group and 5 (24%) of 21 in the control group did not require ocular hypotensive medication. Because treatment compliance is an ongoing concern for most ophthalmologists, trialists sought to keep patients as medication-free as possible postoperatively. After washout of medications, mean IOP was 16.6 in the stent group and 19.2 in the control group. No adverse events related to stent implantation were reported. Four-year follow-up from this study was published in 2015. Twenty-four of 36 patients were available at 4 years. Differences between treatment groups remained nonsignificant (mean IOP, 15.9 mm Hg in the stent group vs 17 mm Hg in the control group).
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CyPass
FDA evaluated the clinical performance of the CyPass Micro-Stent system based on the pivotal COMPASS trial (NCT01085357). COMPASS was a multicenter RCT comparing the safety and efficacy of CyPass Micro-Stent plus cataract surgery with cataract surgery alone for treating mild-to-moderate primary open-angle glaucoma in patients undergoing cataract surgery. Vold et al published 2-year results in 2016. A total of 505 patients (1 eye per patient) were assigned in a 1:3 ratio to phacoemulsification only (control) or to suprachoroidal microstenting with phacoemulsification (microstent). Baseline mean IOPs and number of IOP-lowering medications were similar in the 2 treatment groups (≈24.4 mm Hg and 1.4 medications, respectively). In the intention-to-treat analysis, 58% of controls versus 73% of microstent patients achieved 20% or greater unmedicated IOP lowering at 24 months compared to baseline (p=0.002). The difference in mean IOP reduction at 24 months was 1.8 mm Hg (95% CI, 1.0 to 2.6 mm Hg; p<0.001), favoring the microstent group. In the control group, 59% were medication free at 24 months versus 85% in the microstent group. Mean medication use decreased to 0.6 drugs at 24 months in the control group and to 0.2 drugs in the microstent group (p<0.001). There were no vision-threatening microstent-related adverse events. Thirty-nine percent of microstent patients versus 36% of control patients experienced ocular adverse events in the 24-month period. The following ocular adverse events were reported: hypotony (3% microstent vs 0% control), maculopathy (1.3% microstent vs 0.8% control), corneal edema (4% microstent vs 2% control), cyclodialysis cleft greater than 2 mm in circumference (2% microstent vs 0% control), iritis (9% microstent vs 4% control), and subconjunctival hemorrhage (2% microstent vs 1% control). Best-corrected visual acuity was 20/40 or better in more than 98% of all patients. Eleven patients in the microstent group versus 1 patient in the control group died during the 24-month period; however, the deaths were classified as unrelated to the intervention.

Multiple Stents
Fernández-Barrientos et al (2010) compared 2 iStent devices plus cataract surgery to cataract surgery alone in 33 patients with open-angle glaucoma or ocular hypertension who were undergoing cataract surgery. The study was performed at a single center in Spain. Eligible eyes had a medicated IOP between 17 and 31 mm Hg (exclusive) and between 21 and 35 mm Hg after medication washout. Mean IOP reduction was greater in the iStent plus surgery group (6.6 mm Hg) than in the surgery alone group (3.9 mm Hg; p=0.002). The mean number of IOP-lowering medications was also significantly lower in the iStent group (0.0 vs 0.7, respectively; p=0.007). Use of multiple iStent devices with cataract surgery was reported in an open-label, prospective series of 53 eyes (47 patients) in 2012. Twenty-eight of 53 eyes had implantation of 2 stents and 25 had implantation of 3 stents, based on the need for greater IOP control, as determined by the operating surgeon. Best-corrected visual acuity improved or remained stable in 89% of eyes. IOP decreased from a mean of 18.0 to 14.3 mm Hg, and the number of hypotensive medications decreased from a mean of 2.7 to 0.7 at 1 year postoperatively. Target IOP was reached in 77% of eyes, while 59% of patients discontinued all medications for the study eye. At 1 year, the mean number of hypotensive medications decreased to 1.0 in the 2-stent group and 0.4 in the 3-stent group. Medication use ceased in 46% of eyes in the 2-stent group and in 72% in the 3-stent group. Stent blockage occurred in the early postoperative period in 15% of eyes and was successfully treated with laser. At least 1 other prospective case series has been published. It enrolled 39 patients with open-angle glaucoma and IOP between 18 mm Hg and 30 mm Hg. Each patient
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received 2 microstents and medications as needed, and was followed for 3 years. At study completion, mean reduction in IOP was 9.1 mm Hg (95% CI, 8.0 to 10.1). There was 1 postoperative complication (hyphema), which resolved without further intervention.

Section Summary: Aqueous Microstents
Two identified RCTs compared cataract surgery plus a single iStent to cataract surgery alone. Results of these trials were mixed, with 1 showing a significant benefit in the stent group and the other reporting no statistically significant benefit but similar effect size. A trial comparing 2 iStents with cataract surgery versus cataract surgery alone reported similar results. One RCT compared CyPass plus cataract surgery to cataract surgery alone. Reduction in IOP was greater and fewer IOP-lowering medications were needed in the CyPass group at 2 years. A low rate of complications (eg, stent malposition, hyphema) was reported in all trials.

Aqueous Shunts and Stents Not Approved by the FDA
iStent inject
A 2014 industry-sponsored, multicenter, unblinded, randomized trial compared implantation of 2 iStent inject devices to 2 ocular hypotensive agents. The 192 patients enrolled in this unmasked trial had an IOP not controlled by 1 hypotensive medication. At 12-month follow-up, the 2 groups were comparable for IOP reduction of at least 20%, IOP of 18 mm Hg or less, and mean decrease in IOP. A greater proportion of patients in the iStent inject group achieved an IOP reduction of at least 50% (53.2% vs 35.7%, respectively). One patient in the iStent inject group experienced elevated IOP (48 mm Hg) and 4 required ocular hypotensive medication. Longer term studies are in progress.

Hydrus Microstent
In 2015, Pfeiffer et al reported a single-masked randomized trial with 100 patients (100 eyes) that evaluated the effectiveness of the Hydrus Microstent when combined with cataract surgery versus cataract surgery alone. At the 24-month follow-up, the proportion of patients with a 20% reduction in IOP was significantly higher with the Hydrus Microstent (80% vs 46%, p<0.001) and the mean IOP after medication washout was lower (16.9 mm Hg vs 19.2 mm Hg, p=0.009) compared with cataract surgery alone. The group with the Hydrus Microstent was using significantly fewer medications (0.5 vs 1.0, p=0.019) and proportion of patients using no hypotensive medications was higher when the Hydrus Microstent was inserted at the time of cataract surgery (73% vs 38%, p=0.001).

OTHER INDICATIONS FOR GLAUCOMA TREATMENT
Glaucoma shunts and microstent have also been studied in patients with other indications for glaucoma treatment. The following paragraphs describe the comparison of implantation of single versus multiple stents or multiple stents versus medical management.

One RCT comparing the efficacy of 1 iStent to multiple iStent devices was published in 2015. This study, from a single institution in Armenia, randomized 119 patients with open-angle glaucoma and an IOP between 22 and 38 mm Hg (off medications) to 1 stent (n=38), 2 stents (n=41), or 3 stents (n=40). Randomization was performed using a pseudorandom number generator. The main outcome measure was IOP at 12 months. The primary end point was the percentage of patients with a 20% or more reduction in
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IOP off medications. This end point was reached by 89.2% (95% CI, 74.6% to 97.0%) of the 1-stent group, by 90.2% (95% CI, 76.9% to 97.3%) of the 2-stent group, and by 92.1% (95% CI, 78.6% to 98.3%) of the 3-stent group. The secondary end point (percentage of patients achieving an IOP ≤15 mm Hg off medication) was reached by 64.9% (95% CI, 47.5% to 79.8%) of the 1-stent group, by 85.4% (95% CI, 70.8% to 94.4%) of the 2-stent group, and by 92.1% (95% CI, 78.6% to 98.3) of the 3-stent group. No between-group statistical comparisons were reported.

Vold et al (2016) reported results of an RCT comparing 2 standalone iStent implants to topical travoprost (1:1 ratio) in 101 phakic eyes with IOP between 21 and 40 mm Hg inclusive and newly diagnosed primary open-angle glaucoma, pseudo-exfoliative glaucoma, or ocular hypertension that had not undergone any prior treatment. The patients were not undergoing cataract surgery. The study was unmasked and methods for allocation concealment and calculation of power were not described. One hundred patients (54 iStent; 47 travoprost) completed 24 months of follow-up and 73 completed 36 months of follow-up. The trial was performed at a single center in Armenia. Statistical analyses were not provided. Baseline mean IOP was 25 mm Hg in both groups. Mean IOP at 3 years was 15 mm Hg in both groups. Medication (or second medication) was added in 6 eyes in the iStent group and 11 eyes in the travoprost group. Progression of cataract was reported in 11 eyes in the iStent group versus 8 eyes in the travoprost group, with cataract surgery being performed in 5 eyes in the iStent group and 1 eye in the travoprost group. The results suggest that 2 iStents might reduce the number of medications required to maintain target IOP compared to travoprost but also hasten time to cataract surgery. However, the study methods were poorly reported and statistical analyses were not reported. The study was funded by the iStent manufacturer.

Section Summary: Other Indications for Glaucoma Treatment
One RCT compared a single iStent to 2 or 3 stents; it reported similar rates of the primary outcome among groups (percentage of patients with ≥20% reduction in IOP). There were some numeric group differences in secondary outcomes, but statistical testing was not reported. One RCT compared 2 iStents to travoprost. Two iStents might reduce the number of medications required to maintain target IOP compared to travoprost but could also hasten time to cataract surgery but the RCT was not well reported.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

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<thead>
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<th>NCT No.</th>
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<td>NCT01444040</td>
<td>A Prospective, Randomized Evaluation of Subjects With Open-angle Glaucoma, Pseudoxfoliative Glaucoma, or Ocular Hypertension Naive to Medical and Surgical Therapy, Treated With Two Trabecular Micro-bypass Stents (iStent Inject) or Travoprost Ophthalmic Solution 0.004%</td>
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<td>NCT01456390</td>
<td>A Prospective Evaluation of Open-Angle Glaucoma Subjects</td>
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With One Prior Trabeculectomy Treated Concurrently With One Suprachoroidal Stent and Two Trabecular Micro-bypass Stents and a Postoperative Prostaglandin


NCT02023242* A Prospective, Multicenter, Randomized Comparison of the Hydrus to the iStent for Lowering Intraocular Pressure in Primary Open Angle Glaucoma 152 Jan 2018

NCT01539239# The Safety and Effectiveness of the Hydrus Aqueous Implant for Lowering Intraocular Pressure in Glaucoma Patients Undergoing Cataract Surgery, A Prospective, Multicenter, Randomized, Controlled Clinical Trial 1200 Jan 2018

NCT02700984* An Observational Multicenter Clinical Study to Assess the Long-Term Safety of the CyPass Micro-Stent in Patients With Primary Open Angle Glaucoma Who Have Completed Participation in the COMPASS Trial 300 Mar 2018

NCT01461278* A Prospective, Randomized, Single-Masked, Controlled, Parallel Groups, Multicenter Clinical Investigation of the Glaukos Suprachoroidal Stent Model G3 In Conjunction With Cataract Surgery 1200 Apr 2019

NCT02964676 Clinical Efficacy and Safety of Minimally Invasive Glaucoma Surgery on Chinese Primary Angle Closure Glaucoma 246 Dec 2019

NCT01841450* A Prospective, Randomized, Controlled, Parallel Groups, Multicenter Post-Approval Study Of The Glaukos® iStent® Trabecular Micro-Bypass Stent System In Conjunction With Cataract Surgery 360 Dec 2023

Unpublished

NCT01282346* Clinical Evaluation of the SOLX Gold Shunt for the Reduction of Intraocular Pressure (IOP) in Refractory Glaucoma 60 Dec 2015 (completed)

NCT02024464* A Prospective, Multicenter, Randomized Comparison of the Hydrus Microstent to the iStent for Lowering Intraocular Pressure in Glaucoma Patients Undergoing Cataract Surgery 300 Jan 2017 (unknown)

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty societies and 2 academic medical centers while this policy was under review in 2013. The input supported use of aqueous shunts in patients with moderate to severe glaucoma uncontrolled by medication. Input supported use of a single microstent
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in patients with mild to moderate glaucoma undergoing cataract surgery to reduce side effects of medications and to avoid noncompliance.

Summary
For individuals who have refractory open-angle glaucoma who receive aqueous shunts, the evidence includes RCTs and single-arm studies. Relevant outcomes are change in disease status, functional outcomes, medication use, and treatment-related morbidity. RCTs assessing FDA-approved shunts have shown that the use of large externally placed shunts reduces IOP to slightly less than standard filtering surgery (trabeculectomy). Reported shunt success rates are as good as trabeculectomy in the long term. FDA-approved shunts have different adverse event profiles and avoid some of the most problematic complications of trabeculectomy. Two trials have compared the Ahmed and Baerveldt shunts. Both found that eyes treated with the Baerveldt shunt had slightly lower average IOP at 5 years than eyes treated with the Ahmed but the Baerveldt also had a higher rate of serious hypotony-related complications. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have mild-to-moderate open-angle glaucoma who receive aqueous microstents during cataract surgery, the evidence includes RCTs and safety data from case series. Relevant outcomes are change in disease status, functional outcomes, medication use, and treatment-related morbidity. Two microstents have received FDA approval for use in conjunction with cataract surgery for reduction of IOP in adults with mild-to-moderate open-angle glaucoma currently treated with ocular hypotensive medication. RCTs have been conducted in patients with cataracts and less advanced glaucoma, where IOP is at least partially controlled with medication. Trial results have shown that IOP may be lowered below baseline with decreased need for medication through the first 2 years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with indications for glaucoma treatment other than cataract surgery or refractory open-angle glaucoma who are treated with aqueous shunts or microstents, the evidence includes RCTs. Relevant outcomes are change in disease status, functional outcomes, medication use, and treatment-related morbidity. One RCT compared a single microstent to multiple microstents. This study reported no difference on the primary outcome (percentage of patients with ≥20% reduction in IOP); secondary outcomes favored the multiple microstent group. One RCT compared 2 iStents to travoprost. The study did not report statistical comparisons. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

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Policy History
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Current Effective Date: 06/21/2017
05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. New policy.
09/04/2014 Medical Policy Committee review
01/01/2015 Coding Update
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2016 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2016 Coding update
11/03/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017 Medical Policy Committee review
06/21/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2018

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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