Clinical Review Criteria
Microinvasive Glaucoma Surgery (MIGS)

- Cypass
- XEN Gel Implant (XEN® Gel stent) for Glaucoma

Criteria
For Medicare & Non-Medicare Members
iStent device – CPT 0191T, 0376T
Xen Gel Implant – 0449T, 66183
All requests must go to Medical Director review

Cypass device – CPT 0474T
The Cypass device was taken off the market 8/29/2018 by the manufacturer due to safety concerns. This device will no longer be covered KPWA members.

Background
The term micro-invasive or minimally invasive glaucoma surgery (MIGS) refers to a group of newer surgical procedures that are performed by using an ab interno (from inside the eye) approach via gonioscopic guidance and involve minimal trauma to ocular tissues. In contrast to external filtration surgeries such as trabeculectomy and aqueous tube shunt, these procedures are categorized as internal filtration surgeries. Compared with traditional filtration surgery, MIGS holds the promise of faster recovery time and less severe complications.

It is this potentially improved safety profile that opened up the indications for MIGS to include patients with early-stage glaucoma to reduce the burden of medications and problems with compliance (due to eye drop application difficulty, cost, cosmetic effects, and frequency). Another 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. Therefore, health outcomes of interest are the IOP achieved, reduction in medication use, ability to convert to trabeculectomy, complications, and device durability.

There are three FDA approved/cleared micro-invasive surgical stents, the iStent Trabecular Micro-Bypass Stent (2011), the CyPass Micro-Stent System (July 2016), and the XEN Glaucoma Treatment System (Nov 2016). The iStent is a small (1 mm x 0.5 mm) L-shaped titanium device that is inserted into Schlemm’s canal to augment the natural outflow system. CyPass is a 6.35 mm long fenestrated microstent made of biocompatible polyimide inserted into the supraciliary space, thus using an alternative outflow system. The XEN45 is a 6 mm long porcine-derived gelatin stent inserted into the subconjunctival space, bypassing the natural outflow system.

Both iStent and CyPass were FDA approved for use in combination with cataract surgery to reduce IOP in adults with mild or moderate OAG and a cataract that are currently being treated with medication to reduce IOP. XEN45 was granted FDA clearance for the management of refractory glaucoma, including cases where previous surgical treatment has failed, cases of primary open angle glaucoma, and pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.

07/08/2019: MTAC REVIEW
**XEN Gel Implant (XEN® Gel stent) for Glaucoma**

**BACKGROUND**

Glaucoma is one of the leading causes of blindness affecting almost 65 million people worldwide. It is a progressive eye disease that causes an irreversible, but potentially preventable damage to the optic nerve leading to visual field and acuity loss. Glaucoma is a heterogeneous group of optic neuropathies, the most common etiology of which is primary open angle glaucoma (POAG) caused by either elevated intraocular pressure (IOP-related) or an alternative mechanism (non-IOP-related) (Lavia 2017, Agrawal 2018, Buffault 2019).

Currently, the only proven treatment for IOP-related glaucoma is lowering the intraocular pressure with the aim of preventing additional damage to the ganglionic cells and the optic nerve. Treatment is typically initiated with topical ocular hypotensive medications. Surgery is performed for the treatment of patients with moderate to advanced glaucoma inadequately controlled by the maximally tolerated medical therapy. Currently trabeculectomy is considered the gold standard and most common surgical procedure used for uncontrolled glaucoma. It is an incisional (ab-externo) filtering surgery that lowers the IOP by creating a pathway for release of aqueous humor from the anterior chamber (AC) of the eye into a subconjunctival space known as the filtration bleb (FB). Trabeculectomy is highly effective at lowering the IOP but, is an invasive procedure that requires intense postoperative care and may be associated with complications including hemorrhage, hypotony, scarring, aqueous leak, inflammation of the bleb, and endophthalmitis (Kerr 2017, Hengerer 2017, Agrawal 2018, Yook 2018, Buffault 2019, Heidinger 2019).

Over the last several years, several new devices and less invasive procedures have been developed with the intention of achieving lower IOP with shorter surgical time, less risk, and faster recovery. These are collectively termed “minimally invasive glaucoma surgery (MIGS)” and include trabecular drainage devices (e.g. iStent, iStent inject, and Hydrus microstent), suprachondral drainage devices (such as Cypass and iStent supra), and subconjunctival drainage devices including Express shunt, InnFocus micro shunt, and XEN Gel implant. However, some investigators debate whether XEN Gel should be considered as a MIGS (Kerr 2017, Widder 2018).

The XEN®45 Gel implant or stent (Allergan plc, Dublin), the focus of the current review, is intended to decrease IOP by creating a permanent outflow pathway from the anterior chamber to the subconjunctival space through a scleral channel. It is a 6mm long, 45µm wide, soft hydrophilic tube made of a porcine gelatin cross-linked with glutaraldehyde. The implant is stiff when dehydrated but becomes soft and flexible within 1-2 minutes of contact with the aqueous humor, allowing it to conform to the ocular tissue, thus theoretically minimizing migration, erosion, and endothelial damage (Pillunat 2017, Gregorio 2018, Karimi 2018).

The XEN® Gel implant procedure can be performed under local or topical anesthesia. The device is inserted from the anterior chamber (ab-interno) using a pre-loaded disposable injector and implanted into the subconjunctival space opposite the incision with minimal conjunctival tissue disruption. The tube creates a conduit that is intended to maintain outflow of the aqueous humor at 2-2.5µL/min as calculated by Hagen-Poiseuille equation (where the diameter and length of the tube defines the amount of outflow). The channel created leads to the formation of a bleb that assists in the drainage of the aqueous fluid. The bleb is a significant risk factor for scar formation and thus an antimetabolite such as mitomycin C (MMC) at a concentration of 0.1-0.2 mg/ml is generally injected in the subconjunctiva approximately 20 minutes before the procedure to reduce the risk of scar formation. XEN Gel uses the same pathway as trabeculectomy, but with the difference of leaving a foreign body in the tissue. The implant is frequently used in combination with phacoemulsification and lens implantation. In that case, the implantation of the stent is performed after placement of the posterior chamber intraocular lens (IOL) (Pillunat 2017, Ker 2017, Gregorio 2017, Karimi 2018, Buffault 2019).

There are three generations of XEN Gel implants (diameter sizes 45, 63, and 140 µm), but XEN®45 Gel is the one currently recommended and available.

XEN® Gel Stent and XEN Injector received US Food and Drug Administration (FDA) approval in November 2016 for use in patients with refractory glaucoma who failed previous surgical treatment or in patients with primary open angle glaucoma, pseudo exfoliative or pigmentary glaucoma with open angle that are unresponsive to maximum tolerated medical therapy.

The use of XEN Gel stent is contraindicated in certain conditions including angle closure glaucoma; previous glaucoma shunt/valve in the target quadrant; presence of conjunctival scarring; prior conjunctival surgery; other eye pathologies e.g. pterygium in the target quadrant; active eye inflammation; active iris neovascularization; AC IOL; presence of intraocular silicone oil; vitreous present in the AC; impaired episcleral venous drainage;...
suspected or known allergy to any of the device components or the drugs used with the procedure; and/or a history of dermatological keloid formation (Gregorio 2018).

Reported adverse events associated with XEN Gel implant include hypotony, hyphema, choroidal effusion, choroidal detachment, leaking bleb, bleb inflammation, subconjunctival hemorrhage, conjunctival erosion, conjunctival perforation, stent obstruction, implant migration, extrusion, brakeage, and implant exposure, and the need for secondary interventions and/or intraocular surgeries. Serious complications such as endophthalmitis, and visual acuity loss due to retinal detachment have also been reported (Kerr 2018, Lapira 2018, Lim 2018, Arnold 2019).

**Conclusion:**
- There is no published high-quality evidence from randomized controlled trials (to date) to determine the comparative effectiveness and safety of XEN Gel implantation versus trabeculectomy or other minimally invasive procedure used to lower IOP in patients with open angle glaucoma uncontrolled with optimal local medications.
- Low quality evidence from several prospective and retrospective observational studies suggest that XEN Gel implant lowers the IOP and reduces the number of IOP-lowering medication used in selected patients with open angle glaucoma uncontrolled with optimal local medications. The results, however, must be interpreted with caution due to the non-randomized design, potential confounding, and other inherent limitations of observational studies.
- The success rates varied between studies from 37-68% depending on definition of success based on the level of IOP reached, duration of follow up, use of topical medications, and need for revision surgeries.
- XEN Gel implant is associated with intra-and post-operative adverse events (AEs). Many were reported to resolve spontaneously without the need for intervention. However, few were serious and/or required immediate and inevitable interventions.
- More than one third of the eyes require additional surgeries after XEN Gel implant.

**Articles:** The literature search did not identify any randomized controlled trials that compared the safety and efficacy of XEN45 Gel implant versus trabeculectomy or any other surgical procedure. The search revealed 3 systematic reviews with meta-analyses that pooled the results of the different of MIGS procedures, two studies (published in 3 articles on the earlier generations of the implant (XEN140 and XEN 63), around 10 observational studies with pre-post comparisons after XEN45 Gel implant with or without cataract surgery, and one retrospective observational study that compared the results the microstent implant to those of a trabeculectomy procedure.

The meta-analyses of studies on MIGS as well as the studies using the earlier generations of XEN Gel (60 and 140) were excluded. The observational study with a comparison group (Schlenker, 2017) was critically appraised (Evidence table 1) and the larger prospective and retrospective observational studies were summarized in a following table. See Evidence Table.

The use of light therapy in the treatment of Seasonal Affective Disorder (SAD) does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

<table>
<thead>
<tr>
<th>Date Created</th>
<th>Date Reviewed</th>
<th>Date Last Revised</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/06/2018</td>
<td>02/06/2018MPC, 02/05/2019MPC, 02/04/2020MPC</td>
<td>11/15/2019</td>
</tr>
</tbody>
</table>

MPC Medical Policy Committee

<table>
<thead>
<tr>
<th>Revision History</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/05/2018</td>
<td>MPC approved criteria for commercial members</td>
</tr>
<tr>
<td>10/08/2018</td>
<td>Non-coverage language for the CyPass device</td>
</tr>
<tr>
<td>Date</td>
<td>Event Description</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>11/14/2018</td>
<td>Language regarding iStent added</td>
</tr>
<tr>
<td>08/06/2019</td>
<td>MTAC review for Xen Gel was added</td>
</tr>
<tr>
<td>11/15/2019</td>
<td>Added all requests for Xen Gel must go to Medical Director for review</td>
</tr>
</tbody>
</table>

**Codes**
- CPT: 0253T
- Cypass: 0474T
- iStent: 0191T, 0376T
- Xen Gel: 0449T, 66183