

Flow Dynamics of the EX-PRESS® Glaucoma Filtration Device

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Abstract

Trabeculectomy has been the gold standard of glaucoma surgery for over 40 years, but the technique is imprecise and is associated with complications. Glaucoma filtration implants offer an alternative to trabeculectomy. The EX-PRESS® device is a miniature implant of which the standardized ostium allows a potentially more reproducible outflow by creating a constant diameter channel for fluid to drain out of the anterior chamber into the subconjunctival space. In clinical studies, the EX-PRESS device has demonstrated similar efficacy to trabeculectomy in terms of reduction of intraocular pressure, but with a lower incidence of hypotony and choroidal effusions, a result of its standardized ostium. Glaucoma patients require fewer postoperative interventions and less glaucoma medication after EX-PRESS device compared with trabeculectomy, and have faster visual recovery to their preoperative baseline compared with trabeculectomy.

Keywords

Aqueous outflow, filtration surgery, glaucoma, intraocular pressure, flow dynamics, trabeculectomy

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Glaucoma is one of the leading causes of blindness worldwide. It was estimated that in 2010, 60.5 million people had glaucoma and this was projected to increase to 79.6 million by 2020.¹ Glaucoma is not considered a single disease, but rather a group of diseases associated with three major characteristics: optic neuropathy with excavation of the optic cup and associated loss of the neuroretinal rim; retinal nerve fiber layer thinning; and a resultant loss of visual field.

Advancing age, family history, race, and elevated intraocular pressure (IOP) are the major risk factors for optic nerve degeneration in glaucoma. Currently, the only risk factor that may be modified is the IOP: this can be achieved by either reducing the production of or increasing the outflow of aqueous humor.

An understanding of the complex mechanisms that regulate aqueous humor circulation is essential for the management of glaucoma. Aqueous humor leaves the eye via two pathways: the trabecular meshwork and the uveoscleral pathway, with 75 % of the resistance to aqueous humor outflow being located within the trabecular meshwork and 25 % located beyond Schlemm's canal. The latter possesses internal collector channels and is connected to episcleral and conjunctival veins through the external collector channels, the intrascleral venous plexus, the deep scleral plexus, and the aqueous veins.² These findings form the basis of the surgical treatment of glaucoma.

There are a variety of drugs that lower IOP, as well as surgical techniques that alter the flow dynamics of the eye. These include laser surgery and filtering microsurgery. The latter creates a drainage fistula interconnecting the anterior chamber to the subconjunctival space that creates a route for aqueous humor to exit the eye and results in a filtration bleb. The long-term success of the procedure depends on the capacity of the subconjunctival tissue to absorb this fluid and allow absorption into the capillary network, without generating excessive scar tissue that will impede fluid flow.³

Trabeculectomy has been the standard surgical treatment for glaucoma⁴ and can provide long-term reductions in IOP.⁵ However, some ophthalmologists may avoid the operation due to a potential risk for postoperative complications, a perceived lack of a fully standardized surgical procedure, and intersurgeon variation. Short-term complications after trabeculectomy include anterior chamber shallowing, hypotony, and choroidal detachment. Long-term complications include bleb leaks, blebitis, bleb-related endophthalmitis, overhanging blebs, bleb fibrosis and encapsulation, corneal endothelial cell loss, dellen, and aqueous misdirection.^{6,7} Trabeculectomy presents challenges in terms of creating a reproducible sclerostomy although many surgeons are able to overcome this and achieve reliable results. At the time of surgery, physicians may attempt to estimate the size of the opening needed via the number of bites with a Kelly punch or by removing sclera freehand, both of which introduce a source of variability from patient to patient. Use of a Kelly

Figure 1: The EX-PRESS® Glaucoma Filtration Device

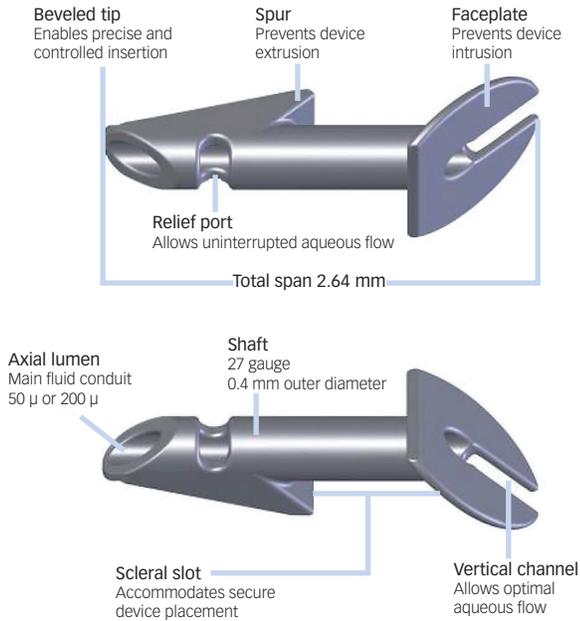
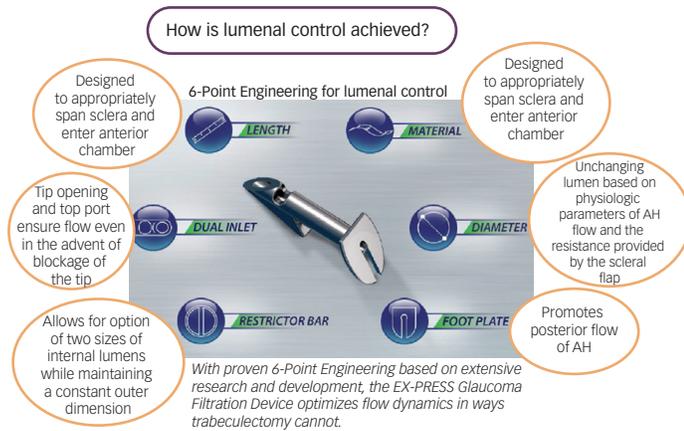


Figure 2: Engineering of Luminal Control in the EX-PRESS® Device



AH = aqueous humor.

punch is associated with complications, including iris prolapse and rapid evacuation of aqueous from the anterior chamber, which causes the chamber to shallow. In addition, patients undergoing the traditional trabeculectomy also have surgical iridectomies. There are inherent risks with iridectomies that include intraoperative bleeding, postoperative hyphema formation, monocular diplopia, and, if zonular dialysis is present, potentially vitreous prolapse through the iridectomy.

Glaucoma implants, known as aqueous shunts or glaucoma drainage devices, were initially developed for use in complex glaucoma patients, many of whom had failed medical, laser, and prior surgical treatments. Many drainage devices include a tube through which the aqueous fluid passes. Others are solid and promote the flow of fluid along the surface

of the implant. However, their use has its own litany of complications and failures. Glaucoma drainage devices with valves or flow regulators may not always provide low enough postoperative IOP and in some cases have been associated with complications.⁸ A 2005 literature review of five commonly used implants reported that surgical failure occurred in ~25 % of cases.⁹ The EX-PRESS® Glaucoma Filtration Device (Alcon, Fort Worth, TX) represents an advance in glaucoma drainage device technology. This article will describe the flow dynamics of the EX-PRESS device and review clinical studies in support of its use.

The EX-PRESS Glaucoma Filtration Device

The EX-PRESS Glaucoma Filtration Device is intended to reduce IOP in glaucoma patients where medical and conventional surgical treatments have failed. The device is a miniature (<3 mm long) aqueous shunt composed of medical-grade stainless steel¹⁰ and is fully biocompatible with the eye¹⁰ (see Figure 1). It has a spur to prevent extrusion and an end-plate to prevent intrusion into the anterior chamber. The trans-scleral miniature tube delivers aqueous from the anterior chamber to the subscleral and subconjunctival spaces, to form a filtration bleb in a similar manner to trabeculectomy. Postoperative outflow is controlled by the flow-modulating design.¹¹ Its standardized ostium size allows a more reproducible channel for fluid to drain out of the anterior chamber into the subconjunctival space.

The EX-PRESS device also offers the advantage of being less invasive than other techniques: implantation does not require scleral or iris tissue removal and requires a small point of entry into the anterior chamber. The device is implanted under a partial-thickness scleral flap that provides additional resistance to aqueous outflow and minimizes the risk for conjunctival erosion.¹² The operative time can be less than trabeculectomy and the procedure does not require the acquisition of a new skill set for many glaucoma surgeons, rather just the refinement of a few procedural steps accounting for the standardized ostium. The EX-PRESS device implantation procedure standardizes the sclerostomy. As a result of the lumen remaining constant, aqueous flow is adjusted by the number and tightness of the sutures used to close the scleral flap without having to consider a varying sclerectomy opening. Since there is no need to perform an iridectomy, the procedure should result in less inflammation.¹³

Flow dynamics modeling has been used to optimize trabeculectomy and glaucoma-filtration devices. The success of implantation of glaucoma filtration devices depends on the formation of an improved outflow facility from the eye. A computational model has been developed describing fluid flow in the eye after glaucoma surgery.³ According to this model, failure of IOP control is more directly related to decreases in hydraulic conductivity, resulting from scar formation, than to decreased absorption. The success of glaucoma surgery therefore depends on the hydraulic conductivity of the fibrous cap that develops around the bleb. Small, encapsulated blebs are less likely to be effective at allowing fluid to move into and be absorbed by subconjunctival tissue, and expose tissues to high pressures, particularly directly above the bleb. This is believed to initiate an ischemic tissue remodeling response, a reduction of hydraulic conductivity, and an elevation of IOP. High blebs are less likely to undergo remodeling but may lead to hypotonous eyes.³ A low, diffuse bleb is therefore the ultimate goal of glaucoma-implant surgery.

The engineering of the EX-PRESS device improves flow dynamics and provides the surgeon luminal control in their filtration surgery (see Figure 2).

Table 1: Overview of Clinical Studies Demonstrating Efficacy of the EX-PRESS® Glaucoma Filtration Device

Study Type	Efficacy Outcomes	Safety Outcomes	Reference
Retrospective comparative series (100 eyes), 3 months follow up	Reduction of IOP was similar in both groups	Number of postoperative glaucoma medications in both groups was not significantly different. Early postoperative hypotony and choroidal effusion were significantly more frequent after trabeculectomy compared with EX-PRESS device	16
Prospective comparative series (40 eyes), 9.7 months	Mean IOP was significantly higher in the early postoperative period in the EX-PRESS group compared with the trabeculectomy group. No differences were seen after the first week	Complications rate in the early postoperative period was significantly higher in the trabeculectomy group. No differences were seen after the first week	17
Comparative consecutive case series of 345 eyes, 3 years follow up	Surgical success was 94.8 % and 95.6 % in EX-PRESS device and combined groups, respectively (p=0.948). IOP and number of glaucoma medications were significantly lowered in both groups.	The most common device-related complication was obstruction of the tube (6 eyes), which was treated successfully with Nd:YAG laser	25
Retrospective, noncomparative study, previous cataract or failed glaucoma surgeries n=100, mean follow up 27 months	Mean preoperative IOP of 27.7 ± 9.2 mmHg with 2.73 drugs declined to 14.02 mmHg with 0.72 drugs (p<0.0001)	Low rate of complication bleb needling in 4 % and persistent hypotony in 1 %	26
Retrospective, noncomparative study, refractory postpenetrating keratoplasty glaucoma, n=15, mean follow up 12.2 months	Complete success (IOP <21 mm Hg without medication) rate was 86.6 %. Average number of glaucoma drugs decreased from 3.20 to 0.26 (p<0.001)	After EX-PRESS device implantation, clear grafts remained clear while edematous grafts became clearer due to IOP decrease. No worsening of preoperatively opaque grafts	18
Randomized, open-label, parallel-arm clinical trial, n=78, 5 years	EX-PRESS device controlled IOP without medication from year 1 (86.8 versus 61.5 %; p=0.01) to year 3 (66.7 versus 41.0 %; p=0.02) compared with trabeculectomy. No significance was observed at years 4 and 5. At year 1, only 12.8 % of patients in EX-PRESS device group required medication compared with 35.9 % after trabeculectomy. The proportions became closer at year 5 (41 % versus 53.9 %)	The EX-PRESS device group experienced fewer complications requiring needling (3 versus 9) and fewer cataract surgeries (5 versus 8)	20
Retrospective, consecutive case-control series, n=70, mean follow up 28 months	IOP lowering was similar between groups (p=0.209). Unqualified success was achieved in 77.14 % of EX-PRESS and 74.29 % of trabeculectomy procedures at last follow up (p=1.00)	Fewer cases of early postoperative hypotony and hyphema and quicker visual recovery in the EX-PRESS device group The EX-PRESS device group required fewer postoperative visits compared with the trabeculectomy group	21
Prospective, randomized study, 30 eyes of 15 patients, mean follow up 23.6 months	Mean preoperative IOP decreased from 31.1 (± 14.2) to 16.2 (± 1.5) mmHg after trabeculectomy, and from 28.1 (± 9.0) to 15.7 (± 1.8) mmHg in EX-PRESS device group (p=0.001). Mean number of IOP-lowering medicines decreased from 3.7 pre-operatively (both groups) to 0.9 after trabeculectomy versus 0.3 after EX-PRESS device implantation (p=0.001)	Postoperative complications were more frequent after trabeculectomy (33 %) compared with EX-PRESS device (20 %), with four trabeculectomy eyes (27 %) needing postoperative interventions, compared with none with EX-PRESS device	22
Prospective, randomized study, n=64, 6 months follow up.	There was no significant difference in mean logMAR VA between groups at baseline or any study visit. A median loss of 0 and 1.5 Snellen lines at 6 months (p=0.03) was observed for EX-PRESS device and trabeculectomy groups, respectively. VA remained reduced after follow-up in 16 % of the EX-PRESS device group and 6-month 47 % of the trabeculectomy group (p=0.01) Most of these (16/19) were mild (a decrease of 2 to 3 Snellen lines compared with before surgery)	No significant difference in complication rates between EX-PRESS device and trabeculectomy although cataract, which was only reported in the trabeculectomy group, was of borderline significance	23

IOP = intraocular pressure; Nd:YAG = neodymium-doped yttrium aluminum garnet; VA = visual acuity.

Its length is designed to scan the sclera and enter the anterior chamber. The vertical slot in the end-plate is designed to direct aqueous flow posteriorly and facilitate the generation of a low-lying, diffuse bleb.¹¹ A restrictor bar allows for the option of two sizes of internal lumens while maintaining a constant outer dimension. Two different models are available: the P-50 and P-200. They differ only in their internal lumen. In fluid dynamics, flow

and resistance are inversely related to each other. The Hagen–Poiseuille equation, also known as the Poiseuille law, describes the pressure drop in a fluid flowing through a long cylindrical tube. Resistance to flow through a tube is determined by three factors: the effective radius or diameter of the tube's internal lumen, the tube length, and liquid viscosity. According to the Hagen–Poiseuille equation, the factor with the greatest impact on

Figure 3: Survival Curve with Complete Success Defined as Intraocular Pressure >5 and <18 mm Hg without Glaucoma Medication¹⁶

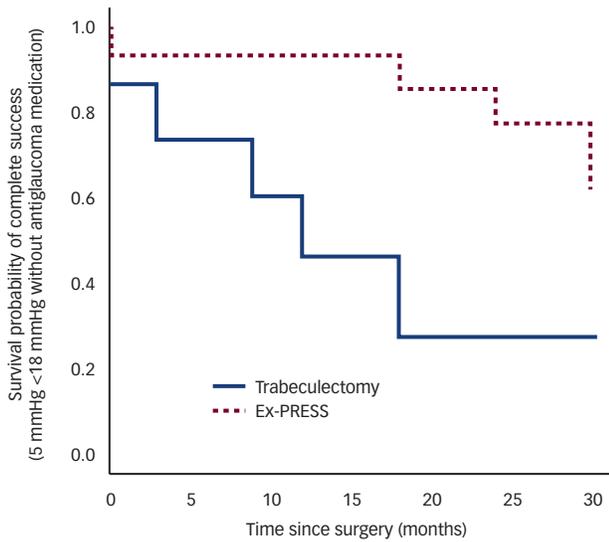
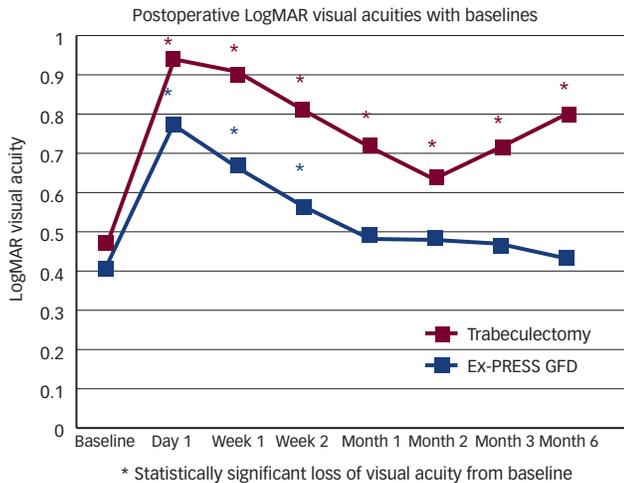


Figure 4: Visual Acuity Recovery after EX-PRESS® Glaucoma Filtration Device (n=31) versus Trabeculectomy (n=30)



GFD = glaucoma filtration device. Source: Beltran-Agullo, 2013.²³

resistance is the diameter of a tube’s internal lumen, i.e. a small change in diameter leads to a large inverse change in resistance.

The EX-PRESS device acts as a simple flow resistor and in a flow dynamics study, created a relatively constant resistance to flow.¹⁴ The P-200 model with the larger internal lumen gave the highest flow rate and generated the least resistance to flow. Compared with the P-50 model, the flow rates were statistically significant ($p < 0.0001$) at all pressure levels. All models tested showed higher flow rates per unit pressure than the outflow facility of a healthy human eye. It has been postulated that the lower rate of hypotony of the EX-PRESS device compared with trabeculectomy can be explained by the resistance to flow that is offered by the 50 μm lumen of the shunt. In

trabeculectomy, the smallest scleral punch available is approximately 750 μm and that is only if one punch alone is used to make the incision.¹⁵

Clinical Studies of the EX-PRESS Device

Several studies to date have demonstrated that the EX-PRESS device has equivalent efficacy to trabeculectomy, but its flow dynamics confer advantages (see Table 1). The EX-PRESS device relies on nonphysiologic subconjunctival flow as its mechanism of IOP lowering similar to that of a trabeculectomy. While the EX-PRESS device standardizes the filtration procedure, as with any surgical procedure, there are complications and adverse events. Additional glaucoma filtration surgery, device removal, bleb revision with or without antimetabolites, device-iris touch, hyphema <2 mm, shallow anterior chamber, hypotony, tenon cyst, corneal complication, anterior chamber reformation, and device exposure are listed in the EX-PRESS directions for use with an occurrence rate above 5 %.

In the first large, retrospective study to compare standard trabeculectomy with the EX-PRESS device, the EX-PRESS device was implanted in 50 eyes of 49 patients and a traditional trabeculectomy performed in 50 eyes of 47 patients. After 12 months, the IOP reduction was similar in both groups, but there was less postoperative hypotony (IOP <5 mm Hg); 32 % hypotony rate in the trabeculectomy group versus 4 % in the EX-PRESS device group.¹⁶ In another study, 345 eyes underwent EX-PRESS device implantation with or without cataract surgery. At 3 years, the success rate was 95 %. Hypotony was seen in 15.6 % of the EX-PRESS device group in the first week, and 7.9 % with hypotony in the combined group. All instances of hypotony during the early postoperative period resolved spontaneously.

Implantation of the EX-PRESS device is also a safe procedure when combined with cataract surgery. In a prospective series of 40 consecutive eyes, patients treated with combined phacoemulsification and EX-PRESS device implantation were compared with those who underwent combined cataract and glaucoma surgery with trabeculectomy. The complications rate in the early postoperative period was significantly higher in the trabeculectomy group. No significant differences were objectified in success between both groups after the first week.¹⁷ In an evaluation of the EX-PRESS device in refractory postpenetrating keratoplasty glaucoma, the complete success rate was 86 %. After implantation of the EX-PRESS device, clear grafts remained clear and edematous grafts became clearer.¹⁸

In a five-year extension of a randomized study ($n=78$),¹⁹ only 41.0 % of the patients in the EX-PRESS device arm required IOP-lowering drugs, compared with 53.9 % of the 39 patients in the trabeculectomy arm and patients required fewer IOP medications and fewer surgical interventions during the 5-year study period. More patients required bleb needling in the trabeculectomy group compared with the EX-PRESS device group (nine versus three, respectively) and more patients required cataract extraction in the trabeculectomy group than in the EX-PRESS device group (eight versus five, respectively).²⁰

A retrospective, consecutive case-control series ($n=70$) focused on the health and integrity of the postoperative bleb. The pressure reduction achieved with the EX-PRESS device was found to be similar to that of a trabeculectomy but visual recovery to the preoperative baseline was significantly quicker in the EX-PRESS group being achieved 1 week after implantation compared with 1 month for trabeculectomy. Evaluation

of bleb morphology by the Moorfields Bleb Grading System revealed less vascularity and height, but more diffuse area associated with the EX-PRESS device blebs, although these differences were not seen at study completion. The EX-PRESS device group had fewer cases of postoperative hypotony, fewer post-operative visits, and underwent a quicker visual recovery.²¹

In a recent prospective, randomized study (30 eyes of 15 patients), each patient underwent trabeculectomy in one eye and EX-PRESS device implantation under a scleral flap in the other eye. (see *Figure 3*) At the last follow-up visit (mean 23.6 months), IOP decreased from 31.1 to 16.2 mmHg in the trabeculectomy group, and 28.1 to 15.7 mmHg in the EX-PRESS device group.²² Complications were generally mild and less common in the EX-PRESS device group (20 % versus 33 %), as were complications requiring surgical intervention (0 % versus 27 %). In addition, one eye in the trabeculectomy group had a postoperative hyphema and an eye in the EX-PRESS group had a wound leak—these mild complications both resolved spontaneously within a week. The most common complication was hypotony (7 % EX-PRESS device group; 33 % trabeculectomy group), but all resolved spontaneously and without serious complications within 1 month of surgery. The major weakness of this study was its small sample size: only 30 eyes were studied (15 patients), due to the difficulty in enrolling primary open angle glaucoma patients who were willing to undergo trabeculectomy in one eye and EX-PRESS device implantation in the other eye in a randomized manner. However, despite the small group size, a statistically significant difference was seen between procedures, particularly in terms of success rates and complication rate. Comparing the two interventions in fellow eyes of the same patient further strengthened the validity of these findings.

The EX-PRESS device also has superior visual outcomes compared with trabeculectomy. A recent prospective, randomized study (n=64), found that although there was no difference in mean visual acuity (VA) between the EX-PRESS device and trabeculectomy groups at any time point, trabeculectomy eyes were more likely to lose ≥ 2 Snellen lines. Furthermore, the study showed that VA recovers to a preoperative baseline more quickly following EX-PRESS device surgery than trabeculectomy. At the 6-month follow up, 47 % of patients in the trabeculectomy group and 16 % (p=0.01) in the EX-PRESS device group had lost ≥ 2 Snellen lines (see *Figure 4*).²³

There is also evidence from previous studies of quicker VA recovery following EX-PRESS implantation: Good and Kahook found that VA returned to baseline by 1 week in the EX-PRESS device group compared with 1 month in the trabeculectomy group.²² The Sugiyama study found that VA was significantly poorer from 1 week to 3 months in the trabeculectomy group while it was stable in the EX-PRESS device group for 12 months of follow up.²⁴

Summary and Concluding Remarks

There is a need for improved surgical treatment options in glaucoma patients, especially those in which a procedure and medications have already failed. The strategy for managing patients who have experienced a failed trabeculectomy or corneal scarring can be challenging. The EX-PRESS device offers another option for these glaucoma patients. Implanting the device in the correct location and entering at the iris plane are important to reach optimal outcomes.

Results of retrospective and prospective clinical studies demonstrate that implantation of the EX-PRESS device has similar success rates as trabeculectomy, but lower rates of hypotony and choroidal effusions. The EX-PRESS device provides a more consistent flow of aqueous than trabeculectomy, and the bleb is low and diffuse, perhaps related to the fact that the egress of aqueous is more posterior with the EX-PRESS than with a manually created sclerostomy (see *Figures 1* and *2*). Furthermore, implantation of the EX-PRESS device in patients with previous glaucoma surgery, allows faster visual recovery to preoperative baselines compared with trabeculectomy, and can be combined successfully with more complex surgical procedures, including cataract surgery.

Implantation of the EX-PRESS device incurs additional costs compared with trabeculectomy, similar to that of tube shunts. However, for many doctors and patients the cost of the EX-PRESS device is outweighed by its benefits in terms of proven IOP lowering, fewer hypotony and choroidal effusions, quicker recovery of VA to the preoperative baseline VA, and fewer postoperative visits.

In summary, the EX-PRESS device offers a step toward the standardization of aqueous outflow that is consistent with the trend in ocular surgery toward smaller incision microsurgery, and is associated with less inflammation, greater predictability with less hypotony, and more rapid visual recovery. ■

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CAUTION:

Federal law restricts this device to sale by or on the order of a physician.

INDICATION:

The EX-PRESS® Glaucoma Filtration Device is intended to reduce intraocular pressure in glaucoma patients where medical and conventional surgical treatments have failed.

GUIDANCE REGARDING APPROPRIATE VERSION SELECTION:

Prior clinical studies were not designed to compare the various versions of the EX-PRESS Glaucoma Filtration Device. The selection of the appropriate version is according to the doctor's discretion.

CONTRAINDICATIONS:

The use of this device is contraindicated if one or more of the following conditions exist:

- Presence of ocular disease such as uveitis, ocular infection, severe dry eye, and severe blepharitis.

- Pre-existing ocular or systemic pathology that, in the opinion of the surgeon, is likely to cause postoperative complications following implantation of the device.
- Patients diagnosed with angle closure glaucoma.

WARNINGS/PRECAUTIONS:

- The surgeon should be familiar with the instructions for use.
- The integrity of the package should be examined prior to use and the device should not be used if the package is damaged and sterility is compromised.
- This device is for single use only.
- Magnetic resonance imaging of the head is permitted, however not recommended, in the first two weeks postimplantation.

ATTENTION:

Reference the Directions for Use labeling for a complete listing of indications, warnings, precautions, complications, and adverse events.