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Original article

Intraocular silicone oil removal: timing, outcome, and silicone oil complications encountered

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Abstract

Introduction: Silicone oil is the preferred tamponade agent used in pars-plana vitrectomy for retinal detachment when a long duration of endotamponade is intended. Due to its possible long-term complications, removal of silicone oil (ROO) is recommended.
Purpose: This study is done to evaluate the mean duration and complications of silicone oil tamponade, and the anatomical and visual outcomes after silicone oil removal.
Study design: Retrospective study.
Materials and methods: Retrospective review was done on 55 eyes of 55 patients, in which ROO was carried out at Hospital Sultanah Bahiyah in 2016 with a minimum six months follow-up postoperatively.
Results: The duration of silicone oil tamponade in these eyes ranged from 1.0 to 55.5 months, with mean duration of 10.8 months (SD 7.74). Common complications of silicone oil tamponade observed were cataract in 30 eyes (54.5%), followed by secondary high intraocular pressure in 6 eyes (10.9%), and band keratopathy in 3 eyes (5.5%). Six eyes (10.9%) developed retinal re-detachment after oil removal.

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The majority in the anatomically attached group post ROO (40 eyes, 81.6%) showed improvement of vision after ROO, with mean best corrected vision of LogMAR 1.38 (6/150) with silicone oil in situ to LogMAR 0.88 (6/48) at the latest follow-up.
Conclusions: Although the recommended duration of silicone oil tamponade ranges from three to six months, the optimal timing for silicone oil removal still remains unknown. ROO is recommended due to oil-related complications, but the anatomical outcome should be evaluated as well. However, in our setting, with limited resources and time, and increasing number of patients indicated for silicone oil, it is impossible to comply with the recommended time for ROO and the timing is usually set on an individual basis.

Keywords: cataract, glaucoma, internal tamponade, keratopathy, pars-plana vitrectomy, retinal detachment, silicone oil

Penyingkiran minyak silikon intraokular: Penentuan masa, hasil, dan penemuan komplikasi minyak silikon

Abstrak

Pengenalan: Minyak silikon adalah agen tamponad pilihan yang digunakan dalam vitrectomy pars-plana untuk masalah retina lekang apabila kesan tamponade dari dalam diperlukan untuk jangkamasa yang panjang. Disebabkan kemungkinan komplikasi jangka panjang, penyingkiran minyak silikon (ROO) adalah disyorkan.
Tujuan: Kajian ini dilakukan untuk menilai jangka masa dan komplikasi minyak silikon tamponad, dan hasil anatomi dan tahap penglihatan selepas penyingkiran minyak silikon.
Reka bentuk kajian: Kajian retrospektif.
Bahan dan kaedah: Kajian retrospektif dilakukan kepada 55 mata daripada 55 orang pesakit, yang mana ROO telah dijalankan di Hospital Sultanah Bahiyah pada tahun 2016 dengan tempoh enam bulan susulan selepas pembedahan.
Keputusan: Tempoh tamponad minyak silikon di dalam mata ini antara 1.0 hingga 55.5 bulan, dengan jangka masa purata 10.8 bulan (SD 7.74). Komplikasi biasa minyak silikon tamponad yang diperhatikan adalah katarak dalam 30 mata (54.5%), diikuti oleh tekanan tinggi intraokular sekunder dalam 6 mata (10.9%), dan keratopati band dalam 3 mata (5.5%). Enam mata (10.9%) mengalami lekang retina semula selepas penyingkiran minyak. Majoriti mata dalam kumpulan melekat secara anatomi selepas ROO (40 mata, 81.6%) menunjukkan peningkatan ketajaman penglihatan, dengan penglihatan yang terbaik LogMAR 1.38 (6/150) sewaktu minyak silikon

masih di dalam mata ke tahap LogMAR 0.88 (6/48) pada susulan terkini.
Kesimpulan: Walaupun jangka masa yang disyorkan minyak tamponade silikon adalah antara tiga hingga enam bulan, masa optimum untuk penyingkiran minyak silikon masih tidak diketahui. ROO disyorkan kerana komplikasi yang berkaitan dengan minyak, tetapi keberkesanan terhadap hasil anatomi harus diambil kira. Walau bagaimanapun, dalam keadaan kekangan sumber dan masa terhad yang kami hadapi, ditambah pula peningkatan ketara jumlah pesakit yang memerlukan pembedahan minyak silikon, adalah mustahil untuk mematuhi masa secara tepat yang disyorkan untuk ROO, kebiasaannya penentuan masa adalah mengikut keperluan individu.

Kata kunci: katarak, glaukoma, tamponad dalaman, keratopati, vitrectomy pars-plana, lekang retina, minyak silikon

Introduction

There are several tamponade agents available to be used in pars-plana vitrectomy (PPV), but silicone oil is the preferred endotamponade agent if longer duration of tamponade is needed for retinal re-attachment. However, silicone oil can lead to long-term complications such as cataract formation, secondary high intraocular pressure (IOP), and corneal endothelial decompensation.[1-6] Hence, removal of silicone oil (ROO) is recommended once anatomical re-attachment has been achieved.[7] The exact timing for silicone oil removal is still controversial and debatable, as it depends on multiple factors such as stability of the retinal status and complications from the silicone oil itself. Therefore, recommendations range from three to six months in successfully attached eyes.[8,9] Most authors reported an improvement in final visual acuity post-ROO, but it is believed that duration of silicone oil tamponade may have an effect on visual acuity. However, current evidence to support this is lacking. Compared to other tamponade agents, silicone oil is more likely to enhance anatomical re-attachment rates, but its functional outcome is still debatable.

This study was conducted to determine the mean duration and complications of silicone oil tamponade, as well as the anatomical and visual outcomes after silicone oil removal.

Materials and methods

The medical and surgical records of all patients who underwent silicone oil removal from January 1 to December 31, 2016 at Hospital Sultanah Bahiyah (Alor Setar, Kedah, Malaysia) were reviewed. A minimum postoperative follow-up duration of

Table 1. Demographic features, initial indication for PPV, and duration of silicone oil tamponade

Variables	Patients
Demographic feature:	
Total number of patients	55
Males, no. (%)	36 (64.5)
Females, no. (%)	19 (35.5)
Age (years) mean (SD) (range)	52.9 (13.33) (11-75)
Indication for PPV with silicone oil tamponade:	
ADED (combined TRD, RRD affecting macula), no. (%)	31 (56.5)
RRD with PVR, no. (%)	21 (38)
Vitreomacular traction, no.	1
Traumatic endophthalmitis with RD, no.	1
Full thickness macula hole, no.	1
Duration of silicone oil tamponade:	
< 3months, no. (%)	1 (1.8)
3-6 months, no. (%)	7 (12.7)
6-12 months, no. (%)	35 (63.7)
> 12 months, no. (%)	12 (21.8)

PPV: pars-plana vitrectomy; ADED: advanced diabetic eye disease; TRD: tractional retinal detachment; RRD: rhegmatogenous retinal detachment; PVR: proliferative vitreoretinopathy

six months was taken to determine the anatomical and visual outcomes after ROO. Ten eyes from an initial 65 ROO cases performed were excluded from the study for lack of follow-up before the six months appointment.

Out of 55 patients with 55 silicone oil-filled eyes who fulfilled our inclusion and exclusion criteria, 36 were males (64.5%) and 19 were females (35.5%). Subjects' age ranged from 11 to 75 years, with mean age of 52.9 years. The demographic features of the analysed eyes are shown in Table 1.

The two common indications for using silicone oil as tamponade agent during PPV were:

1. advanced diabetic eye disease (ADED) with combination of tractional (TRD) and rhegmatogenous retinal detachment (RRD) affecting the macula (n = 31, 56.5%); and
2. proliferative vitreoretinopathy (PVR) from RRD (n= 21, 38%).

The rest of the indications were listed in Table 1. Silicone oil with 5000 Centistokes (CS) viscosity was used in all of these eyes.

Decision for ROO was made once retinal re-attachment had been achieved anatomically, frequently more than three months after vitrectomy. However, the decision was also made based on the initial indication of silicone oil usage as tamponade agent and any severe complications arising from the oil tamponade requiring early ROO.

Surgeries were done by a qualified vitreoretinal surgeon and two vitreoretinal fellows using either the trans-pupillary or pars-plana sclerotomy approach. Thirty eyes (54.5%) had ROO combined with cataract extraction in the same setting (*i.e.*, phacoemulsification followed by controlled posterior capsulotomy and oil removal via trans-pupillary approach before intraocular lens implantation) due to lack of resources. The remaining 25 eyes (45.5%) had ROO via pars-plana sclerotomy approach.

Statistical analysis was performed on the extracted data using the two-sample t-test and simple linear regression test. A p-value of less than 0.05 was set for statistical significance.

Results

Duration of silicone oil tamponade in these 55 eyes ranged from 1 to 55.5 months, with a mean duration of 10.85 months (SD 7.74). We divided the duration of oil tamponade into four categories: less than 3 months, 3 to 6 months, 6 to 12 months, and more than 12 months. The majority had an oil tamponade for 6 to 12 months (n = 35, 63.7%), as shown in Table 1.

Of the 55 eyes that were anatomically attached during preoperative assessment for ROO, 6 eyes (10.9%) developed retinal re-detachment after oil removal (Table 2). The mean duration of silicone oil tamponade in eyes that remained attached post-operatively was 11.0 months (SD 8.0), but was shorter (9.4 months [SD 5.2]) in the re-detached group. The difference of mean duration between these two groups was investigated using the two-sample t-test, which appeared not significant (Table 3). The simple linear regression test was used to find out any correlations between duration of silicone oil tamponade and re-detachment rates after ROO, but the result was not significant (Table 3). Most re-detachment occurred in eyes with PVR (66.7%, n = 4). The earliest re-detachment occurred at day 1 after ROO in a case of poor prognosis with 19.5 months of silicone oil tamponade duration for post-traumatic endophthalmitis and RD complicated with band keratopathy. The latest re-detachment occurred four months after ROO due to severe PVR changes in an eye with a giant retinal tear.

The complications of silicone oil tamponade observed in this study are listed in Table 2. The most common complication was cataract formation (54.5%, n = 30),

Table 2. Complications of silicone oil tamponade, anatomical and visual outcome after ROO

Variables	Patients
Anatomical outcome after ROO:	
Attached, no (%)	49 (89.1)
Re-detached, no. (%)	6 (10.9)
ADED with combined RD, no.	31
Attached, no. (%)	30 (96.8)
Re-detached, no. (%)	1 (3.2)
PVR, no.	21
Attached, no. (%)	17 (81.0)
Re-detached, no. (%)	4 (19.0)
Others, no.	3
Attached, no. (%)	2 (66.7)
Re-detached, no. (%)	1 (33.3)
Complications of silicone oil:	
Cataract, no. (mean duration (months), SD)	30 (9.9, 5.0)
High IOP (mean duration (months), SD)	6 (11.2, 10.9)
Band keratopathy (mean duration (months), SD)	3 (12.8, 5.97)
Emulsified oil (mean duration (months)	1 (12.5)
Visual acuity outcomes after ROO:	
ADED with combined RD, no.	30
Improved vision, no. (%)	24 (80.0)
Unchanged vision, no. (%)	3 (10.0)
Worsening vision, no (%)	3 (10.0)
PVR, no.	17
Improved vision, no. (%)	14 (82.4)
Unchanged vision, no. (%)	2 (11.8)
Worsening vision, no (%)	1 (5.8)
Others, no.	2
Improved vision, no. (%)	2 (100.0)
Unchanged vision, no. (%)	n/a
Worsening vision, no (%)	n/a

n/a: non-applicable; PPV: pars-plana vitrectomy; ADED: advanced diabetic eye disease; TRD: tractional retinal detachment; RRD: rhegmatogenous retinal detachment; PVR: proliferative vitreoretinopathy

Table 3. Association between re-detachment rate after ROO with duration of silicone oil tamponade

	Attached retina	Re-detached retina	P-value
Patients, no.	49	6	
Duration of tamponade:			
Range (months)	1–55.5	5.5–19.5	0.636
Mean (months, SD)	11.0 (8.0)	9.4 (5.2)	0.793

Table 4. Association between visual acuity before ROO and visual outcome after ROO with duration of silicone oil tamponade

	Vision before ROO	Visual outcome after ROO
Range (LogMAR)	0.3-2.6	0.2-2.9
Mean (LogMAR, SD)	1.38 (0.64)	0.88 (0.53)
P-value	0.722	0.507

with mean tamponade duration of 9.9 months (SD 5.0). Six (10.9%) of these eyes developed secondary high IOP with mean tamponade duration of 11.2 months (SD 10.9). Three eyes (5.5%) developed band keratopathy; mean duration of oil tamponade in these eyes was longer, 12.8 months (SD 5.97). All of them underwent chelation of band keratopathy in the same setting of ROO, but the condition persisted postoperatively, and no further chelation was planned.

Visual acuity outcomes after ROO excluding eyes with re-detachment are summarised in Table 2. This was determined by comparing the best corrected visual acuity at the last follow-up visit after ROO with preoperative visual acuity. Improvement of vision of at least 1 line using the Snellen chart was considered as visual improvement, while worsening of vision was defined as a drop of at least 1 line using the Snellen chart. The majority (40 eyes, 81.6%) showed improvement in vision regardless of the underlying ocular problem. Overall, the mean visual acuity of these eyes with silicone oil in situ was LogMAR 1.38 (6/150), while the mean at last follow-up visit was LogMAR 0.88 (6/48). There was no statistically significant correlation between visual acuity before ROO and visual improvement after ROO with duration of silicone oil tamponade, as shown using the simple linear regression test (Table 4).

Discussion

In this study, the mean duration of silicone oil tamponade was 10.85 months (SD 7.74). The majority had an oil tamponade duration of 6 to 12 months (n = 35, 63.6%). The shortest duration was one month, as early ROO was done due to uncontrolled high IOP with persistent vitreous haemorrhage. The longest duration was 55.5 months, in which the patient had the operation done at a different centre and defaulted follow-up for a few years before he was referred to us. Timing of ROO has no significant effect on the re-detachment rate in our study. Re-detachment occurred in 10.9% (n = 6) of the eyes and mostly (n = 4) in eyes with PVR changes. There was no specific timing reported for oil removal, but some authors recommended that it should ideally be done if the retina is anatomically stable in the surgeon's opinion.[9-13] Having said that, there are other factors that affect the decision for timing of ROO, such as causes and severity of retinal detachment before surgery and complications arising from the silicone oil itself (*i.e.*, uncontrolled IOP, emulsified oil).

Various mechanisms of action have been postulated on how silicone oil can cause complications in the eye. More than half of our patients (54.5%) developed or had worsening cataract with silicone oil, hence had combined cataract extraction and intraocular lens implantation done in the same setting during ROO. Cataract formation, mainly posterior subcapsular opacity, was observed to occur after intravitreal silicone oil injection and continued to develop even after ROO.[14] The exact mechanism of cataract formation remains unknown, but it is believed to be related to the following factors:

1. bright and prolonged exposure to intra-operative illumination, leading to changes in the transparency of the lens;
2. increase in oxygen tension within the lens, which increases the risk of cataract formation;
3. changes in lens metabolism; and
4. inflammatory reaction.[15]

New research found that, at the molecular level, silicone oil can cause changes in secondary structures of αB-crystallin protein and amyloid-like aggregation, which have been linked with the mechanism of cataract formation.[15]

As is widely known, silicone oil tamponade may cause secondary high IOP. Different mechanisms of raised IOP either due to secondary open or closed angles have been discussed, such as:

1. mechanical obstruction of aqueous humour outflow by silicone oil in the anterior chamber;
2. pupillary block with silicone oil in the anterior chamber,
3. trabecular meshwork obstruction by silicone oil micro-droplets; and
4. inflammation.[16]

A recent study found that the level of inflammatory mediators in aqueous humour were increased in silicone oil-filled eyes with secondary high IOP, suggesting the

involvement of inflammation in its pathogenesis.[17] About 10.9% of our patients had secondary high IOP. Of these, four eyes were controlled with medical treatment alone, one eye was planned for drainage device implantation, and one eye required early oil removal. The silicone oil was removed a month after initial vitrectomy for ADED, as there was uncontrolled IOP secondary to silicone oil with persistent vitreous haemorrhage. After ROO, the patient developed suprachoroidal haemorrhage and subsequently the eye became pthisical.

The other dreaded complication of silicone oil is corneal decompensation and band keratopathy, but the incidence was generally low. Three of our patients developed band keratopathy. They had chelation done at the time of ROO, and the condition was reversible in two eyes. None of them needed keratoplasty. This complication may occur when silicone oil comes in contact with the corneal endothelium, causing a reduction in endothelial cell density and pleomorphism of remaining endothelial cells, hence resulting in corneal oedema and bullous keratopathy, stromal hypercellularity, superficial stromal calcification, and retro-corneal membrane formation.[18]

There are several types of silicone oil being used as a tamponade agent in vitrectomy for complex retinal detachment, the most widely used types being 1000, 2000, and 5000 CS. The decision of which oil to use may depend on surgeon preference. These oils are almost similar in terms of surface tension and specific gravity, but have significantly different molecular weights.[19] Evidence has shown that there was no significant difference in incidence of complications between these silicone oils,[19] but a study reported that high-viscosity silicone oil (5000 CS) is more resistant to emulsification.[20] There are several more silicone oil complications other than the ones mentioned above, but not observed in our study, such as macular pucker formation, cystoid macular oedema, and rubeosis.[21]

Most of our patients (40 eyes, 81.6%) had improved vision after ROO. Removing the silicone oil bubble reduces optical interference, hence resulting in better visual acuity. About half of these patients had cataract extraction done in the same setting as ROO, which may contribute to better visual acuity post ROO.[13] Only a small number of patients experienced unchanged (five eyes) or worsening vision (four eyes). These eyes were those with ADED with vitreous haemorrhage, persistent macular oedema, epiretinal membrane formation, and unhealthy macula with disruption of ellipsoid-myoid junction on optical coherence tomography observed during the post-operative period. Possible mechanisms for worsening vision after silicone oil usage were: optic nerve damage as a result of direct tissue infiltration of SO, generalized macular dysfunction with lesions of ganglion cells and horizontal-bipolar cells, and significant reduction in the inner retinal thickness indicating neuronal cell loss in the macular area.[21] From this study, the duration of silicone oil tamponade does not affect patients' visual acuity before ROO and visual outcome after ROO. However, very few studies have commented on this correlation, but similar findings were reported in Ellen *et al.*[22]

The mean duration of silicone oil tamponade in our study may not truly reflect the intended practice we want to achieve. With limited time and resources as well as increasing number of patients indicated for silicone oil in our setting, it is impossible for us to comply with the recommended time for ROO.

In conclusion, there should be no exact timing for ROO but, if possible, it should be performed within the recommended duration of three to six months. Having said that, surgeons must also evaluate the anatomical stability and oil-related complications before deciding for ROO. Therefore, the timing for ROO should be made on a case-to-case basis. Thorough examination checking for silicone oil complications is mandatory. This is also applied after ROO to identify early signs of re-detachment. Further study should be carried out to identify the risks of re-detachment among patients after ROO. Patients should also be made aware that even though overall visual improvement after ROO is promising, there is a small risk of vision remaining the same or even worsening after the procedure. This outcome depends greatly on the initial anatomical and functional condition of the retina before vitrectomy. With several types of silicone oil available in the market, the search for an ideal intraocular tamponade with long-acting effect but fewer potential complications will continue.

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IZBA®

Important note: Before prescribing, consult full prescribing information. **Presentation:** Plastic bottle with dispensing plug and closure, containing 2.5 ml, presented in an overwrap. 1 ml of solution contains 30 micrograms of travoprost. Preservative: 1 ml of solution contains 10 micrograms of polyquaternium-1. Excipients with known effect : 1 ml of solution contains 7.5 mg propylene glycol and 2 mg polyoxyethylene hydrogenate castor oil 40 (HCO-40) **Indications:** IZBA® eye drops contains travoprost, a prostaglandin analogue. IZBA® eye drops is indicated for the decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma. **Dosage and administration: •Use in adults (including elderly):** The dose is 1 drop of IZBA® eye drops in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening. If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed 1 drop in the affected eye(s) daily. When substituting another ophthalmic antiglaucoma medicinal product with IZBA® eye drops, the other medicinal product should be discontinued and IZBA® eye drops should be started the following day. **•Use in patients with hepatic or renal impairment:** Travoprost 30 µg / ml has not been studied in patients with hepatic or renal impairment. However, travoprost 40 µg / ml has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml / min). No dosage adjustment is necessary in these patients. Therefore, no need for dose adjustment at the lower concentration of active ingredient is anticipated. **•Use in children and adolescents:** The safety and efficacy of IZBA® eye drops in children and adolescents below the age of 18 years has not been established. No data are available. •For ocular use. For patients who wear contact lenses, patients must be instructed to remove contact lenses prior to application of IZBA® eye drops and wait at least 15 minutes after instillation of the dose before reinsertion. The patient should remove the protective overwrap immediately prior to initial use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Keep the bottle tightly closed when not in use. Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last. **Contraindications:** •Hypersensitivity to the active substance or to any of the excipients in this product. **Warnings and Precautions: •Eye colour change:** Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. The long term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may be become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed. **•Periorbital and eye lid changes:** In controlled clinical trials, periorbital and / or eyelid skin darkening in association with the use of travoprost has been reported in 0.2 % of patients. Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues. Travoprost may gradually change eyelashes in the treated eye(s) ; these changes were observed in about half of the patients in clinical trials and include : increased length, thickness, pigmentation, and / or number of lashes. The mechanism of eyelash changes and their long term consequences are currently unknown. There is no experience of travoprost in inflammatory ocular conditions; nor in neovascular, angle-closure, narrow-angle or congenital glaucoma and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma. **•Aphakic patients:** Caution is recommended when using travoprost in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema. •Iritis / uveitis: In patients with known predisposing risk factors for iritis / uveitis, travoprost can be used with caution. **•Contact with the skin:** Skin contact with travoprost must be avoided as transdermal absorption of travoprost has been demonstrated in rabbits. Prostaglandins and prostaglandin analogues are biologically active materials that may be absorbed through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In the unlikely event of coming in contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately. **•Excipients:** IZBA® eye drops contains propylene glycol which may cause skin irritation. IZBA® eye drops contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions. **•Effects on ability to drive and use machines:** IZBA® eye drops has no or negligible influence on the ability to drive and use machines. Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines. **Interactions:** •No interaction studies have been performed. **Adverse drug reactions: •Summary of the safety profile:** In a clinical trial of 3 months duration (N = 442) involving IZBA® eye drops as monotherapy, the most common adverse reaction observed was hyperaemia of the eye (ocular or conjunctival) reported in approximately 12 % of the patients. **•List of adverse reactions:** The following adverse reactions were assessed to be related with IZBA® eye drops monotherapy and Travoprost 40 µg / ml eye drops, solution (either preserved with benzalkonium chloride or polyquaternium-1). They are classified according to the following convention : very common (≥1 / 10), common (≥1 / 100 to <1 / 10), uncommon (≥1 / 1,000 to <1 / 100), rare (≥1 / 10,000 to <1 / 1,000), very rare (<1 / 10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness. •Travoprost 30 µg / mL eye drops, solution (IZBA® eye drops) **•Very common:** ocular hyperaemia; **•Common:** dry eye, eye pruritus, ocular discomfort; **•Uncommon:** punctate keratitis, anterior chamber inflammation, blepharitis, eye pain, photophobia, visual impairment, vision blurred, conjunctivitis, eyelid oedema, eyelid margin crusting, eye discharge, dark circles under eyes, growth of eyelashes, eyelash thickening, pruritus, rash. •Travoprost 40 µg / ml eye drops, solution **•Very common:** ocular hyperaemia, iris hyperpigmentation; **•Common:** punctate keratitis, anterior chamber inflammation, eye pain, photophobia, eye discharge, ocular discomfort, visual acuity reduced, vision blurred, dry eye, eye pruritus, lacrimation increased, erythema of eyelid, eyelid oedema, growth of eyelashes, eyelash discolouration, skin hyperpigmentation (periocular), skin discolouration; **•Uncommon:** herpes simplex, keratitis herpetic, hypersensitivity, drug hypersensitivity, seasonal allergy, dysgeusia, dizziness, visual field defect, corneal erosion, uveitis, keratitis, eye inflammation, photopsia, blepharitis, conjunctival oedema, halo vision, conjunctivitis, conjunctival follicles, hypoaesthesia eye, meibomianitis, ectropion, anterior chamber pigmentation, mydriasis, cataract, eyelid margin crusting, asthenopia, heart rate irregular, palpitations, heart rate decreased, blood pressure decreased, blood pressure increased, hypotension, hypertension, dyspnoea, asthma, respiratory disorder, oropharyngeal pain, cough, dysphonia, nasal congestion, throat irritation, peptic ulcer reactivated, dry mouth gastrointestinal disorder, constipation, dermatitis allergic, periorbital oedema, dermatitis contact, erythema, rash, hair colour changes, hair texture abnormal, hypertrichosis, madarosis, musculoskeletal pain, asthenia, malaise; **•Not Known:** macular oedema, sunken eyes, vertigo, tinnitus, bradycardia, tachycardia, asthma aggravated, hair growth abnormal, prostatic specific antigen increased.

BSS 75761-0; APPR 08 FEB 18

References :

1. Travatan PI 759430; APPV 03 DEC 2018 2. Izba PI 75761-0; APPR 08 FEB 18 3. DouTrav PI RD FEB 18; APPRV 16 OCT 18 4. Gandolfi S et al. Comparison of a travoprost BAK-free formulation preserved with polyquaternium-1 with BAK-preserved travoprost in ocular hypertension or open-angle glaucoma. Eur J Ophthalmol. 2012;22(1):34-44. 5. Peace JH et al. Polyquaternium-1–Preserved Travoprost 0.003% or Benzalkonium Chloride–Preserved Travoprost 0.004% for Glaucoma and Ocular Hypertension. Am J Ophthalmol. 2015, Aug; 160(2):266-274e1. 6. Barnebey HS et al. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. Am J Ophthalmol. 2005;140(1):1-7.

DUOTRAV®

Important note: Before prescribing, consult full prescribing information. **Presentation:** Oval bottle: Each ml of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate). **Indications:** Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues. **Dosage and administration:** •**Use in adults, including the elderly population (65 years and above)**: The dose is one drop of DUOTRAV® eye drops in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. It should be administered at the same time each day. If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily. •**Special Populations (Hepatic and renal impairment):** No studies have been conducted with DUOTRAV® eye drops or with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment. Travoprost® alone has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dose adjustment was necessary in these patients. Patients with hepatic or renal impairment are unlikely to require dose adjustment with DUOTRAV® eye drops. •**Pediatric population (below 18 years):** The safety and efficacy of DUOTRAV® eye drops in children and adolescents below the age of 18 years have not been established. No data are available. **Contraindications:** •Hypersensitivity to the active substances, or to any of the excipients. •Reactive airway disease including bronchial asthma, a history of bronchial asthma or severe chronic obstructive pulmonary disease. •Sinus bradycardia, sick sinus syndrome (including sino-atrial block), second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock. **Warnings and Precautions:** •**General:** Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic blocking component in ophthalmic timolol, the same types of cardiovascular and pulmonary and other adverse reactions seen with systemic beta adrenergic blocking agents may occur. •**Cardiac disorders:** In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and for adverse reactions. •**Vascular disorders:** Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution. •**Respiratory disorders:** Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. •**Hypoglycaemia/diabetes:** Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia. •**Hyperthyroidism:** Beta-blockers may also mask the signs of hyperthyroidism. •**Muscle weakness:** Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalized weakness). •**Anaphylactic reactions:** While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions. •**Ocular effects:** Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. The change in iris colour occurs slowly and may not be noticeable for months to years. Periorbital and/or eyelid skin darkening has been reported in association with the use of travoprost. Travoprost may gradually change eyelashes in the treated eye(s); these changes include increased length, thickness, pigmentation, and/or number of lashes. Macular edema has been reported during treatment with prostaglandin F2a analogues. Use travoprost with caution in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema. DUOTRAV® eye drops should be used with caution in patients with active intraocular inflammation, as well as patients with predisposing risk factors for uveitis. Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues. •**Choroidal detachment:** Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures. •**Surgical anaesthesia:** Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patients is receiving timolol. •Ability to drive and use machines: As with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines. Interactions: •**Other beta-blocking agents:** The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be exaggerated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended. •**Combination therapy:** •Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol. •There is a potential for additive effects resulting in hypotension and/or marked bradycardia when an ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics. •Beta-blockers can decrease the response to adrenaline used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis. •Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally. **Adverse drug reactions:** • **From clinical trials •Very common (≥ 10%): ocular hyperaemia. •Common (≥ 1/100 to < 1/10):** punctate keratitis, vision blurred, dry eye, eye pain, eye pruritus, ocular discomfort, eye irritation, •**Uncommon (≥ 1/1000 to < 1/100):** hypersensitivity, dizziness, headache, keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes, bradycardia, hypertension, hypotension, dyspnoea, dermatitis contact, hypertrichosis, skin hyperpigmentation (periorbital or eyelid pigmentation) •**Rare (≥ 1/10,000 to < 1/1000):** corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis, dysphonia, bronchospasm, cough, throat irritation, urticaria, skin discolouration • **From spontaneous reports and literature cases (frequency not known):** Depression, macular oedema, eyelid ptosis, lid sulcus deepened, iris hyperpigmentation, chest pain, palpitations, oedema peripheral, dysgeusia, asthma, rash, alopecia.

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For Healthcare Professionals only

TRAVATAN® BAK-free 40 micrograms/ml eye drops, solution travoprost

IZBA™ 30 micrograms/ml eye drops, solution travoprost

DUOTRAV® BAK-free 40 micrograms/ml + 5 mg/ml eye drops solution (travoprost/timolol)