TAILORED MYDRIASIS FOR EFFICIENT PROCEDURES

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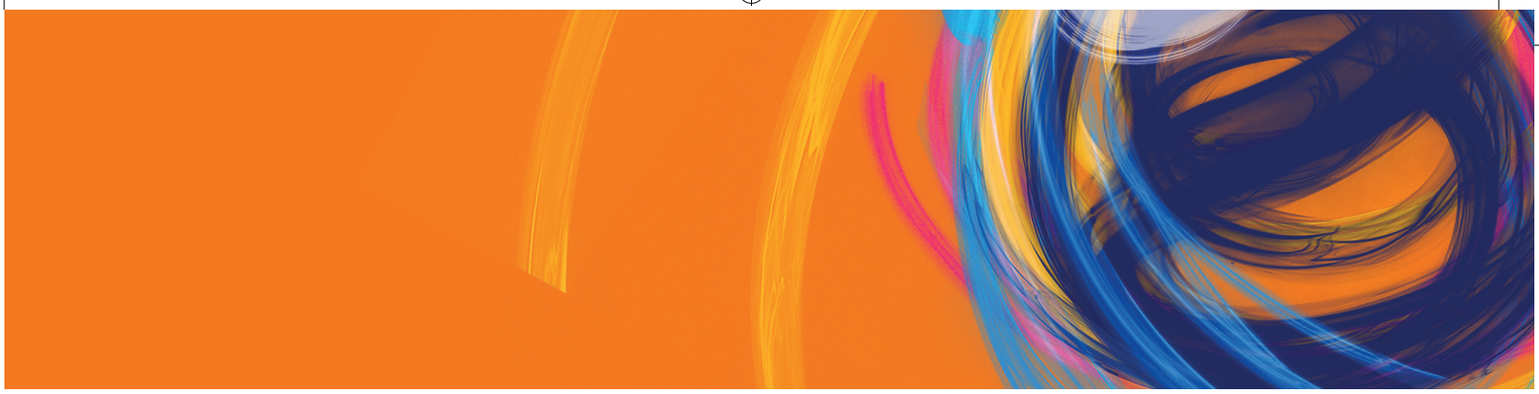
Théa
Driving innovation



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CONTENTS

PREFACE

Since its creation, Théa has been known for numerous innovations in advanced drug delivery systems, in the development of new molecules and in the improvement of existing products through galenic development. For ophtalmic surgeons, Théa provides dedicated products such as intracameral cefuroxime, but also classic drops for eye dilation. Recently, Théa has developed two more interesting alternatives to achieve intraoperative mydriasis:

- An ophthalmic insert* placed in the inferior conjonctival fornix before cataract surgery (or a dilated eye exam).
- An intracameral solution** combining two mydriatic agents and an anaesthetic, tailored for cataract surgery.

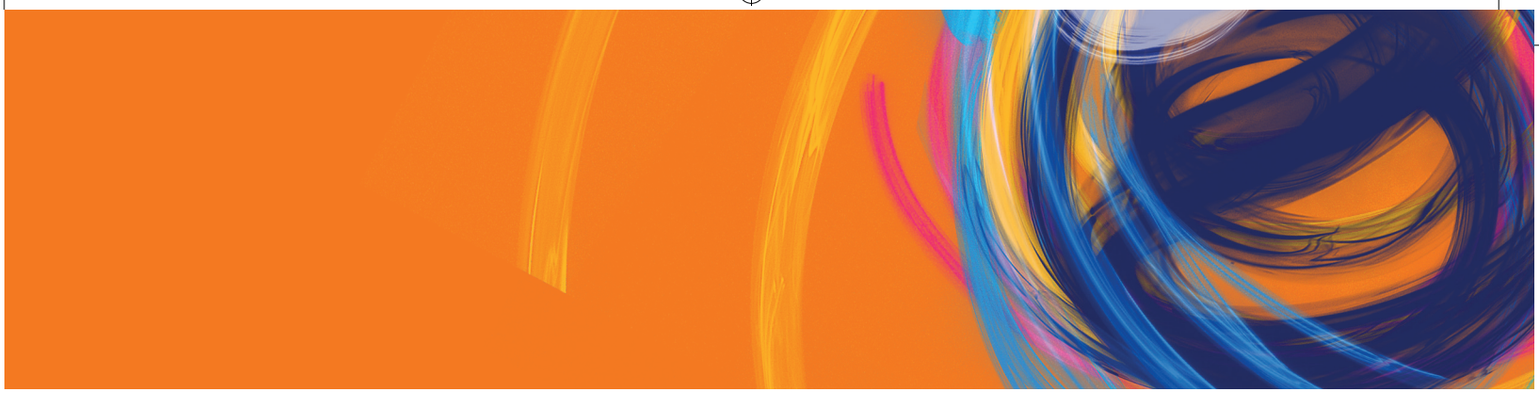
These two formulations allow us to control the amount of active ingredients delivered into the eye, and can thereby simplify patient handling and reduce the risk of potential side effects - systemic as well as local.

A key role in modern ophthalmology

The value of the abovementioned advances can be seen clearly in modern ophthalmological techniques. Sufficient and stable pupil dilation is essential for successful diagnosis and treatment in many ophthalmological situations, in particular in cataract and retinal surgical procedures. Whether one chooses to emphasize cost effectiveness, minimizing patient discomfort and waiting time or limiting side effects, we all benefit from rapid pupil dilation with sufficient duration and with minimal input from our medical staff. Since advanced techniques for treatment and surgery become more widely available globally, the demand for these techniques grows as a reflection of the ageing population.

Increasing burdens on healthcare resources have triggered the development of improved methods of achieving mydriasis that better meet the volume of traffic through the clinic or operating theatre. Hence, while the current standard use of mydriatic eye drops still retains a valuable place, particularly in ophthalmic examinations and more non-invasive treatments, eye drops is likely to get a more prominent role in intraocular surgery in the future.

*Mydriasert®, Tropicamide 0.28 mg & Phenylephrine hydrochloride 5.4 mg, ophthalmic insert.
** Mydrane®, Tropicamide 0.2mg/mL + Phenylephrine 3.1 mg/mL + lidocaine 10mg/mL, solution for injection



The ideal mydriatic agent

The ideal mydriatic agent would be one that acts quickly and effectively in inducing a reliable and stable pupil dilation with an adequate duration. It would be associated with the least possible local or systemic adverse effects (such as patient discomfort or effects on the systemic circulation); it would require minimal time spent in the clinic or hospital for the patient, and minimal effort from medical and nursing staff. Developing the ideal solution for each application has been a focus for research in this field of ophthalmology. The road to success depends on the mode of action of the agents but - not to forget - also on the route of administration. The recent advances mean that ophthalmologists can tailor mydriatic administration according to the situation to attain the best outcome. This booklet summarizes the information relating to the options available for achieving mydriasis and aims to help you choose the best options for your clinical practice, whether it is:

- Pre-examination for diagnosis - options: eye drops; insert
- Therapeutic - eye drops
- Pre-surgery e.g. cataract, retinal procedures - eye drops, insert, or intracameral injection.

Professor A. BEHNDIG

1. ACHIEVING MYDRIASIS

KEY POINTS:

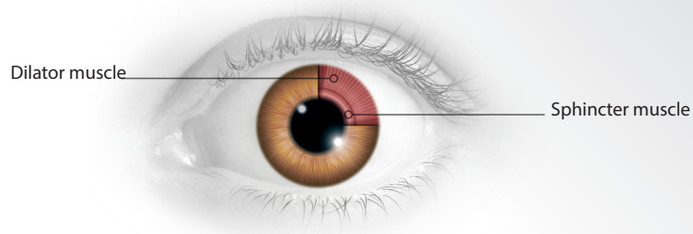
- Pharmacological pupil dilation typically combines cycloplegic and non-cycloplegic agents because of their complementary effects.
- Optimal mydriasis depends not only on the active agents but on the routes of administration, each of which holds advantages depending on the clinical situation.

1.1 Mydriatic agents

Pupil dilation is achieved pharmacologically in two ways (Figure 1):

The pupil is under the control of the autonomic nervous system. Parasympatholytic as well as sympathomimetic drugs have been used to dilate the pupil. The parasympathetic regulation dominates over the sympathetic effect in the control of the pupil. Therefore, application of only the sympathomimetic drug is usually inadequate to sustain the pupil dilatation in bright light during indirect ophthalmoscopy. However, parasympatholytic agents alone may not provide sufficient pupil dilatation. Combination of both drugs offers greater pupil dilatation than single drug use[1].

FIG.1 Complementary modes of action



NON CYCLOPEGIC MYDRIATICS	CYCLOPEGIC MYDRIATICS
• Stimulation of the sympathetic nervous system	• Inhibition of the parasympathetic nervous system • Paralysis of the ciliary muscle (cycloplegia)
→ Sympathomimetics	→ Parasympatholytics
• Contraction of the iris dilatator muscle	• Relaxation of the iris sphincter muscle • Paralysis of accommodation
• Adrenaline • Phenylephrine	• Atropine • Cyclopentolate • Tropicamide

Cycloplegic and non-cycloplegic agents have complementary modes of action and may be used in combination

1.2 Routes of administration

1.2.1 Eye drops

Routinely used in outpatient settings for examinations and diagnosis, topical administration of mydriatics (tropicamide, phenylephrine etc.) can achieve adequate dilation within at least half an hour.

Tropicamide has a more rapid onset whereas maximum mydriasis occurs later with phenylephrine. The topical route may need several administrations to get an adequate pupil dilation.

Pharmacokinetic profiles vary widely within the group, so the choice of mydriatic depends on the objective of the dilation (cycloplegic refraction) or clinical situation, e.g. from 5 to 24 hours for phenylephrine and cyclopentolate[2,3,29].

1.2.2 Sponge & insert

As new forms of timolol sustained release (LP) developed in the treatment of glaucoma, new dosage forms reduce the amount of mydriasis in the eye and therefore the amount of principle potentially absorbed by the systemic route.

In the context of mydriatics, innovative devices associating 2 types of mydriatic molecules, cycloplegic and not cycloplegic have been developed.

Thus forms «sponges» impregnated with mydriatics[36,37] or "inserts"[8,5,38] containing the equivalent about one drop of tropicamide and one drop of phenylephrine are currently available. These new galenic forms containing phenylephrine and tropicamide induce a satisfactory mydriasis[8,5,38] with 5 to 10 times less active ingredients compared to the combination of 10% phenylephrine eye drops and 0.5% tropicamide.

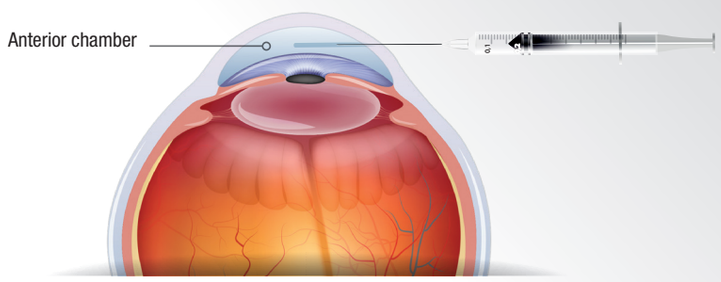
These devices allow not only to better control of the quantities of active ingredients but also to limit the quantity of active ingredients passing into the general circulation, which is one of the key advantages of this galenic form in medical practice. Such devices provide effective and stable mydriasis during 1 hour, which remains comfortable for the surgeon. The satisfactory tolerance of these devices has been demonstrated[35,5,38].

The ophthalmic insert allows mydriasis to be achieved with a lower dose of active agent compared with eye drops

1.2.3 Innovative forms: intracameral injection

The intracameral (IC) route involves injecting the active agents into the anterior chamber after the first incision at the start of surgery (Figure 2).

FIG.2 Injection of mydriatics into the anterior chamber



IC injection holds several advantages (detailed later): it is given in the operating room, exerts its effect in seconds, and offers an effective and safer alternative to topical mydriatics in surgery[3,10,12].

Pioneered by Swedish ophthalmologists over 10 years ago, the technique of IC injection has been routinely used by many centres for some time, but preparations made in their local pharmacies have been prone to human error such as the inclusion of benzalkonium chloride-preserved intracameral lidocaine and phenylephrine with an associated risk of toxic anterior segment syndrome[13]. Some of these risks may be reduced with the use of an approved, pre-packaged mydriatic and anaesthetic solution.

Intracameral injection of mydriatics, achieves almost immediate mydriasis, hence limits delay in surgery while enhancing patient comfort and improving management of the surgical list[3,14,15]

2. CLINICAL APPLICATIONS FOR MYDRIASIS

A good pupil dilation is essential in numerous situations, including for examination in the consultation room to allow accurate diagnosis as well as in surgery.

KEY POINTS:

- Mydriasis is required for a wide range of clinical applications
- Easy to administer, low-cost options are ideal for diagnostic situations
- Burgeoning demand for eye surgery, especially cataract procedures, requires fast, efficient and safe methods of mydriasis
- An essential aspect of route of administration in preoperative situations is to prevent unstable mydriasis, a major cause of complications.

Overview: when is mydriasis needed?

- Cataract surgery
- Retinal surgery
- When there is an unexplained decrease or unexplained difference in visual acuity between the two eyes that has not been detected previously
- To explore a peripheral lesion that cannot be viewed without using mydriatics
- In the presence of visual symptoms, in particular photopsia, metamorphosia, spots, shadows
- In the presence of higher myopia >4D, or in patients showing myopic degeneration
- In cases of any degree of myopia where there is family history of retinal detachment
- When a patient has had previous retinal detachment in either eye
- In aphakic patients
- For the differential diagnosis of either media or fundus lesions
- For lens, vitreous or fundus photography
- For fluorescein, indocyanin, autofluorescence angiography
- In children and some adults to check refraction

2.1 Mydriasis for diagnosis

When is mydriasis needed?

Pupil dilation is essential for examination in the consultation room to allow accurate diagnosis in multiple situations.

Diagnostic examinations requiring mydriasis include:

Examination	Usual size of dilation needed
Refraction examination	6-8 mm
Usual fundus at the end of consultation	6-8 mm
Fluorescein or Indocyanine Green (ICG) angiography	Maximal – 8 mm
Optical Coherence Tomography (OCT)	Mild – 6-7 mm
Electro-Retinogram (ERG)	Maximal – 8 mm

Goals for mydriasis in diagnosis:

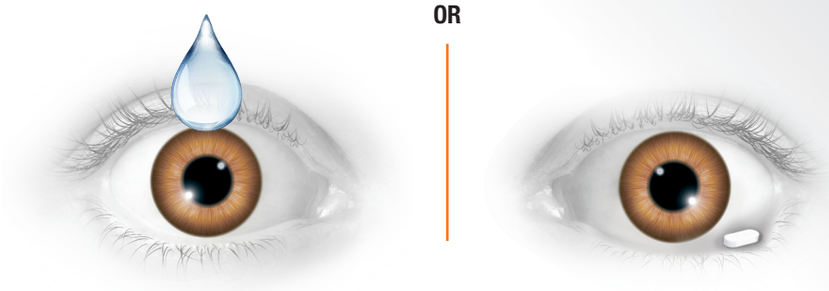
- Fast onset
- Well tolerated
- Easy to administer
- Low cost

Meeting the goals: Routes of administration for diagnosis

- Eye drops - active agents instilled as separate drops up to 1-2 hours before examination
- Insert - slowly releases tropicamide and phenylephrine into the conjunctival sac, inserted 1- 2 hours before examination.

MYDRIASIS FOR DIAGNOSIS THROUGH

EYE DROP **OR** **OPHTHALMIC INSERT**



2.2 Mydriasis for treatment

When is mydriasis needed?

Mydriatic treatments to limit synechia and relax the ciliary body, in cases of uveitis, post cataract surgery, and laser treatment-retinal photocoagulation, require a mydriasis of 6-8 mm. Mydriatics can be also used in limit pain and in some ulcers case. Mydriatics can also be useful post-operatively, for example, following cataract surgery where mydriatics help the eye to stay well-formed and recover when the eye pressure gets too low.

Goals for mydriasis in treatment:

- Well tolerated
- Long duration and stable mydriasis to avoid frequently repeated doses
- Easy to administer
- Low cost

MYDRIASIS FOR TREATMENT THROUGH: EYE DROP

Meeting the goals: Routes of administration for treatment

• Eye drops - the most practical way of achieving mydriasis in the treatment setting. They are almost universally availab le and can be self-administered by patients at home if required.

2.3 Pre-operative mydriasis

When is mydriasis needed?

Pupil dilation, giving the surgeon access to the internal structures of the eye, is needed in several types of procedures, most commonly cataract surgery and retinal surgery. Pupil dilation reduces the risk of complications arising from surgical procedures.

Procedures requiring mydriasis include:

Mydriatics use for dilation in cases of ocular surgeries	Usual size of dilation needed
Cataract surgery	Dilation ≥6 mm
Cataract surgery with femtosecond laser	Dilation ≥6 mm (risk of miosis after laser)
Retina surgery	Maximal dilation 8 mm
Laser surgery of retina	Maximal dilation 8 mm
Laser YAG capsulotomy	Mild dilation 6-7 mm

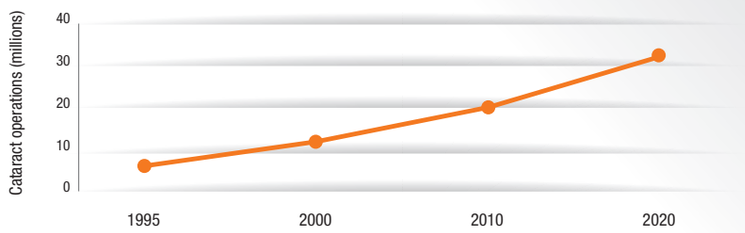
Goals for mydriasis in cataract surgery:

- Minimally invasive
- Well tolerated
- Fast onset
- Adequate pupil size
- Easy to administer
- Low cost
- Stable throughout surgery

2.3.1 Cataract surgery

Cataract surgery is one of the most common surgical procedures worldwide - and demand for the minimally invasive procedure as well as for ambulatory procedures are rising due to our ageing population. Estimates predict that by 2020, some 32 million cataract operations will be carried out around the world that year (Figure 3)[16].

FIG.3 Global cataract target



In cataract surgery, pupil dilation needs a longer time than the procedure itself. In this context, having a safe and effective way to obtain a fast and stable onset of pupil dilation is of great importance.

In high-volume cataract surgery the process of preparing patients' pupil dilation should be as straightforward, safe, simple, repeatable, and effective as possible[3]

2.3.2 Retinal surgery

Retinal surgery includes vitrectomy for:[17,18]

- Retinal detachment
- Macular holes
- Vitreous haemorrhage
- Epiretinal membranes
- Diabetic retinopathy
- Eye trauma
- Complications of cataract surgery

Retinal procedures require long-lasting, stable mydriasis that will maintain a large pupil throughout a potentially lengthy operation.

Stable dilation and rapidly reaching target pupil size are key to allowing fast and efficient surgery

Overcoming the challenge of unstable mydriasis

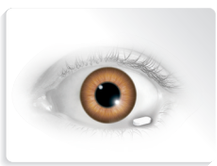
Unstable mydriasis is one of the most challenging issues affecting the outcome of surgical procedure (mainly cataract) and some postoperative problems. Poorly dilated pupils - inadequate mydriasis - can dramatically increase the risk of intraoperative complications such as iris sphincter trauma, posterior capsule tear, vitreous loss, dropping of the lens material into the vitreous chamber or even retinal detachment. Resulting postoperative concerns can include irregular shape of the pupil, atonic pupil, discomfort, glare, photophobia and a lack of expected improvement in visual acuity.

Therefore, use of mydriatics should aim for a pupil diameter of 6.0-9.0 mm depending on the level of experience of the surgeon. It should achieve a mydriasis that is fast, intense and, most importantly, stable for the duration of the procedure.

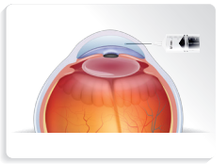
Mydriasis that is unstable is one of the biggest challenges affecting the outcome of surgical procedure and certain postoperative problems

Meeting the goals: Routes of administration for pre-operative use

- Eye drops[28,29] - active agents instilled as separate drops up to 1-2 hours before surgery



- Insert[30] - slowly releases tropicamide and phenylephrine into the conjunctival sac, inserted 1- 2 hours before surgery



- Intracameral (IC) injection[31] - surgery only, after first incision to get immediate pupil dilation

3. CHOOSING THE RIGHT MYDRIATIC GALENIC FORMAT

KEY POINTS:

- Each route of mydriatic administration has its pros and cons
- Eye drops can be self-administered and are useful for treatment situations or due to their rapid onset and recovery for diagnosis purpose
- As insert Mydriasert®* requires a single administration and uses a lower dose of active agent than eye drops, it has improved safety and can be used in most diagnostic situations[30]
- Insert (Mydriasert®*) can be used for other types of ocular surgery when a very large pupil dilation is required for specific surgical conditions
- Intracameral injection Mydrane®** is the gold standard choice for pupil dilation in cataract surgery, achieving almost immediate mydriasis, allowing fast track operation management and futhermore it is associated with pain relief[31]

Each type of mydriatic has its advantages and limitations. The following is a guide to help make the best choice for each clinical situation. Using non-standardised home-made solution or 'kitchen' preparations may be at risk:

- It can increase the risk of dilution error and overdosing which can be a problem especially for people at risk
- It can increase the risk of contamination
- Or it can increase the risk of accidental use of inappropriate product or the risk of ocular safety

*Mydriasert®, Tropicamide 0.28 mg & Phenylephrine hydrochloride 5.4 mg, ophthalmic insert is indicated to obtain pre-operative mydriasis, or for diagnostic purposes when monotherapy is known to be insufficient.
** MYDRANE® is indicated for cataract surgery to obtain mydriasis and intraocular anaesthesia during the surgical procedure. MYDRANE® is indicated in adults only.

3.1 Eye drops

3.1.1 Eye drops in diagnosis and treatment

When eye drops are particularly useful?*

Type of examination	Active compound	Comment
Fluorescein angiography	Tropicamide or cyclopentolate	Mydriasis is mandatory; if mydriatic camera is not used
Asthenopia	Mainly cyclopentolate or atropine	Cycloplegic auto-refraction should be performed in young hypermetropic adults complaining of signs of asthenopia[19]
Refraction measurement	Mainly cyclopentolate (Tropicamide in case of contra-indication)	Cycloplegic refraction is considered the gold standard for refraction in children and adults up to age 50 years[20]
Routine fundus examination	Tropicamide	In some patients the addition of phenylephrine is useful (diabetic...)
LASIK (wavefront-based LASIK procedure aberrometric measurements)	No specific recommendation	The more dilated the pupil is, the more aberrations can be identified
Diabetic retinopathy screening	Tropicamide ± Phenylephrine	Pupillary dilation improves fundoscopy and image quality. One common approach is to use selective mydriasis if the photographer is unable to obtain adequate images with non-dilated pupils

* based on medical consensus; specific guidelines do not exist in many countries.

Advantages of eye drops in diagnosis and treatment

- Choice of the active agent
- Choice of the dosage. Very important fo paediatric use which requires appropriated/lower dosage
- Choice of the posology
- Achieve large pupil dilation
- Lasts long enough for most diagnostic situations
- Easy to administer by a nurse

Limitations of eye drops

- Time consuming for nurse and patient
- When administering eye drops, it can be difficult to control the number of drops
    - hence a risk of overdosing and causing systemic side effects especiallyin elderly, prostatic, cardiovascular patients and children
- Eye drops may trigger acute angle-closure glaucoma
- Local irritation/ ocular surface alteration due to preservative
- Eye drops need to be instilled 30 mins before the examination, hence time consuming for patients waiting in clinic or hospital
- Multiple instillations may be needed to attain satisfactory mydriasis. This in turn:
    - Places a burden on patient and nursing staff tim
    - Increases the risk of side effects

Eye drops achieve a mydriatic effect that is long enough for most diagnostic situations and offer a practical solution for patients needing mydriasis for treatment, but have several drawbacks

WHEN MYDRIATIC EYE DROPS ARE NOT APPROPRIATE

Contraindications include:

- Known or suspected predisposition to angle-closure or presence of angle-closure glaucoma. In these cases, the non-mydriatic camera or three mirror lens may be a suitable alternative for imaging of fundus periphery.

However, it is sometimes suggested that mydriasis with low concentration tropicamide alone seems to be safe in people with chronic glaucoma[21]. It should be advised in all patients with glaucoma when thorough retinal examination is indicated.

- Known hypersensitivity to topically administered mydriatics.
- If the patient is a labile hypertensive or has cardiac disease.

3.1.2 Eye drops in surgery

Eye drops are considered too restrictive to fit with the modern fast track approach to cataract surgery. They have low bioavailability and delayed effect due to the slow penetration of active ingredient through the cornea. The mydriatic effect may weaken during the procedure, requiring repeated drops; in the European Observatory of Cataract Practice[22], additional mydriatics were needed in 14% of cataract operations. The procedure was delayed due to problems with pupil dilation in 7.2% of the cases, with an average delay of almost 13 minutes - close to the time needed for the operation itself.

These delays can disrupt the flow of patients through the operating room, so the subsequent patients on the surgery list may not be sufficiently dilated by the time they reach the operating table.

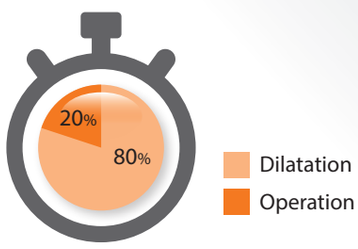
Advantages of eye drops in surgery

- Achieve large pupil dilation
- Easy to administer by a nurse
- Low cost

Limitations of eye drops

- Time-consuming: 80% of time is spent in the dilation phase, only 20% on the surgery itself (Figure 4)
- Slow penetration of the active agent through the cornea means pupils enlarge slowly[3]
- It can be difficult to maintain stable mydriasis throughout the procedure. The weakening of the mydriatic effect can:
  - Increase the risk of surgery-related complications[3]
  - Prolong and disrupt the procedure[22]
  - Repeated instillations lead to increased risk of systemic adverse effects[3]
  - Systemic toxicity to these medications has been reported in all age groups; paediatric patients are particularly prone to these adverse effects. The conjunctival sac retains only one-fifth of one drop with the excess solution overflowing onto the cheek or drained through the nasolacrimal system. Therefore, systemic absorption of excess drug may occur and induce an increased risk when multiple drops are instilled.[23]

FIG.4 Time spent on dilation vs cataract procedure[24] with eye drops procedure



Adapted from Pr Behnding[24]

Average delays caused by weakening mydriasis seen with eye drops are almost equivalent to the time needed for the cataract surgery

3.2 Ophthalmic insert[30]

The ophthalmic insert, Mydriasert®, contains a combination of low-dose phenylephrine (5.38 mg) and tropicamide (0.25 mg) in a controlled release device. The device is applied to the inferior conjunctival fornix; the active agents are then released into the tear film.

The total dose included in the insert is equivalent to 1 drop of tropicamide 0.5% and 1 drop of phenylephrine10%[3]. These active agents are released slowly and progressively at nearly constant tear concentration to produce effective and stable intraocular concentrations[3].

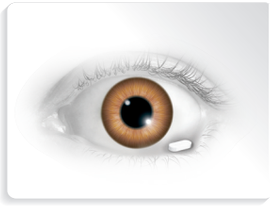
Clinical trial data have demonstrated that combination preparations of reduced concentrations of tropicamide and phenylephrine can produce clinically adequate mydriasis[4].

Trials have shown good efficacy and tolerability both in patients having diagnostic procedures and in those undergoing eye surgery[5,6]. The insert is also well suited to retinal surgery.

Mydriasert® holds several advantages over eye drops[5,7,8]. As the insert requires only a single administration and uses a lower dose of active agents, it has improved systemic and local safety compared with eye drops, and allows more effective time management and a reduced nurse workload which can lead to overall savings in healthcare costs9. In addition, near eyesight recovery is faster with Mydriasert® and this may provide an improvement in patient safety and comfort at the end of an ophthalmic visit[5].

Optimal mydriasis with Mydriasert® is achieved within 30-40 minutes ; stable mydriasis is maintained for 90 minutes.

3.2.1 Mydriasert® in diagnosis[30]



When the insert is particularly useful

- Fluorescein angiography - Mydriasert® allows adequate mydriasis for retinal angiography in both diabetic and non-diabetic patients[5,25].The low total drug dose administered with the insert reduces the risk of potential cardiovascular side effects. Near eyesight recovery is faster with Mydriasert®, so could provide an improvement in patient comfort at the end of the ophthalmologic visit.

- Mydriasert® is suitable for most other diagnostic situations and has the advantage that repeated instillations are not required in incidences where there is a long wait time.

Advantages of Mydriasert® in diagnosis

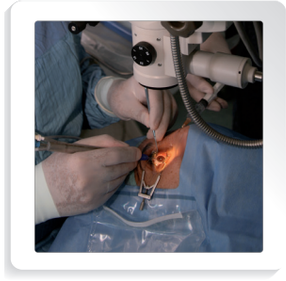
- Induces a large, stable, and persistent mydriasis across various sub-populations including patients with diabetes and dark iris
- Good tolerability increases the patient's acceptance of the medication
- Only minor side effects e.g. foreign body sensation
- Single use and sterile pack reduces risk of local infection
- Preservative-free
- Simple to use - reduces nurse workload

Limitations of insert

- Slower onset of action than eye drops; needs to be inserted at least 1 hour before examination[25]
- Nursing staff require training to ensure that the insert is correctly positionned
- Needs to be removed before the examination

The gradual release of the active agent from the ophthalmic insert means it requires a lower total dose of mydriatic for a consistent pupil dilation; hence a lower risk of side effects

3.2.2 Mydriasert® in surgery



Advantages of Mydriasert® in surgery

A review of studies showed:[3]

- The insert is suitable for all surgical procedures that need pupil dilation
- It induces reliable, large, and persistent mydriasis in all subgroups of patients undergoing cataract surgery
- Maximum dilation is the same or larger than achieved with eye drops
- Preservative-free so no risk of toxicity
- Good tolerability; excellent local and systemic safety
- Reduced nurse workload may cut costs

Limitations of insert

- Onset of dilation is slower than with eye drops[3]

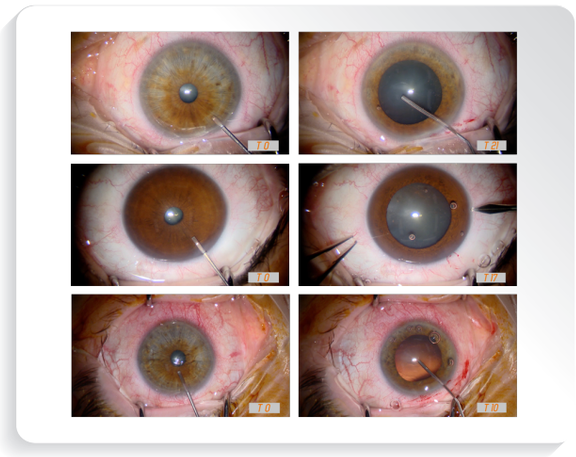
Surgery: Insert and eye drops compared

Compared with eye drops, the maximum mydriatic effect takes longer to reach with the insert but then lasts longer and achieves a larger pupil size. Hence it is well-suited to both lens and retinal surgery[26].

In a study of 80 patients undergoing cataract surgery, Mydriasert® achieved similar levels of mydriasis to that achieved with 3 drops each of phenylephrine and tropicamide both at the beginning and the end of surgery[6].In practice, instillation of eye drops can be time-consuming especially as multiple drops are often needed; hence the insert could result in time savings and improve patient throughput, the authors concluded [8].

With its longer-lasting effect and larger pupil size attained compared with eye drops, the insert is well-suited to both lens and retinal surgery[26]

3.3 Intracameral (IC) injection



Mydrane®: Innovation in mydriasis[31]

Mydrane® is a ready-to-use IC injection combining the mydriatics tropicamide 0.02% and phenylephrine 0.31%, as well as the anaesthetic lidocaine 1%.

Mydrane® is intended for patients who have demonstrated a satisfactory pupil dilation with topical mydriatic therapy at preoperative assessment.

The **efficacy** and **safety** of Mydrane® have been demonstrated in a large scale clinical trial published by Labetoulle et al[14], showing that capsulorhexis has been performed without the need for additional mydriatics in 98.9% of the patients. The need to 'top up' mydriasis is a recognised problem associated with eye drops.

Improving patient comfort through IC anaesthesia

Among mydriatics available on the market, Mydrane® is the only formulation that contains **lidocaine** for improved **patient comfort**.

Anaesthesia given via the IC route as part of Mydrane® enhances the effect of topical anaesthesia, which can be troublesome particularly in unusually long surgical procedures. The IC route for pain control enhances patient comfort, reducing pain and the sensation of pressure just before IOL insertion during cataract surgery[14]. It also has a small **additional effect on pupil dilation** through the anaesthetic effect on the nerves.

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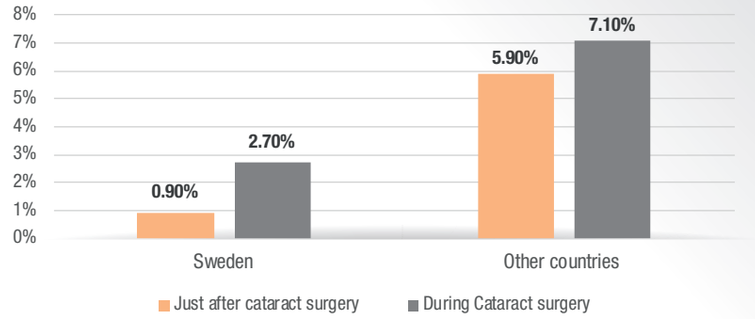
The Swedish experience has found that IC anaesthesia contributes to better pain management during and after cataract surgery, as shown when figures are compared with those from other countries (Figure 5)[15].

FIG.5 The rate of patients perceiving insufficient pain control



When IC injection is particularly useful

As cataract surgery techniques have evolved, the emphasis has been on **cost-effective mydriasis** and **anaesthesia, less time for patients** at the hospital, and fewer demands on time spent by hospital staff. Key to this process is optimal mydriasis allowing for[3,24,27]:

- Visualising the intraocular structures
- Ensuring complete removal of the lens
- Accurate placement of the IOL
- **Reducing the risk of intraoperative complications** e.g. posterior capsule rupture.

The requirements of **stable and large** mydriasis for cataract surgery were confirmed in a survey of surgeons' expectations, as part of the European Observatory of Cataract Practice[22].

Stable dilation and rapidly reaching target pupil size are key to allowing fast and efficient surgery

Advantages of Mydrane® in surgery

- Simplifies pre-operative preparation
- Allows fast track management of patient flow, hence more cataract procedures per theatre session
- No pre-operative waiting time for patients
- Less time spent by nursing staff administering the mydriatic
- Rapid onset of action - 95% mydriasis reached within 30 seconds
- Stable and long-lasting pupil dilation - lasts throughout the operation
- Reduced dose of mydriatics required for desired effect, hence lower risk of systemic side effects compared with eye drops
- Inclusion of lidocaine 1% improves patient and surgeon comfort and adds to pupil dilation
- Having calm patients ensures more comfortable conditions for the surgeon
- Local safety is similar to eye drops: no additional risk to corneal endothelial cell loss
- Less glare. Lack of ocular surface toxicity (no preservative)
- Available as a ready-to-use standardised, preservative-free injectable solution prepared according to industrial quality controls: this may hold benefits over custom preparation

Limitations of Mydrane®

- Use of IC injection requires a reorganisation of the surgical pathway for nursing staff and surgeons - but once in place this allows a more efficient process
- Patients with narrow anterior chamber with risk of irido-corneal angle closure

Cataract surgery: IC route and eye drops compared

A Phase III study comparing Mydrane® with a standard topical regimen of tropicamide 0.5% and phenylephrine 10% in 555 patients undergoing cataract surgery found that more patients receiving the topical regimen needed additional mydriatics than those receiving Mydrane® [14]. Furthermore Mydrane® was associated with less pain for patients during the surgery and an easier procedure for surgeons.

As Mydrane® provides both mydriasis and anaesthesia in less than one minute, it facilitates a fast track approach to surgery[14].This has been confirmed by experience from Sweden, where the IC route has been used for over 10 years with associated reductions in delays due to pupil dilation problems compared with other countries[15].

Compared with eye drops, IC injection offers a faster and more convenient way of dilating pupils and so facilitates a fast track system for surgery

3.4 Which mydriatic route is best for which situation?

3.4.1 Mydriasis for diagnosis: eye drops or insert

	Eye drops	Mydriasert®	Comment
Speed of onset	15-20 mins	45 mins	Mydriasert® has longer duration of mydriasis
Duration / stability	30 mins	2 hrs	
Active compounds	Choice (phenylephrine, tropicamide, atropine, cyclopentolate)	Phenylephrine + tropicamide	Most common recognised active mydriatics
Quantity of active compounds	Higher	Very low	Total dose of mydriatic agents less in insert than in eye drops Good systemic tolerance
Risk of systemic side effects	Higher	Small - Low dosage	Mydriasert®is well tolerated and has reduced risk of systemic side effects
Nurse involvement	Repeated instillations may be needed	Only once	Unlike eye drops, Mydriasert® does not require repeated instillations
Preservative	Yes (Multidose flask)	No	Preservatives can be associated with toxicity
Ocular surface	Could be cloudy	No ocular toxicity	Good local tolerance

Thanks to its two active molecules in a controlled release dose, Mydriasert® is an effective tool to induce stable and large mydriasis in most diagnostic situations

3.4.2 Mydriasis for treatment: eye drops

Eye drops for treatment

- Are simple to administer - patients can administer treatment at home
- Achieve large pupil dilation
- Are low cost

But drawbacks are

- Risk of systemic and local side effects especially as multiple instillations may be required
- Can be difficult to control the number of drops

3.4.3 Mydriasis for eye surgery

	Eye drops	Mydriasert®	Mydrane®	Comment
Speed of onset	15-20 mins	45 mins	30 secs	Mydrane® achieves almost immediate mydriasis, so eradicates delay due to mydriasis problems
Duration / stability	30 mins	2 hrs	Lasts until the end of the surgery	Longer lasting, stable mydriasisis achieved with Mydriasert® or Mydrane® than with eye drops
Active compounds	Choice (phenylephrine, tropicamide, atropine, cyclopentolate)	Phenylephrine + tropicamide	Phenylephrine + tropicamide + lidocaine	Most common recognised active mydriatics
Quantity of active compounds	Relatively High	Low dosage	Very low	Mydriasert® and Mydrane® substantially reduce total administered doses of tropicamide and phenylephrine
Risk of systemic side effects	Higher	Very low	Very low	
Nurse involvement	Repeated instillations may be needed	Only once (needs to be removed prior to the surgery)	None (only pre-surgery test)	Mydrane® reduces nurse workload to achieve effective dilation and this may lead to an economic advantage and improved through put, especially in high-volume surgical centres
Preservative	Yes	No	No	Preservatives can be associated with toxicity
Ocular surface	cloudy trouble	Clear	Clear	Mydriasert® and Mydrane® have no local safety concerns
Patient comfort	- Stressful - Pain and pressure feeling during surgery	- Pain and pressure feeling during surgery	- Less pre-operative stress - Less waiting time - Anaesthetic effect induces very low pressure or pain feeling during surgery	

Mydrane® is the method of choice for patients undergoing cataract surgery, while Mydriasert® can be used for other types of ocular surgery and for patients who are not eligible for Mydrane®

3.5 Overview of clinical applications

	Eye drops	Mydriasert®	Mydrane®
Diagnostic examination	++	++	
Treatment - in-clinic or at-home	++		
Pre-operatively – before entering the operating room	+	++	
Pre-operatively – in the operating room	+		+++
Peri-operatively	+		

4. TOPICAL ANTI-INFLAMMATORY IN EYE SURGERY

IMPORTANT NOTICE:

- **Trauma-induced miosis can lead to potentially serious complications in cataract surgery**
- **Treatment with a topical NSAID inhibits peri-operative miosis during cataract surgery and so helps maintain large pupil size for safe and effective surgery.**

Preventing miosis with topical NSAID eye drops

Surgically-induced miosis during cataract surgery represents an even more critical aspect than the inadequacy of initial mydriasis. A potentially serious problem, it can lead to intraoperative complications (posterior capsule tearing, iris injury, uveitis), significantly increasing the level of difficulty of the surgery. It occurs relatively frequently (5-10% of cataract procedures) and is highly unpredictable.

So far, intraoperative miosis has almost always been managed using mechanical devices such as hooks, rings and multiple rigid retractors.

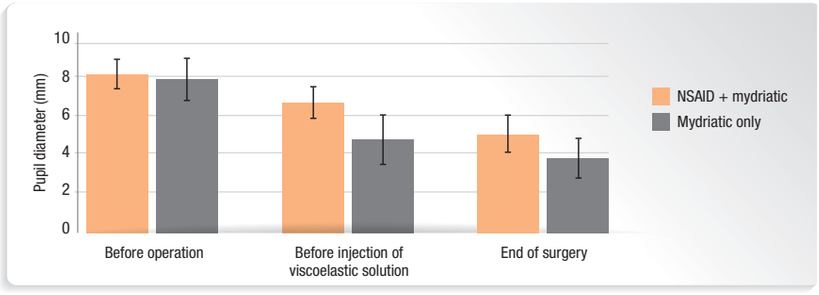
Topical non-steroidal anti-inflammatory drug (NSAID) such as diclofenac treatment given pre-operatively plays a valuable role in inhibiting miosis during ophthalmic surgery, helping maintain the large pupil size required for safe and effective surgery.

Role of topical NSAIDs

Pupillary miosis occurs as a response to the trauma of surgery. Tissue damage caused by surgical manipulation triggers the release of prostaglandins via cyclo-oxygenase activity, and this in turn can lead to constriction of the pupil, inflammation and pain in the eye.

For these reasons, topical NSAIDs are often used for pupil stabilisation pre-operatively during cataract surgery to prevent peri-operative miosis (Figure 6), as well as post-operatively to prevent inflammation and Cystoid Macular Oedema (CME) following the surgical procedure.

Schultz et al demonstrated that short-term non-preserved NSAID treatment (diclofenac) prevented prostaglandin release in patients with image-guided femtosecond laser. Therefore, it has potential to limit intra-operative laser-induced miosis.[34]



The NSAID diclofenac prevents pupillary miosis during surgery and so helps maintain large pupil diameter for a safe and effective operation

FIG 6: Effect of adding the NSAID diclofenac sodium on peri-operative pupil diameter:[32,33]

CONCLUSION

Mydriatics are widely used for several applications such as examination, treatment or pre-operatively. Nowadays, a large range of mydriatics agents is available and can be used via different route of administration. While appropriate mydriasis is usually achieved by the administration of topical eye drops, their use has drawbacks in terms of the time needed to dilate the pupil and the risk of systemic side-effects. That is why ophthalmologists have been looking for alternatives to improve on current methods.

The recent advances mean provide the ophthalmologists with **tailored mydriatic administration according to the application to achieve the best outcomes**. Eye drops should be used for treatment whereas insert is useful for diagnosis, pre-examination or pre-operatively when a very large mydriasis is needed.

Innovative development came out with i**ntracameral injection** of mydriatics. From a **patient and surgeon perspective**, the ideal mydriatic should be easy to administer, offer **pain-free surgery**, be **well tolerated** in the eye and have **low systemic side-effects**. Indeed, Mydrane® fulfil the needs and offers cataract surgeons a **rapid, effective and safe alternative** to topical mydriatics in phacoemulsification surgery, and improves the experience for the patients. The superior **patient comfort** with Mydrane® and a **better efficiency** gains using Mydrane® as part of this new protocol were also confirmed.

Thanks this innovative combination of mydriatics and lidocaine we are entering an era of almost drop-less cataract surgery and this is bringing with it numerous advantages to the patient and the surgeon.

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MYDRANE 0.2 mg/ml + 3.1 mg/ml + 10 mg/ml solution for injection.

QUALITATIVE AND QUANTITATIVE COMPOSITION: 1 ml of solution for injection contains 0.2 mg of tropicamide, 3.1 mg of phenylephrine hydrochloride and 10 mg of lidocaine hydrochloride. One dose of 0.2 ml solution contains 0.04 mg of tropicamide, 0.62 mg of phenylephrine hydrochloride and 2 mg of lidocaine hydrochloride. Excipient with a known effect: sodium (0.59 mg per dose; see section Special warnings and precautions for use). Excipient: Sodium chloride, Disodium phosphate dodecahydrate, Disodium phosphate dehydrate, Disodium edetate, Water for injections. **PHARMACEUTICAL FORM:** Solution for injection. Clear and slightly brownish-yellow solution practically free from visible particles. pH: 6.9 - 7.5. Osmolality: 290 – 350 mosmol/kg. **CLINICAL PARTICULARS: Therapeutic indications:** MYDRANE is indicated for cataract surgery to obtain mydriasis and intraocular anaesthesia during the surgical procedure. MYDRANE is indicated in adults only. **Posology and method of administration:** Intracameral use. One ampoule for single eye use. Mydrane must be administered by an ophthalmic surgeon. Posology: MYDRANE should only be used in patients who have already demonstrated, at pre-operative assessment, a satisfactory pupil dilation with topical mydriatic therapy. *Adults:* Slowly inject, by intracameral route, 0.2 ml of MYDRANE in only one injection, at the start of the surgical procedure. Special population: *Elderly:* No dose adjustment is necessary. *Paediatric population:* The safety and efficacy of MYDRANE in children aged 0 to 18 years have not been established. *Patients with renal impairment:* Considering the low dose and the very low systemic exposure (see section Pharmacokinetic properties), no dose adjustment is necessary (see section Special warnings and precautions for use). *Patients with hepatic impairment:* Considering the low dose and the very low systemic exposure (see section Pharmacokinetic properties), no dose adjustment is necessary. Method of administration: Intracameral use. The following procedure should be followed: Five minutes before performing the preoperative antiseptic procedure and the first incision, one to two drops of anaesthetic eye drops should be instilled in the eye. At the beginning of surgery, 0.2 ml of MYDRANE is slowly injected in only one injection by an ophthalmic surgeon, via intracameral route, through the side port or principal port. For instructions on handling the medicinal product before administration, see section Special precautions for disposal and other handling. **Contraindications:** Hypersensitivity to the active substances (tropicamide, phenylephrine hydrochloride and lidocaine hydrochloride) or to any of the excipients. Known hypersensitivity to anaesthetics of the amide type. Known hypersensitivity to atropine derivatives. **Special warnings and precautions for use:** ***Special warnings:*** The recommended dose is 0.2 ml of MYDRANE; no additional dose should be injected as no significant add-on effect has been demonstrated and as increased endothelial cell loss was observed. Corneal endothelial toxicity has not been reported at the recommended dose of MYDRANE; nevertheless, due to limited data, this risk cannot be excluded. There is no clinical experience with MYDRANE in: insulin-dependent or uncontrolled diabetic patients, patients with corneal disease, especially those with any coexisting endothelial cell impairment, patients with history of uveitis, patients with pupillary abnormalities or presenting an ocular traumatism, patients with very dark irides, cataract surgery when combined with corneal transplantation. There is no experience in patients at risk of floppy iris syndrome with MYDRANE. Such patients should benefit of a step-by-step pupil dilation strategy starting with the administration of mydriatic eye drops. There is no clinical experience during cataract surgery with MYDRANE in patients treated with topical mydriatics and for whom pupil constriction (or even miosis) occurs during surgery. MYDRANE is not recommended to be used in cataract surgery when combined with vitrectomy, due to the vasoconstricting effects of phenylephrine. MYDRANE is not recommended in subjects with a shallow anterior chamber or a history of acute narrow angle glaucoma. ***Special precautions for use:*** MYDRANE was shown to produce undetectable or very low systemic concentrations of active substances (see section Pharmacokinetic properties). Since systemic effects of phenylephrine and lidocaine are dose dependent, it is unlikely that these effects occur with MYDRANE. However, as the risk cannot be excluded, it is reminded that: Phenylephrine has sympathomimetic activity that might affect patients in the event of hypertension, cardiac disorders, hyperthyroidism, atherosclerosis or prostate disorders and all subjects presenting with a contraindication to the systemic use of pressor amines; Lidocaine should be used with caution in patients with epilepsy, myasthenia gravis, cardiac conduction disturbances, congestive heart failure, bradycardia, severe shock, impaired respiratory function or impaired renal function with a creatinine clearance of less than 10 mL/minute. This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free". **Interaction with other medicinal products and other forms of interaction:** No interaction studies have been performed with MYDRANE. Since the systemic exposure is expected to be very low (see section Pharmacokinetic properties), systemic interactions are unlikely. **Fertility, pregnancy and lactation:** Pregnancy: There are no adequate data from the use of phenylephrine and tropicamide in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonic/foetal development, parturition and postnatal development. Although animal studies have revealed no evidence of harm to the foetus, lidocaine crosses the placenta and should not be administered during pregnancy. Even though a negligible systemic uptake is expected, a low systemic exposure cannot be excluded. Therefore, MYDRANE should not be used during pregnancy. Breastfeeding: No data are available concerning the secretion of phenylephrine or tropicamide into breast milk. However, phenylephrine is poorly absorbed orally, implying that absorption by the infant would be negligible. On the other hand, infants may be very sensitive to anticholinergics, and despite the expected negligible systemic exposure, tropicamide is therefore not recommended during breast feeding. Small amounts of lidocaine are secreted into breast milk and there is a possibility of an allergic reaction in the infant. Therefore, MYDRANE should not be used during breast feeding. Fertility: There is no information on whether MYDRANE may affect fertility in human males or females. **Effects on ability to drive and use machines:** MYDRANE has a moderate influence on the ability to drive and use machines, due to its mydriatic effect. Consequently, after cataract surgery with one MYDRANE injection, the patient should be advised not to drive and/or use machines while the visual disturbances persist. **Undesirable effects:** Adverse reactions were reported with MYDRANE during clinical trials (see section Pharmacodynamic properties). Most were ocular and of mild to moderate intensity. *Summary of the safety profile:* Posterior capsule rupture and cystoid macular oedema are well known complications occurring during or after cataract surgery. They may occur uncommonly (less than 1 case per 100 patients). *Tabulated list of adverse reactions:* Adverse events are categorised by frequency as follows: 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); not known (frequency cannot be estimated from available data). Adverse reactions, reported during clinical trials, are presented according to System Organ Class in the table below in order of decreased seriousness within each frequency grouping: *Nervous system disorders* (uncommon): Headache. *Eye disorders* (uncommon): Keratitis, Cystoid macular oedema, Intraocular pressure increased, Posterior capsule rupture, Ocular hyperaemia. *Vascular disorders* (uncommon): Hypertension. Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V. **Overdose:** Due to single administration and low expected systemic passage of MYDRANE, overdose is not expected; however a risk of overdose cannot be excluded. One ampoule of 0.6 ml solution contains 0.12 mg of tropicamide, 1.86 mg of phenylephrine hydrochloride and 6 mg of lidocaine hydrochloride. The symptoms of phenylephrine ophthalmic overdose are likely to be effects resulting from systemic absorption, including extreme tiredness, sweating, dizziness, a slow heartbeat, and coma. Because severe toxic reaction to phenylephrine is of rapid onset and short duration, treatment is primarily supportive. Prompt injection of a rapidly acting alpha-adrenergic blocking agent such as phentolamine (dose 2 to 5 mg in intravenous use) has been recommended. The symptoms of tropicamide ophthalmic overdose include headache, fast heartbeat, dry mouth and skin, unusual drowsiness, and flushing. Systemic effects from tropicamide are not expected. Should an overdose occur causing local effects, e.g. sustained mydriasis, pilocarpine or 0.25% w/v physostigmine should be applied. In the event of excessive absorption of lidocaine into the bloodstream, symptoms may include CNS effects (such as convulsions, unconsciousness and possibly respiratory arrest) and cardiovascular reactions (such as hypotension, myocardial depression, bradycardia and possibly cardiac arrest). Treatment of a patient suffering from systemic toxicity of lidocaine consists of arresting the convulsions and ensuring adequate ventilation with oxygen, if necessary by assisted or controlled ventilation (respiration). **PHARMACOLOGICAL PROPERTIES: Pharmacodynamic properties:** Pharmacotherapeutic group: MYDRIATICS and CYCLOPLEGICS, Tropicamide combinations, ATC code: S01FA56. MYDRANE is a solution for intracameral injection which combines two synthetic mydriatic agents (tropicamide - anticholinergic, and phenylephrine - alpha sympathomimetic) and one local anaesthetic (lidocaine hydrochloride). *Mechanism of action:* Phenylephrine is a direct acting sympathomimetic agent. It causes mydriasis via the stimulation of alpha-adrenergic receptors of the pupillary dilator (the resulting contraction of the pupillary dilator causes pupil dilation). There is almost no cycloplegic effect. Tropicamide is a parasympatholytic agent, which acts by binding to and blocking the M4 muscarinic receptors of the eye muscles. It prevents the iris sphincter muscle and ciliary body muscle from responding to cholinergic stimulation, producing dilation of the pupil and paralysis of the ciliary muscle (cyclopegia). Lidocaine is a local anaesthetic of the amide type. It acts by inhibiting the ionic refluxes required for the initiation and conduction of impulses, thereby stabilising the neuronal membrane. *Pharmacodynamic effects:* Although tropicamide as a monotherapy produces both mydriasis and cycloplegia, additional mydriasis occurs if sympathomimetic agents such as phenylephrine are used simultaneously. Such synergistic combinations are commonly prescribed to achieve maximal dilation of the pupil for cataract extraction. As an average, 95% of the dilation measured before the viscoelastic injection was obtained within 30 seconds after a single 200-µL intracameral injection of MYDRANE during phase II clinical study. Pupil sizes observed during phase

II and III clinical trials are presented in the table below (patients who received a single 200-µL intracameral injection of MYDRANE):

	Phase II study, n=24	Phase III study, n=181		
	Within 30 seconds after Mydrane injection	After injection of Mydrane, and subsequent injection of viscoelastic	After injection of Mydrane, and subsequent injection of viscoelastic	Just before IOL injection
Pupil size (mm)				
Mean (SD)	**6.7 (0.7)**	**7.7 (0.7)**	**7.8 (0.8)**	**7.9 (0.9)**
Median	6.7	7.7	7.8	7.9

In phase III study, after a single 200-µL injection of MYDRANE and injection of viscoelastic (just before capsulorhexis), the pupil size was at least 7 mm for 86.7% of the patients. In these clinical phase II and III studies, mydriasis with MYDRANE was demonstrated to be stable until the end of the surgery. Return to normal pupil size is known to be obtained after 5-7 hours. *Clinical efficacy and safety/* **Clinical efficacy:** The mydriatic and anaesthetic effects of MYDRANE were evaluated in a phase III, multicentre, randomised, open study in comparison with a standard topical treatment (phenylephrine and tropicamide) in 555 patients undergoing cataract surgery with a pupil diameter ≥ 7 mm following topical mydriatic application. Tetracaine 1% eye drops was instilled 5 minutes and 1 minute before surgery in both groups. *Mydriasis:* Non-inferiority of MYDRANE *versus* the Reference treatment (tropicamide 0.5% eye drops and phenylephrine 10% eye drops, application of one drop of each repeated 3 times prior a surgery) was demonstrated for the primary and co-primary efficacy criteria in the mITT Population (see Table below):

mITT Population	**MYDRANE**	**Reference Treatment**	**Difference (%) between groups (MYDRANE - Reference)** [95% CI]
Primary efficacy criterion	N=268	N=281	
Number (%) of responders*	265 (98.9)	266 (94.7)	**4.2**
95% CI	[96.8 ; 99.8]	[91.3 ; 97.0]	[-4.2 ; 12.6]
Co-primary efficacy criterion	N=250	N=261	
Number (%) of responders**	246 (98.4)	246 (94.3)	**4.1**
95% CI	[96.0 ; 99.6]	[90.7 ; 96.7]	[-4.5 ; 12.8]

** A responder was defined as a patient for whom the capsulorhexis was performed without use of any additive mydriatic treatment*

*** A responder was defined as a patient for whom the capsulorhexis was performed without use of any additive mydriatic treatment and for whom the pupil size just before capsulorhexis was ≥ 5.5 mm.*

During the phase III study, in the MYDRANE group (N=268), 197 patients received a single 200-µL intracameral injection and 71 received an additional 100-µL intracameral injection which has not demonstrated a significant add-on effect and for which increased endothelial cell loss was observed. The data analysis on the patients with a single 200-µL intracameral injection, for whom the capsulorhexis was performed without use of any additive mydriatic treatment and for whom the pupil size just before capsulorhexis was > 6 mm, is presented in the table below.

	MYDRANE 200-µL	**Reference Treatment**	**Difference (%) between groups (MYDRANE 200-µL - Reference)** [95% CI]
N	N=181	N=261	
Number (%) of patients with no additive mydriatic treatment and with the pupil size just before capsulorhexis > 6 mm	180 (99.4)	246 (94.3)	**5.2**
95% CI	[97.0; 100.0]	[90.7; 96.7]	[-4.3; 14.6]

Anaesthesia: Before intraocular lens injection, the patients' comfort was statistically significantly better with MYDRANE (p=0.034), and no statistically significant difference between groups was seen at the other time points of the surgery (before viscoelastic injection, capsulorhexis and cefuroxime injection).**Pharmacokinetic properties:** No ocular pharmacokinetic data are available for MYDRANE. Following intracameral injection of MYDRANE in 15 patients undergoing cataract surgery, the concentrations of the active ingredients assayed in plasma 2, 12 and 30 min post-injection were compared to a standard topical treatment (phenylephrine 10% eye drops and tropicamide 0.5% eye drops). Regarding tropicamide, all patients in MYDRANE group were below the limit of quantification (< 0.1 ng/mL) whereas all patients in the Reference group had a level above this limit. Level of phenylephrine (quantification limit < 0.1 ng/mL) was not detectible in all patients of the MYDRANE group with exception of 2 patients (maximum 0.59 ng/mL) versus all patients of the Reference group with a level above limit of quantitation (maximum 1.42 ng/mL). The plasma lidocaine concentration was measured in all MYDRANE-treated patients with a highest concentration of 1.45 ng/mL (well below the values causing some systemic effects: between 1,500 and 5,000 µg/mL). **Preclinical safety data:** In rabbits, the ocular tolerance after single intracameral administration of 200µL of MYDRANE with or without rinsing (slit-lamp, aqueous flare, corneal thickness and cellular density of the endothelium, electroretinography and histology) was very good in the seven days post-dosing period. Signs of ocular intolerance were only observed for formulations with higher concentrations of the three active substances (at or above 5 times the concentrations in MYDRANE). The highest tested concentration (10 fold) showed increases in the thickness of the cornea, and severe ocular changes resulted in one animal being sacrificed on Day 3. Systemic toxicity of the fixed combination of phenylephrine, tropicamide and lidocaine has not been investigated. Nevertheless, since the ophthalmological safety of the three individual substances is considered established and MYDRANE is only administered by single intracameral injection, no particular risk is expected for the combination. Likewise, the safety pharmacology, genotoxicity and reproduction toxicity of the individual substances or the fixed combination has not been evaluated. In rats, administration of phenylephrine (12.5 mg/kg, s.c.) resulted in reduced uterine blood flow (86.8% reduction in about 15 minutes), thereby exhibiting foetotoxic and co-teratogenic properties. For lidocaine, no teratogenic effects were observed in studies of embryonic/foetal development in rats and rabbits. Embryotoxicity and a reduction in postnatal survival were only observed at maternally toxic doses. Lidocaine was also not genotoxic. **PHARMACEUTICAL PARTICULARS: Incompatibilities:** No incompatibility with most commonly used products in cataract surgery was reported in literature with the active ingredients, and during clinical trials. For usual viscoelastics, this was also confirmed by pharmaceutical interaction test. **Shelf life:** 3 years. **Special precautions for storage:** This medicinal product does not require any special storage conditions. **Nature and contents of container:** One 1 ml sterile brown glass (type I) ampoule filled with 0.6 ml of solution for injection, per paper/PVC blister. Box of 1, 20 and 100 ampoules together with respectively 1, 20 and 100, 5-micron sterile filter needles. Not all pack sizes may be marketed. **Special precautions for disposal and other handling:** For single eye use only. Use immediately after first opening of the ampoule. Warning: Do not use if blister or peelable backing is damaged or broken. Open under aseptic conditions only. The content of the blister is guaranteed as sterile. The solution should be visually inspected and should only be used if it is a clear, slightly brownish-yellow and practically free from visible particles solution. MYDRANE must be administered by intracameral injection, by an ophthalmic surgeon in the recommended aseptic conditions of cataract surgery. To prepare the product for intracameral injection, please adhere to the following instructions: 1. Inspect unopened blister to ensure that it is intact. Peel open blister. 2. Break open the ampoule containing the drug product. The One Point Cut (OPC) ampoule must be opened as follows: Hold the bottom part of the ampoule with the thumb pointing to the coloured point. Grasp the top of the ampoule with the other hand, positioning the thumb at the coloured point and press back to break at the existing cut under the point. 3. Assemble the 5-micron filter sterile needle (provided) onto a sterile syringe. Remove the 5-micron filter sterile needle protector and withdraw at least 0.2 ml of the solution for injection from the ampoule into the syringe. 4. Disconnect the needle from the syringe and assemble the syringe with an appropriate anterior chamber cannula. 5. Carefully expel the air from the syringe. Adjust to 0.2 ml. The syringe is ready for injection. 6. Slowly inject the 0.2 ml syringe volume into the anterior chamber of the eye, as only one injection, through the side port or principal port. 7. After use, discard the remaining solution appropriately. Do not keep it for subsequent use. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Discard used needles in a sharps container. **MARKETING AUTHORISATION HOLDER:** Laboratoires THEA - 12, Rue Louis Blériot - 63017 Clermont-Ferrand Cedex 2 – France – Tel: +334.73.98.14.36. **DATE OF EUROPEAN AUTHORISATION:** 02 JUL 2015. **DATE OF REVISION OF THE TEXT:** 29 SEPT 2017.

MYDRIASERT 0.28 MG/5.4 MG OPHTHALMIC INSERT

QUALITATIVE AND QUANTITATIVE COMPOSITION: Each ophthalmic insert contains 0.28 mg of tropicamide and 5.4 mg of phenylephrine hydrochloride. Excipients: Ammonio methacrylate copolymer (Type A), Polyacrylate dispersion 30%, Glycerol dibehenate, Ethylcellulose. **PHARMACEUTICAL FORM:** Ophthalmic insert. White to yellowish-white, oblong, 4.3 mm x 2.3 mm insert. **CLINICAL PARTICULARS: Therapeutic indications:** Mydriasert is indicated: to obtain pre-operative mydriasis, or for diagnostic purposes when monotherapy is known to be insufficient. **Posology and method of administration:** Restricted use to health-care professionals. This medicine is reserved to adults. There are no data in children and adolescents. Mydriasert is not recommended in these patients. **Posology:** One ophthalmic insert per operated eye, a maximum of 2 hours before surgery or the investigative procedure (see also **Pharmacodynamic properties**). **Method of administration:** Cut the sealed edge along the dotted line, open the sachet and locate the insert. Hold the insert with disposable sterile forceps with rounded ends provided in the packaging, making sure not to damage it. Pull down the lower eyelid by pinching it between the thumb and index finger, and apply the ophthalmic insert, using the disposable sterile forceps, in the lower conjunctival sac. **Instructions for use:** Do not leave the ophthalmic insert for more than two hours in the lower conjunctival sac. The practitioner can remove the ophthalmic insert as soon as mydriasis is deemed sufficient for the operation or procedure to be carried out, and at the latest within the next 30 minutes. In the event of discomfort, ensure that the insert has been placed correctly at the base of the lower conjunctival sac. Manipulate aseptically. It is recommended to avoid excessive manipulation of eyelids. **CAUTION: Removal of the ophthalmic insert:** Before an operation or procedure, and as soon as the required mydriasis has been obtained, the ophthalmic insert should be removed from the lower conjunctival sac by using either sterile surgical forceps, or a sterile swab or a sterile irrigation or washing solution, by lowering the lower eyelid. Do not reuse the insert. Discard the insert after use immediately. **Contraindications:** Hypersensitivity to the active substances "phenylephrine hydrochloride and tropicamide" or to any one of the excipients. Risk of angle-closure glaucoma: Patients with closed angle glaucoma (unless previously treated with iridectomy) and patients with narrow angle prone to glaucoma precipitated by mydriatics. **Special warnings and precautions for use:** ***Special warnings:*** Because this medicinal product causes long lasting visual disturbances, the patient should be advised to be accompanied when attending the consultation (see section **Undesirable effects**). Protect the eye against bright lighting after the end of intervention/consultation. Ocular hyperemia can increase the absorption of the active ingredients contained in the insert. ***Special precautions for use:*** The shifting or, more rarely, the expulsion of the insert is possible. In this case, do not re use the removed insert, take a new one (see section **Posology and method of administration**). Mydriasert should not be left in the conjunctival sac for more than 2 hours. In cases where Mydriasert was forgotten, local adverse reactions were observed (see section **Undesirable effects**). Because of uncommon potential irritation on conjunctiva, special care should be taken with patients suffering from severe dry eyes (use of Mydriasert in some patients may necessitate the addition of a drop of saline solution to improve insert tolerance). All mydriatic agents may trigger an acute attack of glaucoma through the mechanical obstruction of the excretory pathways of aqueous humour in subjects presenting with a narrow iridocorneal angle. Although not anticipated with Mydriasert due to negligible systemic passage of active ingredients, it is however reminded that phenylephrine has sympathomimetic activity that might affect patients in the event of hypertension, cardiac disorders, hyperthyroidism, atherosclerosis or prostate disorders and all subjects presenting with a contraindication to the systemic use of pressor amines. Sportsmen and athletes should be warned that this proprietary medicinal product contains an active principle (phenylephrine) which may produce positive results to tests for prohibited substances. The wearing of soft hydrophilic contact lenses is inadvisable during treatment. After the insertion of Mydriasert, and if the administration of other mydriatic agents cannot be avoided, account must be taken of the doses in the insert of approximately one drop of a 10% solution of phenylephrine and approximately one drop of a 0.5% solution of tropicamide. **Interactions with other medicinal products and other forms of interaction:** No specific studies interaction studies have been performed with Mydriasert. **Pregnancy and lactation: Pregnancy:** There are no adequate data from the use of phenylephrine and tropicamide in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see section **Preclinical safety data**). Even though a negligible systemic uptake is expected, a low systemic exposure can not be excluded. Therefore, Mydriasert should not be used during pregnancy unless necessary. **Lactation:** No data are available concerning the passage of phenylephrine or tropicamide into breast milk. However, phenylephrine is poorly absorbed orally, implying that absorption by the infant would be negligible. On the other hand, infants may be very sensitive to anticholinergics, and despite the expected negligible systemic exposure, tropicamide is therefore not recommended during breast feeding. Therefore, Mydriasert should not be used during breast feeding. **Effects on ability to drive and use machines:** Mydriasert has major influence on the ability to drive and use machines. Patients should be warned of the risks related to mydriatic and cycloplegic agents, which may cause visual disturbances like dizziness, drowsiness and impaired concentration: application of the Mydriasert ophthalmic insert causes disabling mydriasis for several hours; consequently, after application, the patient should be advised not to drive and/or use machines while the visual disturbances persist and/or not to perform other hazardous activities. **Undesirable effects:** The following transient effects have been reported during clinical studies: Eye disorders *Common (> 1/100):* stinging, blurred vision, visual discomfort. *Uncommon (> 1/1000, < 1/100):* tearing, irritation, disabling mydriasis because of prolonged pupil dilation, photophobia, superficial punctuate keratitis. *Rare (< 1/1000):* blepharitis, conjunctivitis, risk of angle-closure glaucoma, intraocular hypertension. Very rare cases of corneal ulcer and corneal oedema were observed due to forgotten insert. Although administered via the topical route, the mydriatic agents contained in this insert may cause the following systemic effects which must be taken into account: elevation of blood pressure, tachycardia, very rarely, major accidents such as cardiac arrhythmia, tremor, pallor, headaches, dry mouth. Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. **Overdose:** Although unlikely due to single administration of Mydriasert (for either pre-operative or diagnostic purposes), a risk of overdose may nevertheless occur in the event of the additional instillation of mydriatic eyedrops. Symptoms of a phenylephrine overdose include extreme tiredness, sweating, dizziness, a slow heartbeat, and coma. Because severe toxic reaction to phenylephrine is of rapid onset and short duration, treatment is primarily supportive. Prompt injection of a rapidly acting alpha-adrenergic blocking agent such as phentolamine (dose 2 to 5 mg i.v.) has been recommended. Symptoms of tropicamide ophthalmic overdoses include headache, fast heartbeat, dry mouth and skin, unusual drowsiness, and flushing. Systemic effects from tropicamide are not expected. Should an overdose occur causing local effects, e.g. sustained mydriasis, pilocarpine or 0.25% w/v physostigmine should be applied. **PHARMACOLOGICAL PROPERTIES: Pharmacodynamic properties:** Pharmacotherapeutic group: MYDRIATICS and CYCLOPLEGICS, Tropicamide combinations. ATC code: S01F A56. Mydriasert is an ophthalmic insert which combines two synthetic mydriatic agents (phenylephrine, alpha sympathomimetic, and tropicamide, anticholinergic). Clinical trials have shown a time to reach a stable and sufficient mydriasis between 45 and 90 min. The maximal mydriasis (pupil diameter of 9 mm) was reached in 90 to 120 minutes. The mydriasis, when reached, lasted at least 60 minutes. **The recovery of the pupil reflex was seen at 90 minutes at the average. Pharmacokinetic properties:** After application of an insert for 2 hours in 138 patients scheduled for cataract surgery, the concentrations of the active ingredients assayed in aqueous humour were very low: 1.9±3.4 µg/ml for phenylephrine and 0.85±2.06 µg/ml for tropicamide. The cumulative quantities of the active ingredients released in 2 hours by the insert represent less than 40% of the doses contained in the insert. In the same conditions, the plasma levels of phenylephrine measured during 6 hours in healthy volunteers were not detectable (< 0.5 ng/ml). **Preclinical safety data:** Safety pharmacology, genotoxicity and conventional reproductive studies have not been conducted with phenylephrine, tropicamide or the fixed combination. In rats, administration of phenylephrine (12.5 mg/kg, s.c.) resulted in reduced uterine blood flow (86.8% reduction in about 15 minutes), thereby exhibiting foetotoxic and co-teratogenic properties. A 14-day local tolerance study was conducted in the rabbit, with insertion during 6 hours daily. This study demonstrated a mild irritating effect of the conjunctiva at the site of application. **PHARMACEUTICAL PARTICULARS: Shelf life:** 18 months. After first opening of the sachet: Use immediately. After first use: Discard the used insert immediately. **Special precautions for storage:** Do not store above 25°C. Use immediately after first opening the sachet. **Nature and contents of container:** Ophthalmic insert in a sachet (Paper/PE/Aluminium/PE) and disposable sterile forceps in a sachet (Paper/PE/Aluminium/PE). Box of 1, and 20 inserts together with respectively 1 and 20 forceps. **Special precautions for disposal:** Cut the sealed edge along the dotted line, open the sachet and locate the insert. Hold the insert with disposable sterile forceps with rounded ends provided in the packaging, making sure not to damage it; place it at the base of the lower conjunctival sac, having pulled down the lower eyelid with the thumb and index finger. For single use only. Use immediately after first opening the sachet. Discard the used insert immediately. Any unused product or waste material should be disposed of in accordance with local requirements. **MARKETING AUTHORISATION HOLDER:** LABORATOIRES THEA - 12, rue Louis Blériot - 63017 CLERMONT-FERRAND CEDEX 2. FRANCE. Tel: +33 (0) 4.73.98.14.36. **MARKETING AUTHORISATION NUMBER(S): AT:** Zul.Nr. 1-27374; **BE:** BE310572; **DE:** 65710.00.00. **DK:** 23325; **ES:** 70710; **FI:** 21979; **FR:** 353 728-4 (B/1) – 353 729-0 (B/20); **IT:** AIC n.0377160038/M; **LU:** 0479405; **NL:** RVG 33701; **PT:** 5893987; **SE:** 20060308000014; **UK:** PL 20162/0011. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:** 01/03/2010. **DATE OF REVISION OF THE TEXT:** 16/03/2015.

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