SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 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 monohydrate.

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 monohydrate.

Excipient with a known effect: sodium (0.59 mg per dose; see section 4.4).

For the full list of excipients, see section 6.1.

3 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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mydrane is indicated for cataract surgery to obtain mydriasis and intraocular anaesthesia during the surgical procedure.

Mydrane is indicated in adults only.

4.2 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 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 5.2), no dose adjustment is necessary (see section 4.4).

Patients with hepatic impairment:
Considering the low dose and the very low systemic exposure (see section 5.2), no dose adjustment is necessary.

Method of administration
Intracameral use.

The following procedure should be followed:
1. 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.
2. 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 6.6.

4.3 Contraindications

- Hypersensitivity to the active substances (tropicamide, phenylephrine hydrochloride and lidocaine hydrochloride monohydrate) or to any of the excipients listed in section 6.1.
- Known hypersensitivity to anaesthetics of the amide type.
- Known hypersensitivity to atropine derivatives.

4.4 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 (see also section 4.9).

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.
Use of Mydrane in patients with shallow anterior chamber, a history of acute narrow angle glaucoma and/or insufficient pupil dilation can increase the risk of both iridocele and floppy iris syndrome.

Special precautions for use:

Mydrane was shown to produce undetectable or very low systemic concentrations of active substances (see section 5.2). 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 10mL/minute.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium-free”.

4.5 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 5.2), systemic interactions are unlikely.

4.6 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.

4.7 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.

4.8 Undesirable effects

Adverse reactions were reported with Mydrane during clinical trials (see section 5.1). 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:

System Organ class	Frequency	Adverse reaction
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 Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Systemic effects
Due to single administration and low expected systemic passage of Mydrane, the risk of systemic effects due to overdose is considered minimal.

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).

Local effects
Overdosage can cause endothelial cell loss (see section 4.4 and 5.1).

5 PHARMACOLOGICAL PROPERTIES

5.1 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 monohydrate).

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	246 (98.4)	246 (94.3)	**4.1** [-4.5 ; 12.8]

responders** 95% CI	[96.0 ; 99.6]	[90.7 ; 96.7]	
** 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 (see also section 4.9).

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).

5.2 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).

5.3 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 of the fixed combination have 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium phosphate dodecahydrate
Disodium phosphate dihydrate
Disodium edetate
Water for injections

6.2 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.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

One paper/PVC blister containing 1 ml sterile brown glass (type I) ampoule filled with 0.6 ml of solution for injection. Separated 5-micron sterile filter needles packed in individual blisters are provided.
Box of 1, 20 and 100 sterile ampoules together with respectively 1, 20 and 100, 5-micron sterile filter needles.

Kit of one paper/PVC blister containing one 1 ml sterile brown glass (type I) ampoule filled with 0.6 ml of solution for injection and one 5-micron sterile filter needle.
Box of 1, 20 and 100 kits (i.e. blister containing a sterile ampoule and a sterile filter needle).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single eye use only.
Use immediately after first opening of the ampoule.
Only for the presentation in kit (i.e. blister containing an ampoule and a needle): stick the flag label of the blister on the patient's file.

Warning: Do not use if blister or peelable backing is damaged or broken. Open under aseptic conditions only. The content of the blister are 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 under aseptic conditions to guarantee the sterility of the content.

2. Break open the sterile 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.

7 MARKETING AUTHORISATION HOLDER

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