

MIPHTEL 2ML SOLVENT FOR SOLUTION FOR INTRAOCULAR IRRIGATION

PL 20985/0007-8

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products MIPHTEL 20mg powder for solution for intraocular irrigation and MIPHTEL 2ml solvent for solution for intraocular irrigation (Product Licence numbers: 20985/0007 and 20985/0008).

MIPHTEL 20mg powder for solution for intraocular irrigation contains the active ingredient acetylcholine chloride, a susbstance involved in the transmission of nerve impulses. It is used during cataract and other types of eye surgery to make the pupil contract, which helps the surgeon carry out the procedure. Before use, the powder is reconstituted using MIPHTEL 2ml solvent for solution for intraocular irrigation, which is supplied in a separate container.

These products raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using them outweigh the risks; hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products MIPHTEL 20mg powder for solution for intraocular irrigation and MIPHTEL 2ml solvent for solution for intraocular irrigation to Regulatory Pharma Net s.r.l. on 28 January 2008. These medicines are only available on prescription.

These standard abridged applications were submitted under Directive 2001/83/EC Article 10a, as so-called bibliographical applications. The products consist of a freeze dried powder containing 20 mg acetylcholine chloride and a solvent for solution, which is water for injection (2ml). The solution should be immediately reconstituted prior to use to give a 20mg/2ml solution for intraocular irrigation.

Acetylcholine is an endogenous chemical transmitter with a very wide range of actions in the body. It is used as a miotic to reduce postoperative rises in intra-ocular pressure associated with cataract surgery, penetrating keratoplasty, iridectomy, and other anterior segment surgery but is ineffective when applied topically as it is hydrolysed more rapidly than it can penetrate the cornea. Acetylcholine chloride solution is instilled directly into the anterior chamber of the eye (intracameral instillation). Miosis occurs within seconds and lasts for about 20 minutes.

On the basis of it well documented clinical safety and efficacy from over 50 years experience, acetylcholine chloride can be considered to be a known entity with well established use for the proposed indication. The proposed therapeutic indication is: to obtain rapid and complete miosis after delivery of the lens in cataract surgery as well as in penetrating keratoplasty, iridectomy and other anterior segment surgery where rapid complete miosis is required.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Acetylcholine chloride (2-(Acetyloxy)-*N*,*N*,*N*-trimethylethanaminium chloride) is a white, very hygroscopic, crystalline powder. It is very soluble in water, yielding unstable solutions; very soluble in ethanol and propylene glycol; freely soluble in chloroform and practically insoluble in ether.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

DRUG PRODUCT

Description and Composition of the Drug Product

Other ingredients consist of pharmaceutical excipients, namely mannitol and sodium hydroxide. Water for injections is provided in a separate vial as solvent. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph.

A 10% overage in the active substance is included to compensate for retention of reconstituted solution in the vial during administration. There are no overages used for the solvent.

Manufacture

Descriptions and flow-charts of the manufacturing methods for the powder and solvent has been provided. In-process controls are appropriate considering the nature of the products and the methods of manufacture. Process validation has been carried out on batches of powder and batches of solvent. The results are satisfactory.

Finished product specification

The finished product specifications are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Container Closure System

Both the powder and the solvent are packed in Type I colourless glass ampoules (each pack contains 6 powder ampoules and 6 solvent ampoules). Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The solvent is packed in a 2ml ampoules.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 and 4 years has been set for the powder and solvent, respectively. Based on the stability data a shelf life of 30 minutes has been set for the reconstituted solution. The powder must not be frozen and should be stored in the original package. The solvent does not require any special storage precautions.

Product literature

All product literature (SPCs, PIL and labels) are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Bioequivalence / Bioavailability

This is a bibliographical application for a well established product and therefore a therapeutic study is not deemed necessary.

Assessor's Overall Conclusions

A product license may be granted for these products.

PRECLINICAL ASSESSMENT

NON CLINICAL ASPECTS

Acetylcholine is an endogenous chemical transmitter with a very wide range of actions in the body. It is a powerful parasympathomimetic agent but its action is transient because it is rapidly destroyed by cholinesterases. Doses of 0.5 to 2mL of a freshly prepared 1% solution of acetylcholine chloride are, therefore, instilled directly into the anterior chamber of the eye. Miosis occurs rapidly and persists for about 20 minutes.

In view of the well established clinical use of the active ingredient, no additional nonclinical data have been submitted. This is acceptable.

NON CLINICAL OVERVIEW

An overview and written summary have been submitted. The overview was written by a suitably qualified academic.

SUMMARY OF PRODUCT CHARACTERISTICS

Section 5.3 (Preclinical Safety Data) is acceptable.

CONCLUSION

There are no non-clinical objections or concerns.

CLINICAL ASSESSMENT

PRODUCT PROFILE

MIPHTEL solution for use must be prepared freshly immediately before use. When the powder is reconstituted with the solvent the resulting solution contains acetylcholine hydrochloride (20mg/2mL) (equivalent to 1% solution) and is intended for intraocular use. It is indicated:

"To obtain rapid and complete miosis after delivery of the lens in cataract surgery as well as in penetrating keratoplasty, iridectomy and other anterior segment surgery where rapid complete miosis is required."

The dose is 0.5-2.0 mL of the constituted solution, which is claimed to produce complete miosis within seconds and lasting 20 minutes. A second application may be made at the discretion of the surgeon for extended miosis.

The use of acetylcholine as a miotic agent for surgical procedures was first adopted in 1948 and it has spread since. Products containing acetylcholine have been marketed for more than 20-30 years in many EU countries (including the UK) and many non-EU countries (including the USA).

PHARMACOKINETICS

Following topical administration into the eye, the drug is rapidly hydrolysed by cholinesterases and its systemic bioavailability is poor.

PHARMACODYNAMICS

Much of the information is derived from dose-ranging and efficacy studies, which are discussed below.

DRUG INTERACTIONS

An interaction with metoprolol, leading to bronchoconstriction during an extracapsular cataract extraction has been reported (Rasch et al 1983).

Pre-treatment with NSAIDs is a common surgical practice to obtain maximal dilatation of the pupil at surgery. Although earlier studies suggested that NSAIDs may reduce the efficacy of acetylcholine, the findings from two studies (Holmes and Jay 1991 and Jackson *et al.* 1994) have failed to confirm this and this has been corroborated in a number of clinical trials.

DOSE-RESPONSE STUDIES

Three studies have evaluated dose-response effect, using concentrations of 0.02 to 1.0%.

Acetylcholine dilution	N. of patients	Pupillary diameter before intracapsular extraction (mm)	Pupillary diameter after intracapsular extraction (mm)	Miosis obtained (mm)
1:5000	5	6.20	6.60	4.80
1:2500	6	6.60	6.60	4.66
1:1000	5	6.60	7.20	3.40
1:500	6	6.83	7.16	2.50
1:100	6	6.33	6.83	2.00

The only concentration at which there was consistent high activity was 1% solution (Barraquer, 1964).

Effect of various dilutions on pupil size

Acetylcholine dilution	N. of patients	Pupillary diameter after intracapsular extraction (mm)	Pupillary diameter 1 minute after acetylcholine treatment (mm)
1:1000	7	7.1x6	4.8x3.8
1:500	21	7.0x5.6	4.8x3.7
1:200	8	7.4x6.2	4.3x3.3
1:100	9	7.2x6.3	4.0x3.0

Solutions of 1:100 and 1:200 were the most effective (Harley and Misher, 1964)

Acetylcholine dilution	N. of patients	Pupillary diameter after intracapsular extraction (mm)	Pupillary diameter 1 minute after acetylcholine treatment (mm)
1:1000	7	7.1x6	4.8x3.8
1:500	21	7.0x5.6	4.8x3.7
1:200	8	7.4x6.2	4.3x3.3
1:100	9	7.2x6.3	4.0x3.0

Supplemental Group - n = 61

Acetylcholine dilution	N. of patients	Pupillary diameter after intracapsular extraction (mm)	Pupillary diameter 1 minute after acetylcholine treatment (mm)
1:200	30	6.8x5.8	4,2x3.2
1:100	31	6.6x5.2	3.8x2.7

(Harley and Misher, 1966)

Pupillary diameters

Pupillary diameter (mm)	Control (n=43)	Acetylcholine chloride 1% (n=34)	Carbamylcholine chloride 0.01% (n=44)
Immediately before incision	7.2	7.5	7,0
After lens extraction	5.0	5.6	5.2
2 minutes after injection	4.3	3.4	3.2
5 minutes after injection	4.3	3.4	3.1
15 hours after injection	4.4	4.2	3.1

(Beasley 1972)

Catford and Millis (1967) reported that the average pupil size after removal of the lens before 1% acetylcholine injection was 5.6 mm and 3.5 mm after. The effect was achieved in an average of 76.6 seconds.

EFFICACY

The clinical summary contains 11 clinical trials evaluating the miotic effects of acetylcholine on 945 patients. The majority of these patients were undergoing cataract surgery.

Earlier studies were open studies with the more recent studies being randomised, double-blind controlled studies.

The comparators most frequently used were 0.01% carbachol, 0.25% dapiprazole and 0.02% thymoxamine.

Most studies have used 1% acetylcholine solution. When reported, the volume used is in the range of 0.3 to 0.5mL.

Study	Design	Disease	Number of patients
Harley and Mischer, 1964	Open	Cataract	45
Barraquer, 1964	Open	Cataract	28
Harley and Mischer, 1966	Open	Cataract	106
Catford and Millis, 1967	Open	Cataract	9
Rizuti, 1967	Open	Cataract	130
Rizuti, 1967	Open	Keratoplasty	30
Rizuti, 1967	Open	Glaucoma	12
Silvester and Haik, 1970	Controlled	Cataract	37
Beasley, 1971	DB, R, Controlled	Cataract	121
Douglas, 1973	Controlled	Cataract	70
Holland et al, 1987	Placebo controlled	Cataract	36
Elliott and Carter, 1989	DB, R, Controlled	Cataract	39
Ponte et al, 1991	DB, R, Controlled	Cataract	90
Pfeffier et al, 1994	DB, R, Controlled	Cataract	228

Data from some of the recent studies are tabulated below:

Mean decrease in papillary size:

Drug	n	2 min	5 min	Operation day	Day 1	Day 2	Day 3	Day 5
Acetylcholine	42	2.2±0.2	2.8±0.2	2.9±0.5	3.4±0.3	2.1±0.3	1.4±0.3	1.0±0.3
Carbachol	28	2.3±0.2	3.0±0.2	4.4±0.3	4.2±0.2	2.2±0.2	1.5±0.3	1.0±0.2

(Douglas GR 1973)

Placebo controlled study

Time of measurement	Mea	n intraocular pressure (mm	Hg)
	Acetylcholine	Control	P value
Preoperative	16.5	16.7	0.823
3 hours postoperative	11.9	21.8	0.000
6 hours postoperative	15.4	22.3	0.003
9 hours postoperative	18.7	22.3	0.159
24 hours postoperative	19.9	22.6	0.203

(Holland et al, 1987)

Pupil measurements

Group	Time After End of Surgery (hours)							
(number)	Pre-oper	0	2	4	6	10	24	48
Control (9)	8.6	6.1	7.4	7.6	6.7	6.8	4.2	3.4
Acetylcholine (11)	7.4	3.7	3.3	5.4	6.3	5.5	3.7	2.5
Epinephrine (10)	7.8	6.6	7.1	7.4	6.4	6.0	3.4	2.7
Acetylcholine + Epinephrine (9)	7.8	5.3	3.4	6.3	6.1	5.2	3.5	2.9

(Elliott and Carter, 1989)

Active-controlled studies

Group		Time after anterior chamber irrigation					
(Males/Females)	Before irrigation	After wound closure	2 hours	4 hours	8 hours		
Control (16M/14F)	6.7±0.7	6.7±0,8	6.7±0.7	6.2±0.8	6.0±0.9		
0.1% acetylcholine (17M/13F)	6.9±1.0	4.3±1.1	5.6±1.2	5.5±1.1	5.3±1.0		
0.25% dapiprazole (14M/16F)	6.5±0.8	5.1±0.9	4.8±0.8	4.8±0.7	4.7±0.8		

(Ponte et al, 1991)

Group	Mean pupillary diameter (mm)			Mean pupillary constriction (mm)	
	Pre-inject.	5 min.	10 min.	5 min.	10 min.
Placebo	7.06	7.08	6.99	-0.01	0.07
Acetylcholine 1%	7.32	5.46	5.34	1.86	1.97
Thymoxamine 0.02%	6.82	5.29	4.78	1.53	1.95
Acetylcholine 0.5% + thymoxamine 0.01%	7.13	3.70	3.10	3.42	4.04

(Pfeffier et al, 1994)

In patients undergoing cataract extraction, acetylcholine produced an average miotic effect of 2-4 mm in 90% of the patients and the effect lasted about 20 minutes. The effect was comparable for acetylcholine and carbachol but the duration of effect was longer with carbachol. It is believed that post-operative pain is intensified by prolonged and deeper miosis. Thus, acetylcholine may have advantages over carbachol.

In early postoperative period, there is frequently a rise in intraocular pressure and there have been concerns about the deleterious effect of this intraocular hypertension. Ten clinical trials in 693 patients (all needing cataract surgery, except 36 glaucoma patients) have evaluated the effect of 1% acetylcholine on intraocular pressure.

Nine of these 10 studies were prospective studies. Eight studies were controlled with placebo, carbachol, pilocarpine or acetazolamide as comparators.

Study	Design	Comparator	Disease	Number of patients
Hollands et al, 1987	Prospective	Placebo	Cataract	36
McKenzie and Boggs, 1989	Retrospective	Carbachol	Cataract	120
Ruiz et al, 1989	Prospective	Placebo and carbachol	Cataract	60
Hollands et al, 1990	Prospective	Pilocarpine and carbachol	Cataract	66
West et al, 1992	Prospective	Acetazolamide	Cataract	36
Wedrich and Menapace, 1992a	Prospective	Placebo and carbachol	Cataract	90
Wedrich and Menapace, 1992b	Prospective	Placebo	Cataract	40
Wedrich et al, 1994	Prospective	None	Cataract	60
Kim et al, 1994	Prospective	Placebo and carbachol	Cataract	56
Lai et al, 2001	Prospective	None	Cataract	129

Ruiz et al (1989) compared the effect of carbachol and acetylcholine on intraocular pressure 24 hours after extracapsular cataract extraction. All agents were administered intracamerally at the time of surgery. Sixty patients scheduled for routine extracapsular cataract extraction and intraocular lens implantation were randomly

assigned into one of three treatment groups: (1) carbachol, (2) acetylcholine, or (3) 0.5% balanced salt solution (placebo). Baseline intraocular pressures were determined the day before surgery, and postoperative pressures were measured approximately 24 hours after surgery. The group intraocular pressures averaged over preoperative and postoperative values were 21.06 mm Hg in the acetylcholine group, 19.36 mm Hg in the control group, and 17.30 mm Hg in the carbachol group. The average difference between preoperative and postoperative intraocular pressure measurements for the three groups were 7.33 mm Hg for the acetylcholine group, 8.73 mm Hg for the control group, and 2.20 mm Hg for the carbachol group. Only carbachol was significantly different from placebo on subsequent statistical testing. Carbachol is suggested as the agent of choice both for achieving intrasurgical miosis and prophylaxis of increasing intraocular pressure after cataract surgery.

Kim et al (1994) performed a randomized, prospective study to evaluate the effect of intraoperative, intracameral carbachol or acetylcholine on early postoperative intraocular pressure (IOP) after extracapsular cataract extraction (ECCE) and posterior chamber lens (PCL) implantation. Fifty-six eyes of 56 patients scheduled for routine ECCE and PCL implantation were randomly assigned into three groups:

- (1) carbachol infusion (19 eyes)
- (2) acetylcholine infusion (15 eyes)
- (3) balanced salt solution (BSS) infusion (control, 22 eyes).

We compared the preoperative IOP, early postoperative IOP, 24 hours postoperative IOP and 1 week postoperative IOP. In the measurement of early postoperative IOP, IOP was measured at least twice at 3, 6 or 9 hours postoperatively. There were no significant differences in IOP between the three groups preoperatively, nor at 3 hours postoperative, and 1 week postoperative. At 6 hours postoperative both the carbachol infusion group and acetylcholine infusion group were significantly different from the BSS infusion group. At 9 and 24 hours postoperative only carbachol infusion group had a significant difference from BSS infusion group in suppression of postoperative IOP increase. The results suggest that intraoperative, intracameral administration of carbachol or acetylcholine prevents early postoperative IOP increase, and that carbachol has a more lasting effect.

Patients with uncomplicated cataract having phacoemulsification with PC IOL implantation were included in the prospective randomized double-masked clinical trial by Lai et al (2001). The eyes were randomly assigned to 1 of 4 groups based on postoperative application of latanoprost 0.005% alone (Group 1), latanoprost 0.005% with intracameral acetylcholine (Group 2), intracameral acetylcholine alone (Group 3), and no medication (controls (Group 4). Intraocular pressure (IOP) was measured 3 and 24 hours postoperatively. The anterior chamber was examined for the level of cells and flare using slitlamp biomicroscopy. Three and 24 hours after surgery, the decrease in mean IOP in eyes receiving latanoprost alone was not statistically significantly different from that in control eyes (P >0.05). Eyes receiving intracameral acetylcholine alone had a significant decrease in the mean IOP at 3 hours (P <.05) but not at 24 hours compared to control eyes (P >0.05). There were no significant differences in the mean postoperative IOP decrease between eyes receiving latanoprost with intracameral acetylcholine and those receiving intracameral acetylcholine alone (P >0.05). The investigators concluded that a single application of

latanoprost did not significantly lower IOP in the first 24 hours after phacoemulsification with PC IOL implantation. Eyes receiving intracameral acetylcholine alone had a significantly greater decrease in IOP than control eyes at 3 hours but not at 24 hours. The addition of intracameral acetylcholine to latanoprost did not enhance or reduce latanoprost's IOP-lowering effect.

Although both carbachol and acetylcholine were effective in preventing the rise in intraocular pressure for 3-6 hours, carbachol was more effective

SAFETY

Acetylcholine when applied topically may produce ciliary or accommodative spasms, blurred vision, myopia and poor vision in dim light. Formation of iris cysts, anterior chamber flare or hyperaemia, aggravation of inflammation, lens opacity, hypersensitivity reaction and retinal detachment may also occur.

Systemic effects include nausea, vomiting, diarrhoea, abdominal pain, frequency of micturition, salivation, sweating, lacrimation, bronchoconstriction, pulmonary oedema, cardiac arrhythmias, hypotension and CNS excitation may also occur. These generally occur with more frequent or prolonged topical administration.

These effects, however, are also seen with other active comparators.

In special settings, caution is recommended. For example, some investigators have recommended caution in the use of acetylcholine in patients with pre-operatively compromised endothelium.

A recent study by Roszkowska AM (1998) evaluated differences in corneal endothelial cell loss after intraocular use of two different miotics in subjects who have undergone extracapsular cataract extraction with posterior chamber intraocular lens implantation. The patients were divided into two groups: the first received 1 ml of 1% acetylcholine chloride and the second 0.5 ml of 0.01% carbachol as intraocular miotics. The endothelial count was done preoperatively and then 1 month after cataract extraction. There were no statistically significant differences in the mean cell loss between both groups.

CONCLUSIONS

The published data provided support the conclusions that:

- 20mg/mL solution is the most appropriate concentration.
- 20mg/mL solution is more effective than placebo in its miotic effect.
- 20mg/mL acetylcholine solution is not as effective as 0.05% carbachol solution in terms of intensity and duration of miotic effect but this is acceptable given the potential complications of intense and prolonged miosis
- Potential interaction with β -blockers is rare but a matter of concern.
- Carbachol is more effective than acetylcholine both for achieving intrasurgical miosis and prophylaxis of increasing intraocular pressure after cataract surgery.
- 20mg/mL acetylcholine solution has an acceptable safety profile.

RECOMMENDATION

There are no major clinical public health issues and the recommendation is to grant marketing authorisations for these preparations.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of MIPHTEL 20mg powder for solution for intraocular irrigation and MIPHTEL 2ml solvent for solution for intraocular irrigation are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

In view of the well established clinical use of the active ingredient, no additional nonclinical data has been submitted. This is acceptable.

EFFICACY

The efficacy of acetylcholine chloride has been well documented in the past. No new or unexpected safety concerns arise from this application.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with MIPHTEL 20mg powder for solution for intraocular irrigation and MIPHTEL 2ml solvent for solution for intraocular irrigation. The risk benefit is therefore considered to be positive.

MIPHTEL 2ML SOLVENT FOR SOLUTION FOR INTRAOCULAR IRRIGATION

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 3 October 2005
2	Following standard checks and communication with the applicant the MHRA
	considered the application valid on 1 November 2005
4	Following assessment of the application the MHRA requested further
	information relating to the quality dossier on 20 December 2005
5	The applicant responded to the MHRA's requests, providing further information
	on the quality dossier on 14 February 2006
6	Following assessment of the application the MHRA requested further
	information relating to the clinical dossier on 11 July 2006
7	The applicant responded to the MHRA's requests, providing further information
	on the clinical dossier on 1 August 2006
8	Following assessment of the response the MHRA requested further information
	relating to the quality dossier on 4 June 2007
9	The applicant responded to the MHRA's requests, providing further information
	on the quality dossier on 2 August 2007
10	The application was determined on 28 January 2008

SUMMARY OF PRODUCT CHARACTERISTICS

PL 20985/0007:

1 NAME OF THE MEDICINAL PRODUCT

MIPHTEL 20mg powder for solution for intraocular irrigation.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 20mg acetylcholine chloride.

2ml of the reconstituted solution contain 20mg of acetylcholine chloride. Each ml of the reconstituted solution provides 10mg of acetylcholine chloride.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for intraocular irrigation.

White lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

To obtain rapid and complete miosis after delivery of the lens in cataract surgery as well as in penetrating keratoplasty, iridectomy and other anterior segment surgery where rapid complete miosis is required.

4.2 Posology and method of administration

MIPHTEL is for intraocular use.

The lyophilised powder should be reconstituted with the solvent just before use as described in section 6.6. The reconstituted solution should be clear and colourless.

The reconstituted solution should be slowly withdrawn from the ampoule into a suitable sterile syringe and should be administered into the anterior chamber of the eye during surgery.

In cataract surgery, acetylcholine should be used only after delivery of the

Following surgery, if miosis is necessary, it must be maintained by longer acting topical miotics such as pilocarpine or physostigmine.

Adults and Elderly

In most cases a satisfactory miosis, which will last for approximately 20 minutes, is produced in seconds by 0.5-2.0ml. A second application may be made at the discretion of the surgeon if prolonged miosis is required. *Children*

Safety and effectiveness in children has not been established.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Acetylcholine for intraocular use should be used with caution in patients suffering from bronchial asthma, heart failure, hyperthyroidism, gastrointestinal spasm, peptic ulcer, urinary tract obstruction, parkinsonism.

Miosis will occur to a lesser extent in acute angle-closure glaucoma or in eyes which demonstrate posterior synechiae or atrophy of the iris. For rapid and complete miosis with acetylcholine, obstructions such as synechiae may require surgery.

Following lens extraction, the rapid miosis produced by acetylcholine protects the vitreous face and facilitates the placement of corneal sutures by reducing the hazard of incarceration of its iris tissue during the closure of the wound. Following iridectomy, the traction produced by acetylcholine upon the released iris helps to reposit it towards its original position within the anterior chamber and in this taut condition there is less danger of its prolapse. Following surgery, miosis must be augmented by longer acting topical miotics such as pilocarpine or physostigmine.

4.5 Interaction with other medicinal products and other forms of interaction

Although clinical studies with acetylcholine chloride and animal studies with acetylcholine revealed no interference, and there is no known pharmacological basis for an interaction, there have been reports that acetylcholine has been ineffective when used in patients treated with topical non-steroidal anti-inflammatory agents.

Use of MIPHTEL in patients receiving β -blockers may result in bronchospasm.

4.6 Pregnancy and lactation

The potential risk for humans is unknown (see also section 5.3). MIPHTEL should not be used during pregnancy and lactation unless clearly necessary.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, the surgical procedure may impair vision. Patients should not drive or use machines until such disturbances have subsided.

4.8 Undesirable effects

Adverse reactions which are indicative of systemic absorption have been reported rarely in the literature. Symptoms include bradycardia, hypotension, flushing, breathing difficulties and sweating. Isolated cases of corneal oedema, corneal clouding and corneal decompensation have been reported with the use of acetylcholine 1% solutions although a causal relationship has not been established.

4.9 Overdose

The symptoms of overdosage are likely to be effects resulting from systemic absorption, ie bradycardia, hypotension, flushing, breathing difficulties and sweating. Atropine sulphate (0.5–1mg) should be given intramuscularly or intravenously and should be readily available to counteract possible overdosage. Adrenaline (0.1–1mg subcutaneously) is also of value in overcoming severe cardiovascular or bronchoconstrictor responses.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, parasympathomimetics.

ATC code: S01EB09

Acetylcholine is a physiological neuromediator of postganglionic parasympathetic nerve fibres (muscarinic action), skeletal muscles and ganglia of the sympathetic system (nicotinic action).

The ocular parasympathetic receptors of the muscarinic type are very numerous and localised:

- at the level of the pupillary sphincter, whose contraction causes miosis;
- at the level of the ciliary muscle, whose contraction allows accommodation and facilitates the flow of the aqueous humor by opening of the trabecular meshwork. In addition, the acetylcholine can have an inhibitory effect on the aqueous secretion. These two last factors result in a decrease in the intraocular pressure;
- at the level of the lacrimal glands, whose stimulation causes tearing.

5.2 Pharmacokinetic properties

After topical instillation to the eye acetylcholine is almost immediately destroyed by cholinesterases. The bioavailability of ophtalmic acetylcholine solutions is poor: corneal penetration using topical application is not effective. The product must be administered via instillation into the anterior chamber of the eye. Following instillation of a 1% solution of acetylcholine chloride into the anterior chamber of the eye, miosis occurs promptly and persists for approximately 10–20 minutes.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421) Sodium Hydroxide (E 524)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or solvents.

Acetylcholine is incompatible with solutions of acidic or alkaline pH but this is unlikely to be relevant during clinical use.

6.3 Shelf life

3 years.

Shelf-life after reconstitution: 30 minutes.

6.4 Special precautions for storage

Do not freeze.

Store in the original package.

6.5 Nature and contents of container

Type I colourless glass ampoule.

Each pack contains 6 powder ampoules and 6 solvent ampoules.

6.6 Special precautions for disposal

The reconstituted solution should be clear and colourless.

Warning: Do not use if the PVC holder or peelable backing is damaged or broken.

Directions for preparing MIPHTEL

- 1. Inspect unopened PVC holder to ensure that it is intact. Peel open the holder.
- 2. Aseptically withdraw the entire content of the solvent ampoule into a sterile syringe. Discard ampoule.
- 3. Transfer the solvent from the syringe to the powder ampoule.
- 4. Shake gently to dissolve drug.
- 5. Visually inspect the reconstituted solution for particulate matter. Do not use solutions containing particulate matter.

The reconstituted solution should be slowly withdrawn from the ampoule into a suitable sterile syringe and should be administered into the anterior chamber of the eye.

The product provides 10mg/ml of acetylcholine chloride when diluted as recommended.

In most cases a satisfactory miosis, which will last approximately 20 minutes, is produced within seconds by 0.5–2ml of reconstituted solution. If a prolonged miosis is required a second application may be made.

The solution must be prepared just before use, since aqueous solutions of acetylcholine are unstable. Only clear and colourless solutions should be used.

The product is sterile until opened and should not be re-sterilised.

For single use only. Any unused solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

Regulatory Pharma Net s.r.l. Corso Italia, 108 I-56125 PISA Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL 20985/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/01/2008

10 DATE OF REVISION OF THE TEXT

28/01/2008

PL 20985/0008:

1 NAME OF THE MEDICINAL PRODUCT

MIPHTEL 2ml solvent for solution for intraocular irrigation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

No active ingredient present.

3 PHARMACEUTICAL FORM

Solvent for solution for intraocular irrigation for use with MIPHTEL 20mg powder for solution for intraocular irrigation.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

None.

4.2 Posology and method of administration

For intraocular use.

The reconstituted solution is administered into the anterior chamber of the eye during surgery.

4.3 Contraindications

Not applicable.

4.4 Special warnings and precautions for use

Not applicable.

4.5 Interaction with other medicinal products and other forms of interaction

Not applicable.

4.6 Pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Not applicable.

4.9 Overdose

Not applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: solvents and diluting agents incl. irrigation solutions, ATC code: V07AB.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

Following reconstitution with MIPHTEL powder: 30 minutes

6.4 Special precautions for storage

The solvent does not require any special storage conditions.

6.5 Nature and contents of container

2ml type I colourless glass ampoule.

Each pack contains 6 powder ampoules and 6 solvent ampoules.

6.6 Special precautions for disposal

See Summary of Product Characteristics for MIPHTEL 20mg powder for solution for intraocular irrigation.

7 MARKETING AUTHORISATION HOLDER

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PATIENT INFORMATION LEAFLETS



Miphtel 20 mg powder and solvent for solution for intraocular irrigation



Acetylcholine chloride



Patient Information Leaflet

Read all of this leaflet carefully before you are given this medicine

Keep this leaflet. You may need to read it again. If you have further questions, please ask your doctor or the medical staff looking after you.

- In this leaflet:

 1. What MIPHTEL is and what it is used for
 2. Before using MIPHTEL
 3. How to use MIPHTEL

- 4. Possible side effects 5 Storing MIPHTEL
- 6. Further information

1. WHAT MIPHTEL IS AND WHAT IT IS USED FOR
The active substance in MIPHTEL 20 mg powder and solvent for solution for intraocular irrigation is acetylcholine chloride. It belongs to a group of substances called parasympathomimetics (neurohormones) involved with the transmission of nerve impulses in

MIPHTEL is used during cataract surgery and other types of eye surgery to make the pupil (at the

front of the eye) contract. This helps the surgeon carry out the surgical procedure. If you have any questions about how MIPHTEL works or why this medicine has been prescribed for you, ask your doctor or the medical staff looking after you.

It is available only for hospital use.

NOTE: This is a patient information leaflet. Doctors and other health professionals involved in the administration of MIPHTEL should consult the administration instructions for healthcare professionals before use.

2. BEFORE USING MIPHTEL

2. BEFORE USING WIPHTEL:

You must not be given MIPHTEL:

If you are allergic (hypersensitive) to acetylcholine chloride or to any of the other ingredients (mannitol) of this medicine listed at the beginning of this leaflet.

Children: the use of MIPHTEL in children has not been studied and therefore children must not be given this medicine.

Take special care with MIPHTEL:

If the severe to specify the following greating is here! talk to your deater before you are given this.

If the answer to any of the following questions is 'yes', talk to your doctor before you are given this

- Are you taking ß-blockers (drugs used to treat high blood pressure and certain heart conditions)?
- Are you taking or have you recently taken non-steroidal anti-inflammatory agents (used to treat pain and swelling)?
- Do you suffer from bronchial asthma?
 Do you suffer from heart disease such as heart failure?
 Do you have overactive thyroid gland?
- Do you suffer from gastrointestinal complaints? Do you have a stomach ulcer? Do you have any difficulty passing urine? Do you suffer from Parkinson's disease?

Taking other medicines

Tell your doctor if you are taking or have recently taken any other medicines, even those you have bought without a prescription. In particular, you should inform your doctor if you are taking:

• B-blockers (used to treat high blood pressure and certain heart conditions)

• topical non-steroidal anti-inflammatory agents (used to treat pain and swelling).

Pregnancy and Breastfeeding
Tell your doctor if you are or think you may be pregnant. Tell your doctor if you are breastfeeding.
The doctor will discuss with you the risks and benefits involved.

Miphtel 20 mg powder and solvent for solution for intraocular irrigation

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

MIPHTEL 20 mg powder and solvent for solution for intraocular irrigation (acetylcholine chloride)

Warning: Do not use if the PVC holder or peelable backing is damaged or broken.

How to prepare MIPHTEL

- 1. Inspect unopened PVC holder to ensure that it is intact. Peel open the holder.
- 2. Aseptically withdraw the entire content of the solvent ampoule into a sterile syringe. Discard ampoule.
- 3. Transfer the solvent from the syringe to the powder ampoule.
- 4. Shake gently to dissolve drug
- 5. Visually inspect the reconstituted solution for particulate matter. Do not use solutions containing particulate matter.







Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. However, the surgical procedure may impair vision. You should not drive or use machines until such disturbances have subsided.

3. HOW MIPHTEL IS GIVEN

This medicine will be given to you only by the surgeon. Your surgeon will work out the correct dose of MIPHTEL for you. In most cases 0.5 ml to 2 ml of solution is a suitable dose. The solution should be made up just before it is given for intraocular use (i.e. use in the eye). It contains 10mg/ml of acetylcholine chloride (20mg/2ml). Each ampoule of powder and solvent is for single use only.

If too much is given
If you are given more medicine than you need, your doctor may need to give you an injection of either atropine sulphate or adrenaline to control symptoms. Symptoms of overdose may include slow heart rate, low blood pressure, flushing, breathing difficulties and sweating. Because acetylcholine is rapidly broken down by the body, symptoms of overdose are unlikely to occur. If you have any further questions on the use of this product, ask your doctor or the medical staff looking after you.

4. POSSIBLE SIDE EFFECTS

Like all medicines, MIPHTEL can have side effects, even when used as directed.

The following side effects have rarely been reported:

Slow heart rate

- Low blood pressure Flushing
- · Breathing difficulties
- Sweating Cloudiness of the cornea

If any of these affects you or if you notice any other side effects not mentioned in this leaflet, tell your doctor or the medical staff looking after you.

5. STORING MIPHTEL

Keep out of the reach and sight of children. Do not use this medicine after the expiry date stated on the label. The doctor should check that the solution is clear and colourless before use Do not freeze

Store in the original package.

6. FURTHER INFORMATION What MIPHTEL contains

Powder ampoule: Each ampoule contains: acetylcholine chloride 20 mg. Also contains: mannitol (E421), sodium hydroxide (for pH adjustment).

Solvent ampoule: Each ampoule contains water for injections 2 ml (for ophthalmic use only).

What MIPHTEL looks like and contents of the pack

MIPHTEL is supplied as a powder in a glass container called ampoule that requires reconstitution with the solvent provided in a separate ampoule.

Each pack contains 6 holders each containing one ampoule of powder and one ampoule of

Marketing Authorisation Holder and Manufacturers

Marketing Authorisation Holder: Regulatory Pharma Net s.r.l. Corso Italia, 108 I - 56125 PISA – Italy

Manufacturers responsible for batch release: Alfa Wassermann S.p.A. Via Enrico Fermi, $\mathbf{1}$

I - 65020 Alanno - Pescara - Italy

Farmigea S.p.A. Via G.B. Oliva, 8

I - 56121 Ospedaletto - Pisa - Italy

This leaflet was last approved in

The reconstituted solution should be slowly withdrawn from the ampoule into a suitable sterile syringe and should be administered into the anterior chamber of the eye. The product provides 10 mg/ml of acetylcholine chloride when diluted as recommended.

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The solution must be prepared just before use, since aqueous solutions of acetylcholine are unstable. Only clear and colourless solutions should be used.

The product is sterile until opened and should not be re-sterilised. For single use only. Any unused solution should be discarded.

How to store MIPHTEL

- Keep out of the reach and sight of children.
- Do not use any pack that is damaged or shows signs of tampering.
 Do not freeze.
- Store in the original package.
- Do not use after the expiry date stated on the label.

LABELLING

Internal label (solvent):

MIPHTEL 2ml solvent for solution for intraocular irrigation Water for injections

Solvent for MIPHTEL 20mg

Lot EXP

Carton:

