HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MITOSOL® safely and effectively. See full prescribing information for MITOSOL®.

MITOSOL® (mitomycin for solution) for ophthalmic use
Initial U.S. Approval: 1974

----------INDICATIONS AND USAGE----------
Mitosol® is an antimetabolite indicated as an adjunct to ab externo glaucoma surgery. (1)

----------DOSAGE AND ADMINISTRATION----------
Mitosol® is intended for topical application to the surgical site of glaucoma filtration surgery. It is not intended for intraocular administration. (2)
- Each vial of Mitosol® contains 0.2 mg of mitomycin and mannitol in a 1:2 concentration ratio. To reconstitute, add 1 mL of Sterile Water for Injection, then shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until the product has dissolved into solution. (2.2)
- Fully saturate sponges provided within the Mitosol® Kit utilizing the entire reconstituted contents of the vial in the manner prescribed in the Instructions for Use. (2.3)
- Apply fully saturated sponges equally to the treatment area, in a single layer, with the use of a surgical forceps. Keep the sponges on the treatment area for two (2) minutes, then remove and return to the Mitosol® Tray for defined disposal. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Each vial contains a sterile lyophilized mixture of 0.2 mg mitomycin and 0.4 mg mannitol; when reconstituted with Sterile Water for Injection, the solution contains 0.2 mg/mL mitomycin. (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to mitomycin. (4.1)

----------WARNINGS AND PRECAUTIONS----------
- Cell Death: Mitomycin is cytotoxic. Use of mitomycin in concentrations higher than 0.2 mg/mL or use for longer than 2 minutes may lead to unintended corneal and/or scleral damage including thinning or perforation. Direct contact with the corneal endothelium will result in cell death. (5.1)
- Hypotony: The use of mitomycin has been associated with an increased incidence of post-operative hypotony. (5.2)
- Cataract Development: Use in phakic patients has been correlated to a higher incidence of lenticular change and cataract formation. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to use. (5.4, 8.1, 8.3)

----------ADVERSE REACTIONS----------
The most frequent adverse reactions to Mitosol® occur locally and include hypotony, hypotony maculopathy, blebitis, endophthalmitis, vascular reactions, corneal reactions, and cataract. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mobius Therapeutics LLC 1-877-393-6486 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION

Revised 4/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Mitosol® is an antimetabolite indicated for use as an adjunct to ab externo glaucoma surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions
Mitosol® is intended for topical application to the surgical site of glaucoma filtration surgery. Mitosol® is a cytotoxic drug. It is not intended for intraocular administration. If intraocular administration occurs, cell death leading to corneal infarction, retinal infarction, and ciliary body atrophy may result. Verify pregnancy status in females of reproductive potential prior to using Mitosol®.

2.2 Method of Reconstitution
Each vial of Mitosol® contains 0.2 mg of mitomycin and mannitol in a 1:2 concentration ratio. To reconstitute, add 1 mL of Sterile Water for Injection, then shake to dissolve. If product does not dissolve immediately, allow to stand at room temperature until the product dissolves into solution.

2.3 Method of Use
Sponges provided within the Mitosol® Kit should be fully saturated with the entire reconstituted contents in the manner prescribed in the Instructions for Use. A treatment area approximating 10mm x 6mm +/- 2mm should be treated with the Mitosol®. Apply fully saturated sponges equally to the treatment area, in a single layer, with the use of a surgical forceps. Keep the sponges on the treatment area for two (2) minutes, then remove and return to the Mitosol® Tray for defined disposal in the Chemotherapy Waste Bag provided.

2.4 Stability
Lyophilized Mitosol® stored at 20°C to 25°C (68°F to 77°F) is stable for the shelf life indicated on the package. Avoid excessive heat. Protect from light.

Reconstituted with 1 mL of Sterile Water for Injection at a concentration of 0.2 mg/mL, mitomycin is stable for one (1) hour at room temperature.

3 DOSAGE FORMS AND STRENGTHS
Mitosol® is a sterile lyophilized mixture of mitomycin and mannitol, which, when reconstituted with Sterile Water for Injection, provides a solution for application in glaucoma filtration surgery. Mitosol® is supplied in vials containing 0.2 mg of mitomycin. Each vial also contains mannitol 0.4 mg, at a 1:2 ratio of mitomycin to mannitol. Each mL of reconstituted solution contains 0.2 mg mitomycin and has a pH between 5.0 and 8.0.

4 CONTRAINDICATIONS

4.1 Hypersensitivity
Mitosol® is contraindicated in patients that have demonstrated a hypersensitivity to mitomycin in the past.

5 WARNINGS AND PRECAUTIONS

5.1 Cell Death
Mitomycin is cytotoxic. Use of mitomycin in concentrations higher than 0.2 mg/mL or use for longer than 2 minutes may lead to unintended corneal and/or scleral damage including thinning or perforation. Direct contact with the corneal endothelium will result in cell death.

5.2 Hypotony
The use of mitomycin has been associated with an increased incidence of post-operative hypotony.

5.3 Cataract Formation
Use in phakic patients has been correlated to a higher incidence of lenticular change and cataract formation.

5.4 Embryo-Fetal Toxicity
Based on findings in animals and mechanism of action, Mitosol® can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, parenteral administration of mitomycin resulted in teratogenicity *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in the labeling:
- Cell Death *[see Warnings and Precautions (5.1)]*
- Hypotony *[see Warnings and Precautions (5.2)]*
- Cataract Formation *[see Warnings and Precautions (5.3)]*

6.1 Ophthalmic Adverse Reactions
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most frequent adverse reactions to Mitosol® occur locally, as an extension of the pharmacological activity of the drug. These reactions include:

Blebitis: bleb ulceration, chronic bleb leak, encapsulated/cystic bleb, bleb-related infection, wound dehiscence, conjunctival necrosis, thin-walled bleb

Cornea: corneal endothelial damage, epithelial defect, anterior synechiae, superficial punctuate keratitis, Descemet's detachment, induced astigmatism

Endophthalmitis

Hypotony: choroidal reactions (choroidal detachment, choroidal effusion, serous choroidal detachment, suprachoroidal hemorrhage, hypotony maculopathy, presence of supraciliochoroidal fluid, hypoechogenic suprachoroidal effusion)

Inflammation: iritis, fibrin reaction

Lens: cataract development, cataract progression, capsule opacification, capsular constriction and/or capsulotomy rupture, posterior synechiae

Retina: retinal pigment epithelial tear, retinal detachment (serous and rhegatogenous)

Scleritis: wound dehiscence

Vascular: hyphema, central retinal vein occlusion, hemiretinal vein occlusion, retinal hemorrhage, vitreal hemorrhage and blood clot, subconjunctival hemorrhage, disk hemorrhage

Additional Reactions: macular edema, sclera thinning or ulceration, intraocular lens capture, disk swelling, malignant glaucoma, lacrimal drainage system obstruction, ciliary block, corneal vascularization, visual acuity decrease, cystic conjunctival degeneration, upper eyelid retraction, dislocated implants, severe loss of vision.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Based on findings in animals and mechanism of action *[see Clinical Pharmacology (12.1)]*, Mitosol® can cause fetal harm when administered to a pregnant woman. There are no available data on Mitosol® use in pregnant women to inform the drug-associated risk.

In animal reproduction studies, parenteral administration of mitomycin resulted in teratogenicity (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

Data
Animal Data
Parenteral administration of mitomycin in animal reproduction studies produced fetal malformations and embryofetal lethality.

8.2 Lactation
Risk Summary
There are no data on the presence of mitomycin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during and for 1 week following administration of Mitosol®.

8.3 Females and Males of Reproductive Potential
Mitosol® can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

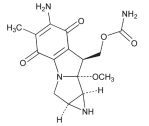
Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to using Mitosol®.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION
Mitomycin is an antibiotic isolated from the broth of *Streptomyces verticillus Yingtanensis* which has been shown to have antimetabolic activity.

Mitomycin is a blue-violet crystalline powder with the molecular formula of $C_{15}H_{18}N_4O_5$ and a molecular weight of 334.33. Its chemical name is 7-amino-9α-methoxymitosane and it has the following structural formula:



Mitosol® is a sterile lyophilized mixture of mitomycin and mannitol, which, when reconstituted with Sterile Water for Injection, provides a solution for application in glaucoma filtration surgery. Mitosol® is supplied in vials containing 0.2 mg of mitomycin. Each vial also contains mannitol 0.4 mg, at a 1:2 ratio of mitomycin to mannitol. Each mL of reconstituted solution contains 0.2 mg mitomycin and has a pH between 5.0 and 8.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Mitosol® inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. Cellular RNA and protein synthesis may also be suppressed.

12.3 Pharmacokinetics
Absorption
The systemic exposure of mitomycin following ocular administration of Mitosol® in humans is unknown. Based on a comparison of the proposed dose of up to 0.2 mg to intravenous (IV) doses of mitomycin used clinically for treatment of oncologic indications (up to 20 mg/m^2), systemic concentrations in humans upon ocular administration are expected to be multiple orders of magnitude lower than those achieved by IV administration.

Elimination

Metabolism

In humans, mitomycin is cleared from ophthalmic tissue after intraoperative topical application and irrigation, as metabolism occurs in other affected tissues. Systemic clearance is affected primarily by metabolism in the liver. The rate of clearance is inversely proportional to the maximal serum concentration because of saturation of the degradative pathways.

Excretion

Approximately 10% of an injectable dose of mitomycin is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with Mitosol®. Intravenous administration of mitomycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical injectable dose in humans, mitomycin produces a greater than 100 percent increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50 percent increase in tumor incidence in female Swiss mice. The effect of Mitosol® on fertility is unknown.

14 CLINICAL STUDIES

In placebo-controlled studies reported in the medical literature, mitomycin reduced intraocular pressure (IOP) by 3 mmHg in patients with open-angle glaucoma when used as an adjunct to ab externo glaucoma surgery by Month 12.

In studies with a historical control reported in the medical literature, mitomycin reduced intraocular pressure (IOP) by 5 mmHg in patients with open-angle glaucoma when used as an adjunct to ab externo glaucoma surgery by Month 12.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Mitosol® (mitomycin for solution) is available in a kit containing:

One	Vial containing 0.2 mg mitomycin
One	1 mL syringe (Sterile Water For Injection) with Safety Connector
One	Plunger Rod
One	Vial Adapter with Spike
One	1 mL TB Syringe, Luer Lock
One	Sponge Container
Six	3 mm Absorbent Sponges
Six	6 mm Absorbent Sponges
Six	Half Moon Sponges
One	Instrument Wedge Sponge
One	Protective Foam Pouch
One	Chemotherapy Waste Bag
One	Label, MMC (mitomycin)

Three kits are supplied in each carton (NDC49771-002-03).

16.2 Storage and Handling

Storage

Store kits at 20°C to 25°C (68°F to 77°F). Avoid excessive heat. Protect from light.

Handling Procedures

Mitosol® is a cytotoxic drug. Procedures for Proper Handling and Disposal of anti-cancer drugs should be followed. Appropriate containment and disposal devices are included within the Mitosol® (mitomycin for solution) Kit for Ophthalmic Use.

17 PATIENT COUNSELING INFORMATION

- Instruct patients to discuss with their physician if they are pregnant or if they might become pregnant *[see Use in Specific Populations (8.1)]*.
- Instruct patients to discuss with their physician if they have demonstrated a hypersensitivity to mitomycin in the past *[see Contraindications (4.1)]*.
- Nursing mothers should be advised that it is not known if Mitosol® is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during and for 1 week following administration of Mitosol® *[see Use in Specific Populations (8.2)]*.
- Patients should be advised of the toxicity of Mitosol® and potential complications.

Manufactured for:
Mobius Therapeutics, LLC
1000 Executive Parkway
Suite 224
St. Louis, MO 63141

Mitosol®

(mitomycin for solution)

0.2 mg/vial

Kit for Ophthalmic Use

Read INSTRUCTIONS FOR USE Before Proceeding

Instructions for Use

A. Outer Pack (Figure A)

One	Sterile Chemotherapy Waste Bag
One	Instructions for Use
One	Package Insert
One	Inner Tray
Two	Patient Chart Labels

The Outer Pack is to be handled, opened, and its ***STERILE*** *contents dispensed by the non-sterile circulating nurse.*

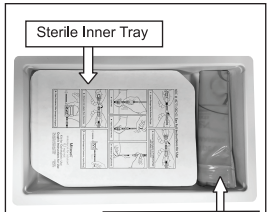


Figure A: Outer Pack

B. STERILE Inner Tray (Figure B)

One	Vial Containing 0.2 mg mitomycin (inside protective foam pouch)
One	1 mL Syringe (Sterile Water for Injection)
One	Plunger Rod
One	Safety Connector
One	Vial Adaptor with Spike (inside protective foam pouch)
One	1 mL TB Syringe, Luer Lock
One	Sponge Container Containing:
• Six	3 mm Absorbent Sponges
• Six	6 mm Absorbent Sponges
• Six	Half Moon Sponges
• One	Instrument Wedge Sponge
One	Label, MMC (mitomycin)

The Sterile Inner Tray is to be handled, opened, and its contents assembled and dispensed by the sterile scrub technician. ***This tray and its contents are STERILE.***

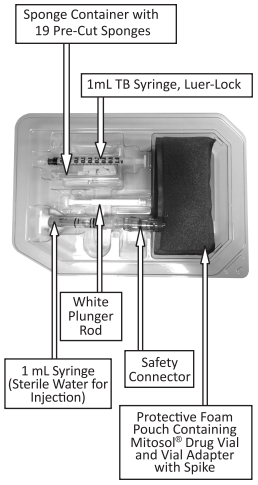


Figure B: Sterile Inner Tray

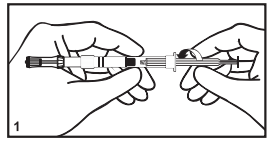
1. Getting Started

Non-Sterile Circulating Nurse:

Open outer pack. Affect sterile transfer of **ALL** contents to the sterile field.

Sterile Surgical Technician:

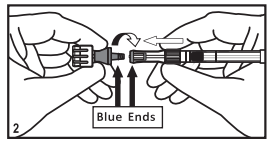
Open sterile inner tray.



2. Reconstituting Mitosol®

a. Remove vial and vial adapter from blue foam pouch.

b. Screw white plunger rod to rubber plunger of pre-filled syringe. **(Fig. 1)**



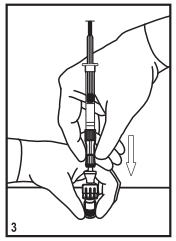
c. **Press firmly** and screw the **blue end** of vial adapter into the **blue end** of the syringe connector. **(Fig. 2)**

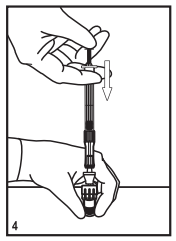
NOTE: Do not force plunger. Syringe will not operate if vial adapter and syringe connector are not properly connected. Forcing plunger may result in syringe leakage and Mitosol® exposure.

d. Stand vial upright on a sturdy, flat surface and push on the vial lid until seated and secure. **(Fig. 3)**

e. Inject entire contents of sterile water (1 mL) into vial. **(Fig. 4)** Do not force syringe plunger. See note at step 2.

f. **IMPORTANT**: INVERT VIAL REPEATEDLY to saturate **ALL** drug product, including that adhering to stopper, then shake until complete reconstitution of Mitosol®. If product does not dissolve immediately, allow to stand at room temperature until the product has dissolved into solution.



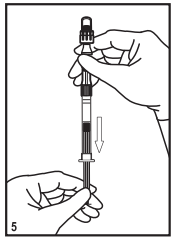


3. Preparing sponges

a. ***Invert vial and syringe*** and draw full volume of medication into syringe. **(Fig. 5)**

b. Remove all sponges from sponge tray.

c. Return to sponge tray only those sponges to be saturated with Mitosol®.

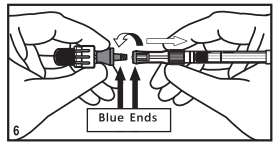


d. Unscrew the syringe with safety connector from vial and vial adapter. **(Fig. 6)** Note: **DO NOT** remove safety connector from syringe.

e. Place vial and vial adapter in chemotherapy waste disposal bag (yellow bag), and set bag aside, within sterile field, for additional use.

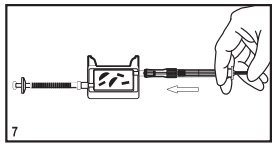
f. Take sponge container from sterile inner tray.

g. Screw both syringes into sponge container; the TB syringe to one end, the syringe with reconstituted Mitosol® to the other.



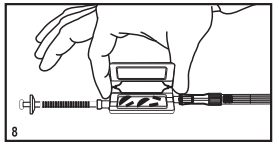
h. *Mitosol® must be used within 1 hour of reconstitution:*

- Inject medication into sponge container, saturating sponges. Reconstituted Mitosol® should remain undisturbed in sponge container for **60 seconds**. **(Fig. 7)** Do not force syringe plunger. See note at step 2.
- If any excess fluid remains, withdraw plunger of TB syringe, drawing excess fluid/air into syringe.



4. Using Mitosol®

a. With both syringes connected, the TB syringe to one end, the pre-filled syringe to the other, open sponge container, offering contents to surgeon for placement on surgical site. **(Fig. 8)**



b. Apply saturated sponges to surgical site for two minutes. Remove sponges from eye and copiously irrigate surgical site.

c. As used sponges are removed from surgical site, accept used sponges back into sponge container for disposal. Close container lid.

d. With syringes still connected to sponge container, remove entire assembly from surgical field in chemotherapy waste disposal bag.

DISPOSE OF CHEMOTHERAPY WASTE BAG AND ITS CONTENTS AS CHEMOTHERAPY WASTE

US Patents #7,806,265, #8,186,511, #D685,962, #D685,963, #9,205,075, #9,539,241 and #9,649,428; other international patents pending.

A4807999-3 Rev. 4/21