HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Mitosol® (mitomycin for solution) safely and effectively. See full prescribing information for Mitosol® (mitomycin for solution).

Mitosol® (mitomycin for solution)

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. (2.1)
- 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. (2.2)
- 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. (2.2)

----------**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)
- Women who are or may become pregnant during therapy. (4.2)

----------**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 instance of post-operative hypotony. (5.2)
- Cataract Development. Use in phakic patients has been correlated to a higher instance of lenticular change and cataract formation. (5.3)

----------**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 at 1-877-393-6486 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised 01/2012

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4 CONTRAINDICATIONS
4.1 Hypersensitivity
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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

Mitosol® is intended for topical application to the surgical site of glaucoma filtration surgery. 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.

2.1 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.

2.2 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.

2.3 Stability

Lyophilized Mitosol® stored at controlled room temperature (i.e., 20 – 25°C or 68° – 77° F) is stable for the shelf life indicated on the package. Avoid excessive heat. Protect from light.

Reconstituted with 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.

4.2 Pregnant women

Mitosol® may cause fetal harm when administered to a pregnant woman. Mitomycin administered parenterally has been shown to be teratogenic in mice and rats when given at doses equivalent to the usual human intravenous dose. Mitosol® is contraindicated in women who are or may become pregnant during therapy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

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 instance of post-operative hypotony.

5.3 Cataract Formation

Use in phakic patients has been correlated to a higher instance of lenticular change and cataract formation.

6. ADVERSE REACTIONS

6.1 Ophthalmic Adverse Reactions

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, conjunctivial 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

Teratogenic Effects: Pregnancy Category X (*see Contraindications, 4.2*).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Mitosol®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women receiving Mitosol® not breast feed because of the potential for serious adverse reactions in nursing infants.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

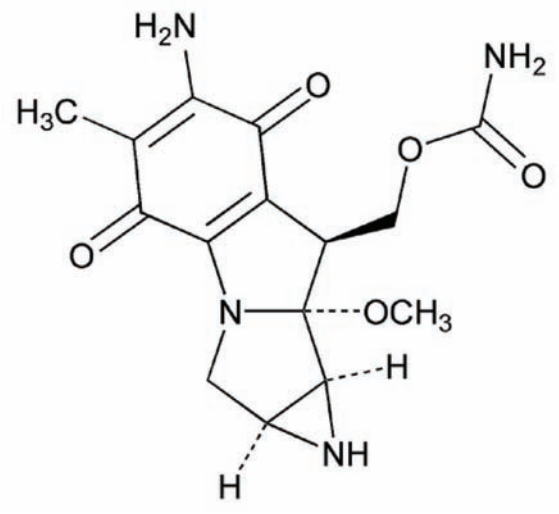
8.5 Geriatric Use

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 lyophiliized 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.

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 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	Alcohol Prep Pad, Sterile
One	Chemotherapy Waste Bag

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

16.2 Storage and Handling

Storage
Store kits at 20° – 25° C (68° – 77° F). Protect from light.

Handling Procedures
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 Contraindications, 4.2*).

- 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 many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue use of the drug, taking into account the importance of the drug to the mother. It is recommended that women receiving Mitosol® not breast feed because of the potential for serious adverse reactions in nursing infants (*see Use in Specific Populations, 8.3*).

- Patients should be advised of the toxicity of Mitosol® and potential complications.

Manufactured for:
Mobius Therapeutics, LLC
4041 Forest Park Avenue
St. Louis, MO 63108

Mitosol®

(mitomycin for solution)
0.2 mg/vial

Read INSTRUCTIONS FOR USE Before Proceeding

Instructions for Use

A. **Black Outer Pack** (Figure A)

One Chemotherapy Waste Bag
One Instructions for Use
One Package Insert
One Inner Tray

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

Figure A: Black Outer Pack

B. **STERILE Inner Tray** (Figure B)

One	Vial Containing 0.2 mg mitomycin
One	1 mL Syringe (Sterile Water for Injection) with Connector
One	Plunger Rod
One	Vial Adaptor 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	Alcohol Prep Pad, Sterile

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.***

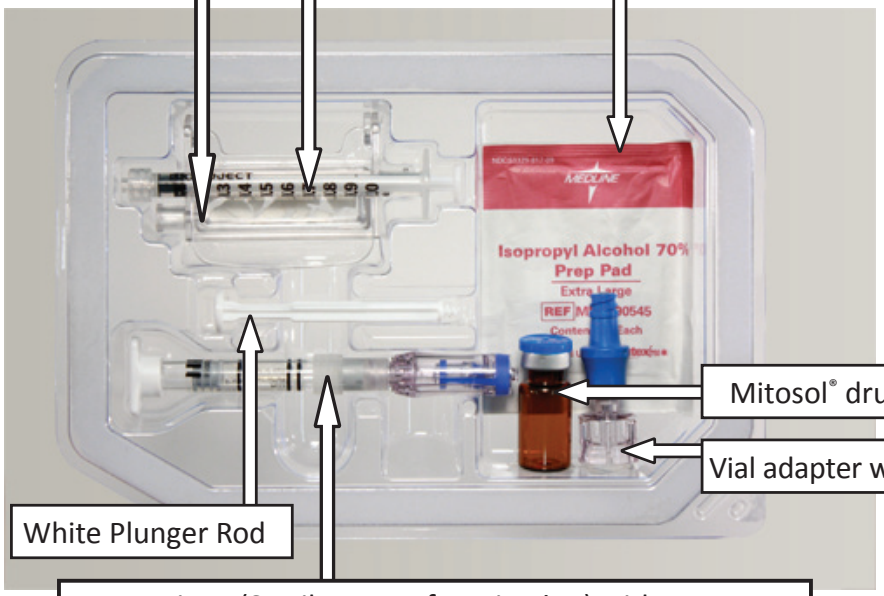


Figure B: Sterile Inner Tray

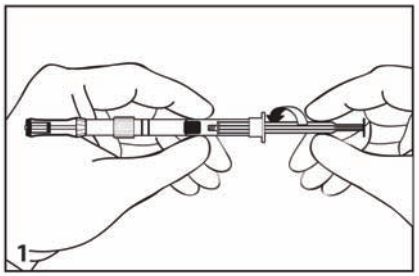
1. Getting Started

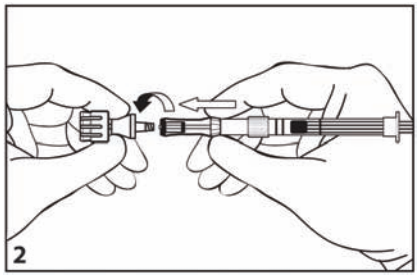
Non-Sterile Circulating Nurse:

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

Sterile Surgical Technician:

Open sterile inner tray.





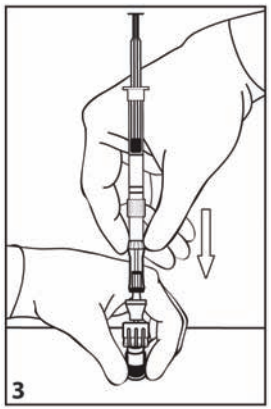
2. Reconstituting Mitosol®

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

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

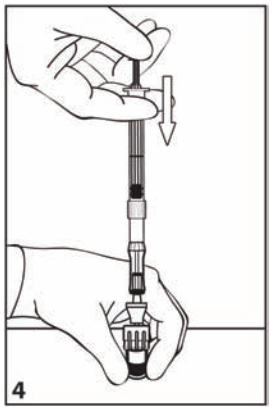
c. Open and remove alcohol prep pad. Remove vial cap; disinfect vial stopper with alcohol prep pad.

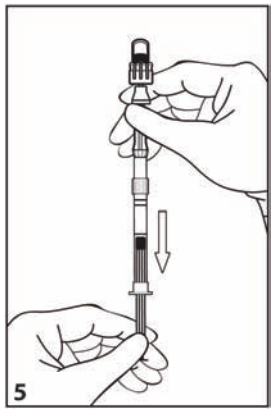
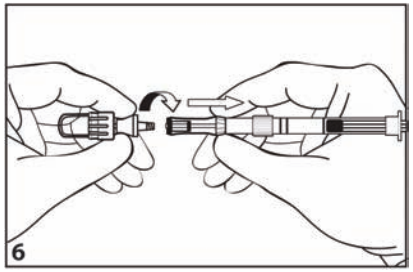
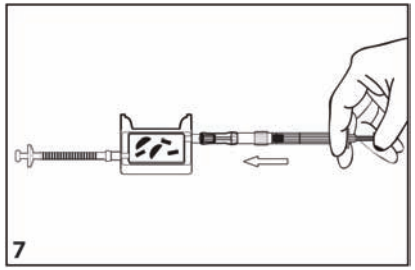
d. Holding vial face up, push spiked end of vial adapter down on the vial lid until seated and secure. **(Fig. 3)**

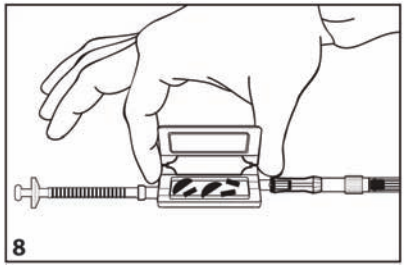


e. Inject entire contents of sterile water (1 ml) into vial. **(Fig. 4)**

f. Gently swirl vial and contents 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.	
b. Unscrew the syringe and connector from vial and vial adapter **(Fig. 6)** c. Place vial and vial adaptor in chemotherapy waste disposal bag (yellow bag). d. Take sponge container from sterile inner tray. e. Screw both syringes into sponge container; the TB syringe to one end, the pre-filled syringe to the other.	
f. ***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)** • 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 back into 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.	 8

DISPOSE OF CHEMOTHERAPY WASTE BAG AND ITS CONTENTS AS CHEMOTHERAPY WASTE

MOB0022 Rev. D