PRODUCT MONOGRAPH

Pr RIMSO-50

(Dimethyl Sulfoxide 500 mg/g)

Intravesical Instillation for the
Treatment of Interstitial Cystitis

Mylan Pharmaceuticals ULC
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Date of Preparation: March 11, 2014

Submission Control No: 171866

[Pr] RIMSO-50

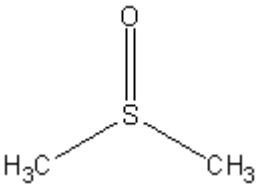
(Dimethyl Sulfoxide 50%)
NOT FOR I.M or I.V Injection

THERAPEUTIC CLASSIFICATION

Intravesical instillation for the treatment of interstitial cystitis.

STRUCTURAL FORMULA AND CHEMISTRY

The active component of RIMSO-50 is dimethyl sulfoxide which has the empirical formula C_2H_6OS, and is structurally represented as:



Dimethyl sulfoxide is a clear, colorless and essentially odorless liquid which is miscible with water and most organic solvents. Other physical characteristics include: molecular weight 78.13, melting point 18.4°C, boiling point 189°C, and a specific gravity of 1.100.

ACTION

The mode of action of RIMSO-50 (DMSO) as a treatment for interstitial cystitis is speculative at this time. Hypotheses center around the following:

a) Anti-inflammation
b) Analgesic
c) Improvement of blood supply
d) Softening of collagen due to action on cross-linking

METABOLISM

Dimethyl sulfoxide is metabolised by oxidation to dimethyl sulfone or by reduction to dimethyl sulfide. Dimethyl sulfoxide and dimethyl sulfone are excreted in the urine and feces. Dimethyl sulfide is eliminated through the breath and skin and is responsible for the characteristic odor from patients on dimethyl sulfoxide medication. Dimethyl sulfone can persist in serum for longer than two weeks after a single intravesical instillation. No residual accumulation of dimethyl sulfoxide has occurred in man or lower animals who have received treatment for protracted periods of time. Following topical application, dimethyl sulfoxide is absorbed and generally distributed in the tissues and body fluids.

INDICATIONS AND CLINICAL USES

RIMSO-50 (dimethyl sulfoxide) is indicated for the symptomatic relief of patients with interstitial cystitis. RIMSO-50 has not been approved as being safe and effective for any other indication.

There is no clinical evidence of effectiveness of dimethyl sulfoxide in the treatment of bacterial infections of the urinary tract.

CONTRAINDICATIONS

None.

WARNINGS

DIMETHYL SULFOXIDE CAN INITIATE THE LIBERATION OF HISTAMINE AND THERE HAS BEEN AN OCCASIONAL HYPERSENSITIVITY REACTION WITH TOPICAL ADMINISTRATION OF DIMETHYL SULFOXIDE. THIS HYPERSENSITIVITY HAS NOT OCCURRED IN PATIENTS RECEIVING INTRAVESICAL RIMSO-50; HOWEVER, THE PHYSICIAN SHOULD BE COGNIZANT OF THIS POSSIBILITY IN PRESCRIBING RIMSO-50. IF ANAPHYLACTOID SYMPTOMS DEVELOP, APPROPRIATE THERAPY SHOULD BE INSTITUTED. SOME DATA INDICATES THAT DIMETHYL SULFOXIDE POTENTIATES OTHER CONCOMITANTLY ADMINISTERED MEDICATIONS.

PRECAUTIONS

Changes in the refractive index and lens opacities have been seen in monkeys, dogs and rats given dimethyl sulfoxide chronically. No ophthalmic changes attributable to intravesical instillation of dimethyl sulfoxide have been reported in patients carefully followed for up to 17 months; nevertheless, full eye evaluations, including slit lamp examinations are recommended prior to and at six month intervals during treatment.

Along with the ophthalmological examinations, patients should be investigated with respect to biochemical parameters, particularly renal and hepatic function, at six month intervals.

Intravesical instillation of RIMSO-50 may be harmful to patients with urinary tract malignancy because of dimethyl sulfoxide-induced vasodilation.

USE IN PREGNACY

The safety of dimethyl sulfoxide for the human fetus has not been established, hence it should be given to pregnant women only when the potential benefits to the mother have been weighted against possible hazards to the child.

Dimethyl sulfoxide caused teratogenic responses in hamsters, rats and mice when administered intraperitoneally at high doses (5 - 12 gm/kg). Oral or topical doses of dimethyl sulfoxide did not cause problems of reproduction in rats, mice and hamsters. Topical doses (5 gm/kg - first two days, then 2.5 gm/kg - last eight days) produced terata in rabbits, but in another study, topical doses of 1.1 gm/kg days three through sexteen of gestation failed to produce any abnormalities. Mothers receiving dimethyl sulfoxide should not nurse their infants. It must be assumed, although data are lacking, that dimethyl sulfoxide is excreted in human milk.

ADVERSE REACTIONS

A garlic-like taste may be noted by the patient within a few minutes after instillation of RIMSO-50 (dimethyl sulfoxide). This taste may last several hours and because of the presence of metabolites, an odor on the breath and skin may remain for 72 hours. Transient chemical cystitis has been noted following instillation of 100% dimethyl sulfoxide.

The patient may experience moderately severe discomfort on administration. Usually this becomes less prominent with repeated administration.

PHARMACOLOGY

Dimethyl sulfoxide in some lower animals, including rabbits, dogs and pigs has been shown to produce changes in the refractive index of the lens of their eye. The oral route appears more likely to cause such ocular changes which occur at doses of 1 g/kg/day of dimethyl sulfoxide for treatment periods as short as 69 days. The rabbit was the most susceptible of the species treated while the rheus monkey was most resistant.

Dimethyl sulfoxide has a wide spectrum of primary pharmacologic activity, including:

a) Membrane penetrant
b) Solute "carrier" across membranes
c) Anti-inflammatory
d) Analgesia
e) Diuresis
f) Cholinesterase inhibitor
g) Muscle relaxation
h) Vasodilation

TOXICITY

A refractive index change in the lens (not an opacity) had been observed after 3 months at a dose of approximately 5 g/kg in dogs, rabbits and pigs. No microscopic or chemical differences could be found between the lenses of the treated animals and the controls. In the affected animals, there appeared two distinct zones of different refraction. This could easily be observed with an opthalmoscope and with a slit lamp. It appeared to be a dose-related effect, and it diminished as the dose was reduced. It is noteworthy that the effect was produced 50 to 100 times the usual human therapeutic dose.

Extensive toxicology studies have been conducted in numerous animal species, at 3 to 30 times the dose anticipated for humans, for periods of up to 18 months. Dimethyl sulfoxide appears to be a relatively safe drug for human administration and the lens changes which have been noted in animals have not yet been reported in humans.

DOSAGE AND ADMINISTRATION

Instillation of 50 mL of RIMSO-50 (dimethyl sulfoxide) directly into the bladder may be accomplished by catheter or asepto syringe and allowed to remain for 15 minutes. Application of an analgesic lubricant gel such as Lidocaine jelly to the urethra is suggested prior to insertion of the catheter to avoid spasm. The medication is expelled by spontaneous voiding. It is recommended that the treatment be repeated every two

weeks until maximum symptomatic relief is obtained. Thereafter, time intervals between therapy may be increased appropriately. In selected cases where symptomatic relief is not complete, the bladder may be gently distended by gravity instillation with up to 500 mL of a solution prepared immediately prior to instillation in a glass vial, with one part RIMSO-50 and one part sterile water prior to the instillation of the standard dose of 50 mL of RIMSO-50. After retention of RIMSO-50 for 15 minutes the medication is again expelled by spontaneous voiding. Administration of oral analgesic medication or suppositories containing belladonna and opium prior to the instillation of RIMSO-50 can reduce bladder spasm in particularly sensitive patients. In patients with very sensitive bladders, the initial treatment should be done under anesthesia (preferable saddle block type).

RIMSO-50 is recommended for bladder instillation only.

DOSAGE FORMS

Bottles contain 50 mL (54 gm) of sterile and pyrogen-free RIMSO-50 (50% w/w dimethyl sulfoxide aqueous solution).

STORAGE CONDITIONS

RIMSO-50 (50% w/w dimethyl sulfoxide aqueous solution) should be stored between 15° and 30°C and protected from light.

RIMSO-50 is manufactured by Mylan Pharmaceuticals ULC. For more information please call the customer service line at 1-800-575-1379.

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