FORT DODGE ANIMAL HEALTH
Division of Wyeth, a subsidiary of Pfizer, Inc.

235 E. 42ND ST., NEW YORK, NY, 10017

Telephone: 269-833-4000

Customer Service: 800-733-5500 and 800-793-0596

Veterinary Medical Investigations & Product Support: 800-366-5288

Technical Services (USA): 800-366-5288

Website: http://pfizerah.com

DOMOSO® GEL

℞

Fort Dodge

DIMETHYL SULFOXIDE

90% Dimethyl Sulfoxide

For Animal Use Only

NADA 47-925, Approved by FDA

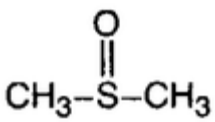
CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

GENERAL

Dimethyl sulfoxide (DMSO), an oxidation product of dimethyl sulfide, is an exceptional solvent possessing a number of commercial uses.

DMSO is the lowest member of the group of alkyl sulfoxides with a general formula of RSOR. Its structural formula is:



It freely mixes with water with the evolution of heat and lowers the freezing point of aqueous solutions. It is soluble in many other compounds including ethanol, acetone, diethyl ether, glycerin, toluene, benzene and chloroform. DMSO is a solvent for many aromatic and unsaturated hydrocarbons as well as inorganic salts and nitrogen-containing compounds. DMSO has a high dielectric constant due to the polarity of the sulfur-oxygen bond. Its basicity is slightly greater than water due to enhanced electron density at the oxygen atom. It forms crystalline salts with strong protic acids and coordinates with Lewis acids. It modifies hydrogen bonding.

DMSO is a hygroscopic stable organic liquid essentially odorless and water white in color. Other physical characteristics include:

Molecular weight	78.13
Melting point	18.45°C
Boiling point	189°C

DOMOSO Gel contains 90% dimethyl sulfoxide, carbomer 934, disodium edetate, NaOH and purified water q.s.

PHARMACOLOGY

The original biological applications of DMSO were primarily confined to its use in preserving various tissues and cellular elements including blood (1), blood cells and bone marrow (2), leukocytes (3), lymphocytes (4), platelets (5), spermatozoa (6, 7, 8), corneal grafts (9, 10), skin (11), tissue culture cells (12, 13, 14, 15) and trypanosomes (16), by freezing techniques. DMSO has also been investigated as a radioprotective agent (17, 18).

DMSO has been stated to increase the penetration of low molecular weight allergens such as penicillin G but not large molecular weight allergens such as house dust (19).

The rate of passage of tritiated water in the presence of DMSO on the epidermis of the hairless mouse was measured *in vitro.* DMSO did not appear to promote the passage of water by its presence, but when concentrated solutions (60% to 100%) were used, permanent changes were produced in the rate of passage of water. It was concluded that the concentration of DMSO used seemed more significant than the time of exposure in establishing the effect on the water barrier (20).

When the tails of mice were immersed in a 5% solution of various psychoactive drugs in DMSO, the drugs appeared to exert their usual pharmacological effects, indicating drug penetration as judged by the behavioral effects observed in the experimental subjects. Other solvents, including water, also appeared to permit some drug penetration in this study (21).

Using ten quaternary ammonium salts as test compounds and either water or DMSO as solvents, the oral LD_{50} values were determined in rats and mice. Toxicity changes were obtained in some instances by 50% DMSO and more changes were observed in rats than mice although the results in the two species were not always parallel. When toxicity was altered by DMSO it increased in all instances except one (22).

When administered systemically in another study, however, various drugs dissolved in DMSO did not differ significantly in their lethality or cellular penetration as compared to the same drugs administered in saline (23).

When evaluated as a solvent for biologic screening tests, low doses of hormones in DMSO stimulated a response similar to that of the hormone in the control vehicle. Higher doses of hormone, however, failed to give

the expected response suggesting a partition coefficient in favor of the solvent (24). DMSO was also shown to carry physostigmine and phenylbutazone through the skin of the rat (25).

The absorption of phenylbutazone dissolved in an aqueous solution of DMSO was impaired when administered orally to the rabbit. Absorption of the same drug was not improved using the subcutaneous route simultaneously with DMSO.

However, phenylbutazone could be detected in the rabbit's blood for several hours when an ointment containing DMSO and 5% phenylbutazone was applied to the skin. When the DMSO content of the ointment was increased, the phenylbutazone levels increased. An increase of phenylbutazone in the muscle tissues underlying the site of application over a control ointment containing phenylbutazone without DMSO could be demonstrated in rats (26).

In a number of other studies in experimental animals (21, 25, 27) where DMSO has been chiefly administered orally or by injection, no anti-inflammatory or analgesic activity could be established.

Following experimental hypersensitization to human gamma globulin in the horse, antigen challenge resulted in massive erythema, necrosis and slough. This reaction could be markedly reduced by the hourly application of undiluted DMSO to the reaction site, after challenge (19).

DMSO, by itself, at concentrations of 100%, 66% and 33% has been shown to produce neurolysis following perineural injection in the rat's sciatic nerve (28).

The conflicting reports cited above for the anti-inflammatory and analgesic properties of DMSO are partially dependent upon the experimental models and methods used to measure these parameters. DMSO fails to show analgesic or anti-inflammatory activity in certain of these situations, particularly when used by the systemic route or when administered topically preceded by an irritant substance. In clinical studies in the horse, it was noted that when iodine, liniments or other strong irritants were present on the skin from previous therapy and DMSO applied, a temporary but marked local reaction would occur. This was due to the ability of DMSO to carry these substances into the underlying skin tissues where their irritant actions could be displayed.

Using the isolated guinea pig heart it was found that DMSO did not influence the amplitude of cardiac contractions, heart rate or coronary flow, although high intravenous doses in the rat and cat resulted in a transient lowering of blood pressure (25).

Isolated, innervated guinea pig preparations were also used to study the effects of DMSO on skeletal, smooth and cardiac muscles. The compound depressed diaphragm response to both muscle and nerve stimulation and also caused spontaneous skeletal muscle fasciculations. Actual contraction amplitude was augmented although contraction rate appeared unaffected. Vagal threshold was lowered almost 50% by a bath concentration of 6% DMSO. The fasciculations and increased tone of skeletal muscle, and lowering of the vagal threshold by DMSO could be due to cholinesterase inhibition (29). The *in vitro* oxygen consumption of liver, brain and hemidiaphragm tissues of rats is not affected by the intravenous administration of 75 mg DMSO/100 g body weight during the 7 subsequent days.

Urease, trypsin and chymotrypsin are inhibited by DMSO dependent upon its concentration. The *in vitro* metabolism of corticosterone by rat liver slices is not affected by the intravenous administration of 100 mg DMSO/100 g body weight during 3 subsequent days (30).

DMSO treatment administered intraperitoneally to rats for 35 days decreased experimentally induced intestinal adhesions by 80% over controls as compared to saline, cortisone acetate or a combination of cortisone and DMSO administered separately (31).

In rabbits the application of 70% DMSO, adjacent to but not on the wound incision site, appeared to increase the development of wound tensile strength over controls (32).

Increasing the concentration of DMSO resulted in an increasing inhibition of fibroblast proliferation, *in vitro,* which was reversible (19).

TOXICOLOGY

In a study designed to evaluate the effects of DOMOSO® (dimethyl sulfoxide) Solution at a total daily dose of 100-300 mL administered for a total period of 90 days, no essential or clinically meaningful ophthalmological effects were seen in the horse. There were no significant variations in glucose, sodium, potassium, SGOT or SGPT measurements. There were a few fluctuations in hematologic values but no changes appear to be drug-related or of significance.

Another study was conducted in the dog to determine the effects of DOMOSO Solution at a total daily dose of 20-60 mL administered topically for 21 consecutive days. No clinically meaningful ophthalmological effects were noted. No significant variations were observed in blood measurements, including glucose, BUN, SGOT and plasma electrophoresis. Hematologic values were similar to control animals used in this study.

Long-term topical applications of the drug to guinea pigs resulted in histopathologic changes similar to those observed in allergic contact dermatitis. The observed clinical changes were compatible with either an allergic contact dermatitis or a primary irritant effect (33). DMSO was shown to cause erythema and blistering of human and rat skin resulting in increased permeability of venules and capillaries (34).

In most cases the local irritation of the skin characterized by erythema, vesicle or blister formation and scurfing abates even with continued treatment. The phenomenon has been described as “accommodation” or “hardening” of the skin, and has been noted with other solvents.

The undiluted compound has low systemic toxicity but a marked local necrotizing and inflammatory effect when it is injected subcutaneously. In rats the subcutaneous injection of 10 g/kg or the intravenous injection of 2.5 g/kg of undiluted DMSO for 2 weeks showed no definite indication of systemic toxicity. The local necrotizing effects produced at these dose levels, however, prevented a longer period of treatment. No significant hematologic or biochemical changes were noted in 3 dogs receiving 0.4 g/kg for 33 days (24).

Four dogs were administered topical DMSO at 1 g/kg body weight, 5 days weekly for 18 months. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), prothrombin time, alkaline phosphatase, bilirubin, total protein and albumin globulin (AG) ratio, and blood urea nitrogen (BUN) were determined at the beginning of treatment and at monthly intervals. Significant abnormalities did not occur (41).

Upon injection of DMSO into the rat pleura, there is an accumulation of fluid, initially appearing as a transudate, but later as a protein-rich exudate. Exudate formation is thought to be due to increased vascular permeability, predominantly in venules, brought about by a delayed release of histamine together with activation of a vaso-active slow contracting substance (34).

A compilation of the results for a number of acute toxicity (LD_{50}) determinations derived from several published reports (24, 40, 42, 43, 44) in several experimental animal species is as follows:

Species		**Rt. of Administr.**		**LD50 g/kg**
Mouse	-	SQ	-	13.9-20.5

Mouse	-	IV	-	3.82-10.73
Mouse	-	Oral	-	15.0-22
Mouse	-	IP	-	20.06
Rat	-	IV	-	5.25-5.36
Rat	-	Oral	-	16.0-28.3
Rat	-	IP	-	6.5-13.621
Dog	-	IV	-	2.5
Guinea Pig	-	IP	-	6.5
Chicken	-	Oral	-	12.5

Hemolysis resulting in hemoglobinuria and methemoglobinuria was noted in anesthetized cats following single intravenous doses of 200 mg/kg DMSO. The intraperitoneal administration of DMSO or the dilution of DMSO with isotonic saline prior to intravenous administration reduced its hemolytic activity (39).

Tests *in vitro* showed that washed rabbit erythrocytes are hemolyzed in a short time with 40% to 60% DMSO solution. Higher concentrations caused, without hemolysis, an agglutination of the erythrocytes (40).

Teratology

The intraperitoneal administration of 5.5 g/kg of DMSO as a single dose to pregnant hamsters induced developmental malformations of their embryos (35). Both dimethyl sulfoxide and diethyl sulfoxide are teratogenic when injected into the chick embryo, the classification of malformations being dependent upon the stage of embryonic development at the time of treatment. The same drugs when administered by various techniques to mice, rats and rabbits in which fertility had been established, did not cause any embryonic malformations (36).

Ocular Effects

In a variety of experimental animals including rats, dogs, swine, rabbits and primates, following oral or topical administration of DMSO, certain eye changes have been noted. These consist mainly of a change in the refractive index of the lens described as a “lens within a lens”. The lens changes are characterized by a decrease in the normal relucency of the lens cortex, causing the normal central zone of the lens to act as a biconvex lens. When viewing the fundus of affected animals, it is necessary to interpose biconcave lenses in order to see the retinal vessels clearly. The functional effect would be a tendency toward myopia (37).

The lens changes were first observed in dogs receiving 5 g DMSO/kg after 9 weeks of administration. At lower dose levels the change was observed later. In rabbits these changes were seen after 90 days of dermal application, (8 mg 50% DMSO/kg/day and 4 mg 100% DMSO/kg/day and higher). In swine, dermal application of 4.5 g 90% DMSO/kg twice daily caused similar lens changes by 90 days of treatment (38).

The lens changes appear earlier with oral administration, and also bear a relation to the dosage employed; the higher the dose the more rapid their appearance.

The eye changes are slowly reversible but with a definite species difference, the dog being the slowest to exhibit improvement.

No effects were seen following direct application of aqueous solutions varying from 10% to full strength into the eyes of albino rabbits for a total dosage of DMSO between 0.1 and 0.2 g/kg body weight per day for six

months. Rabbits which received daily doses as high as 10 g/kg orally or topically showed lines of discontinuity in their lenses. No cataract was seen after ten weeks of such daily treatment, although discontinuous lens lines could be detected in about two weeks by slit lamp examination. Chemical studies on these lenses revealed reduction in the usual concentrations of urea, glutathione, uric and amino acids (19).

INDICATIONS

Canine and Equine

DOMOSO (dimethyl sulfoxide) Gel is recommended as a topical application to reduce acute swelling due to trauma.

ADMINISTRATION AND DOSAGE

DOMOSO Gel is to be administered topically to the skin over the affected area.

Dogs - Liberal application should be administered three to four times daily. Total daily dosage should not exceed 20 g. Total duration of therapy should not exceed 14 days.

Horses - Liberal application should be administered two to three times daily. Total daily dosage should not exceed 100 g. Total duration of therapy should not exceed 30 days.

SIDE EFFECTS

In general, adverse reactions are local, and while they may prove to be annoying to some patients, they are usually not of a serious nature. Upon topical application, an occasionally animal may develop transient erythema, associated with local “burning” or “smarting”. Even when erythema or vesiculation occurs, they are self-limiting reversible states, and not necessarily an indication to discontinue medication. Dryness of the skin and an oyster-like breath odor have been reported. These effects are temporary and are not considered to be of serious consequence. Changes in the refractive index of the lens of the eye and nuclear cataracts have been observed in animals, with the use of this drug. This appears to be related to dosage and duration of therapy.

PRECAUTION AND CONTRAINDICATIONS

Contact between DOMOSO Gel and the skin should be avoided. Rubber gloves should be worn while applying this drug. Forceps and swabs may be used to facilitate application. If absorbed through the skin, DOMOSO Gel will cause odorous breath and unpleasant mouth taste. Mild sedation or drowsiness, sensations of warmth, burning, irritation, itching and mild erythematous localized or generalized dermatitis have been reported in some persons following exposure to DOMOSO Gel. Treatment of such side effects is symptomatic. Consult a physician immediately if adverse effects appear.

DOMOSO Gel may mask certain disease signs such as seen in fractures, etc.; this does not obviate the need for specific therapy in such conditions.

Since DOMOSO Gel effectively alters the biologic membrane, it will in some cases facilitate the systemic absorption of other topically applied drugs and may have a potentiating effect on drugs administered systemically.

DOMOSO Gel should be judiciously used when administered in conjunction with other pharmaceutical preparations, especially those affecting the cardiovascular and central nervous systems.

DOMOSO Gel may enhance the absorption of other materials into the skin. The veterinarian should make certain that other medications are not present prior to its application.

Keep DOMOSO Gel out of the reach of children.

DOMOSO Gel is recommended for topical application only. **DO NOT ADMINISTER BY ANY OTHER ROUTE.**

DOMOSO Gel should not be used under occlusive dressings.

DOMOSO Gel is contraindicated in horses and dogs intended for breeding purposes.

DOMOSO Gel is a potent solvent and may have a deleterious effect on fabrics, plastics and other materials. Care should be taken to prevent physical contact with DOMOSO Gel.

DOMOSO Gel should not be administered to horses that are to be slaughtered for food.

CAUTION: HYGROSCOPIC. CLOSE CAP TIGHTLY AFTER USE. AVOID FREEZING. DUE TO THE RAPID PENETRATION ABILITY OF DOMOSO GEL, RUBBER GLOVES SHOULD BE WORN WHEN APPLYING THIS DRUG.

HOW SUPPLIED

DOMOSO (dimethyl sulfoxide) Gel is supplied in 2.1 Oz (60 g) and 4.2 Oz (120 g) collapsible tubes.

NDC 0856-0046-50 - 2.1 Oz (60 g) - tube

NDC 0856-0046-51 - 4.2 Oz (120 g) - tube

Store at controlled room temperature 15° to 30°C (59° to 86°F).

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Fort Dodge Animal Health, Fort Dodge, Iowa 50501 USA

00606

Revised March 2006

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NAC No.: 10030403