Merck Animal Health
One Merck Dr.
Whitehouse Station, NJ 08889

MATERIAL SAFETY DATA SHEET

Merck Animal Health urges each user or recipient of this MSDS to read the entire data sheet to become aware of the hazards associated with this material.

SECTION 1. IDENTIFICATION OF SUBSTANCE AND CONTACT INFORMATION

MSDS NAME: **POSATEX**

SYNONYM(S): ORBIMAX Otic Suspension
POSATEX Otic Suspension
POSATEX Ear Drops Suspension

MSDS NUMBER: SP000139

EMERGENCY NUMBER(S): (908) 423-6000 (24/7/365) English Only

Transportation Emergencies - CHEMTREC:
(800) 424-9300 (Inside Continental USA)
(703) 527-3887 (Outside Continental USA)

Rocky Mountain Poison Center (For Human Exposure):
(303) 595-4869

Animal Health Technical Services:
For Animal Adverse Events: Small Animals and Horses: (800) 224-5318
For Animal Adverse Events: Livestock: (800) 211-3573
For Animal Adverse Events: Poultry: (800) 219-9286

INFORMATION: Animal Health Technical Services:
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MERCK MSDS HELPLINE: (800) 770-8878 (US and Canada)
(908) 473-3371 (Worldwide)
Monday to Friday, 9am to 5pm (US Eastern Time)

SECTION 2. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

Oily Suspension
White to off-white
Odorless
May cause allergic reactions in susceptible individuals.
May be an aspiration hazard if ingested (mineral oil).
May cause developmental effects.
May cause effects to:
fetus
gastrointestinal tract
central nervous system
liver
blood

POTENTIAL HEALTH EFFECTS:

The following summary is based upon available information about the individual ingredients of the mixture, or of the expected properties of the mixture.

Orbifloxacin is a broad-spectrum antibacterial agent from the class of fluoroquinolone carboxylic acid derivatives. The effects of orbifloxacin in animals are characteristic of fluoroquinolone antimicrobial agents where the target organs are the cartilage and gastrointestinal tract. In immature animals, quinolones and fluoroquinolones are known to cause lesions in the cartilage of weight bearing joints and other signs of diseases affecting the joints. In humans, this class of compounds may cause central nervous system disturbances such as dizziness, insomnia and convulsions, gastrointestinal disturbances, rashes, including photosensitive eruptions, elevated liver enzymes, hepatitis, blood in urine, and anaphylactic reactions.

Mometasone furoate (MF) is a very potent intranasal steroid. MF, when given as a nasal suspension or when applied as an ointment (0.1% MF) to intact skin for eight hours, without occlusion, is <1% bioavailable. Several factors including degree of occlusion, inflammation, and/or integrity of skin will increase the percutaneous absorption of topical corticosteroids. Due to its lack of bioavailability, the systemic toxicity of MF is significantly lower than that of traditional steroids and is not observed at therapeutic doses.

MF appears to have little or no effect on HPA axis function. Studies using higher than therapeutic inhaled doses up to 4 mg MF/day and oral doses up to 8 mg MF/day have not demonstrated suppression of the HPA axis. Long-term treatment with lower, recommended therapeutic doses has also been reported not to affect HPA axis function as measured by cortisol levels in plasma and urine. This observation is believed to be related to the low systemic bioavailability of MF.

Reported occupational effects from mometasone furoate include allergic skin reactions such as inflammation and rash.

Corticosteroids are teratogenic in laboratory animals and may be considered teratogenic in non-human primates as well. Widespread clinical use of corticosteroids has resulted in very few reports of teratogenic activity in humans. There is no evidence of impaired fertility in humans treated with corticosteroids although hypo-adrenalism may occur in infants born to mothers receiving corticosteroids during pregnancy.

Posaconazole is a broad-spectrum triazole antifungal compound developed for the treatment and/or prophylaxis of a wide variety of superficial and invasive fungal infections. The most common serious adverse effects with posaconazole in human clinical trials were a low incidence of cardiac arrhythmias, decreased neutrophils (white blood cells), nausea or vomiting, abnormal liver function tests, anemia, headache, dizziness, fatigue, fever, abdominal pain, back pain, flatulence, insomnia, dry mouth, rashes, anorexia, and diarrhea. At therapeutic doses, posaconazole has been shown to bioaccumulate with repeated daily dosing which may increase the incidence and severity of adverse effects. Antifungal triazoles may cause adverse effects in the adrenal glands and reproductive organs.

Repeated administration of posaconazole to laboratory animals for months or years produces clear evidence of phospholipidosis (disorder of phospholipid metabolism) in a wide variety of organ systems. This effect is species-specific and is shared by other antifungal triazoles already extensively used in clinical settings without adverse effects in humans.

POSATEX Otic Suspension has been shown to alter HPA axis function in dogs with exaggerated/prolonged dosing.

Ingestion of mineral oil may cause laxative effect, nausea, dehydration or lipid pneumonia. Long-term dermal exposure to mineral oil may cause dermatitis and oil acne.

LISTED CARCINOGENS

INGREDIENT	CAS NUMBER	OSHA	IARC	NTP	ACGIH
Mineral Oil	8012-95-1				A2

No carcinogens or potential carcinogens listed by OSHA, IARC, NTP or ACGIH are present in concentrations >0.1% in this mixture.

SECTION 3. COMPOSITION AND INFORMATION ON INGREDIENTS

CHEMICAL FAMILY: Antibacterial-Antifungal-Anti-inflammatory

PRODUCT USE: Veterinary product

CHEMICAL FORMULA: Mixture.

The formulation for this product is proprietary information. Only hazardous ingredients in concentrations of 1% or greater and/or carcinogenic ingredients in concentrations of 0.1% or greater are listed in the Chemical Composition table. Active ingredients in any concentration are listed. For additional information about carcinogenic ingredients see Section 2.

CHEMICAL COMPOSITION

INGREDIENT	CAS NUMBER	PERCENT
Orbifloxacin	113617-63-3	1
Posaconazole	171228-49-2	0.1
Mineral Oil	8012-95-1	60-70
Ethene Homopolymer (Polyethylene)	9002-88-4	30-40
Mometasone Furoate	83919-23-7	0.1

ADDITIONAL INFORMATION: This MSDS is written to provide health and safety information for individuals who will be handling the final product formulation during research, manufacturing, and distribution. For health and safety information for individual ingredients used during manufacturing, refer to the appropriate MSDS for each ingredient. Refer to the package insert or product label for handling guidance for the consumer.

SECTION 4. FIRST AID MEASURES

INHALATION: Remove to fresh air. If any trouble breathing, get immediate medical attention. Administer artificial respiration if breathing has ceased. If irritation or symptoms occur or persist, consult a physician.

SKIN CONTACT: In case of skin contact, while wearing protective gloves, carefully remove any contaminated clothing, including shoes, and wash skin thoroughly with soap and water. If irritation or symptoms occur or persist, consult a physician.

EYE CONTACT: In case of eye contact, immediately rinse eyes thoroughly with plenty of water. If wearing contact lenses, remove only after initial rinse, and continue rinsing eyes for at least 15 minutes. If irritation occurs or persists, consult a physician.

INGESTION: DO NOT induce vomiting or give any liquid to drink. IMMEDIATELY consult a physician for treatment advice.

NOTE TO PHYSICIAN: POSATEX Otic Suspension is indicated for the treatment of canine otitis externa. It exerts antibacterial, and antifungal activity. Treat symptomatically.

SECTION 5. FIRE FIGHTING MEASURES

FLAMMABILITY DATA:

Flash Point: Not determined (liquids) or not applicable (solids).

SPECIAL FIRE FIGHTING PROCEDURES:
Wear full protective clothing and self-contained breathing apparatus (SCBA).

SUITABLE EXTINGUISHING MEDIA:
Carbon dioxide (CO2), extinguishing powder or water spray.

See Section 9 for Physical and Chemical Properties.

SECTION 6. ACCIDENTAL RELEASE MEASURES

PERSONAL PRECAUTIONS:
Wear appropriate personal protective equipment as specified in Section 8. Keep personnel away from the clean-up area.

SPILL RESPONSE / CLEANUP:
All spills should be handled according to site requirements and based on precautions cited in the MSDS. In the case of liquids, use proper absorbent materials. For laboratories and small-scale operations, incidental spills within a hood or enclosure should be cleaned by using a HEPA filtered vacuum or wet cleaning methods as appropriate. For large dry or liquid spills or those spills outside enclosure or hood, appropriate emergency response personnel should be notified. In manufacturing and large-scale operations, HEPA vacuuming prior to wet mopping or cleaning is required.

See Sections 9 and 10 for additional physical, chemical, and hazard information.

SECTION 7. HANDLING AND STORAGE

HANDLING:
Keep containers adequately sealed during material transfer, transport, or when not in use. Wash face, hands, and any exposed skin after handling. Do not eat, drink, or smoke when using this substance or mixture.

Appropriate handling of this material is dependent on many factors, including physical form, duration and frequency of process or task, and effectiveness of engineering controls. Site-specific risk assessments should be conducted to determine the feasibility and the appropriateness of all exposure control measures. See Section 8 (Exposure Controls) for additional guidance.

STORAGE:
Store in a cool, dry, well ventilated area. Store at room temperature (ambient conditions).

SPECIAL PRECAUTIONS:
Keep out of the reach of children.

See Section 8 for exposure controls and additional safe handling information.

SECTION 8. EXPOSURE CONTROLS AND PERSONAL PROTECTION

OCCUPATIONAL EXPOSURE GUIDELINE (OEG):
An Occupational Exposure Guideline of 8 mcg/m^3 (8-hr TWA) has been established for mometasone (base).

An Occupational Exposure Guideline of 60 mcg/m^3 (8-hr TWA) has been established for posaconazole.

EXPOSURE CONTROLS
The health hazard risks of handling this material are dependent on many factors, including physical form, duration and frequency of process or task, and effectiveness of engineering controls. Site-specific risk assessments should be conducted to determine the feasibility and the appropriateness of all exposure control measures. Exposure controls for normal operating or routine procedures follow a tiered strategy. Engineering controls are the preferred means of long-term or permanent exposure control. If engineering controls are not feasible, appropriate use of personal protective equipment (PPE) may be considered as alternative control measures. Exposure controls for non-routine operations must be evaluated and addressed as part of the site-specific risk assessment.

RECOMMENDED PERSONAL PROTECTIVE EQUIPMENT (PPE):

Respiratory Protection:	Respiratory protective equipment (RPE) may be required for certain laboratory and large-scale manufacturing tasks if potential airborne breathing zone concentrations of substances exceed the relevant exposure limit(s). Workplace risk assessment should be completed before specifying and implementing RPE usage. Potential exposure points and pathways, task duration and frequency, potential employee contact with the substance, and the ability of the substance to be rendered airborne during specific tasks should be evaluated. Initial and ongoing strategies of quantitative exposure measurement should be obtained as required by the workplace risk assessment. All RPE must conform to local and regional specifications for efficacy and performance. Consult your site or corporate health and safety professional for additional guidance.
Skin Protection:	Gloves that provide an appropriate barrier to the skin are recommended if there is potential for contact with this material. Consult your site safety staff for guidance.
Eye Protection:	Safety glasses with side shields. Use of goggles or full face protection may be required based on hazard, potential for contact, or level of exposure. Consult your site safety staff for guidance.
Body Protection:	In small-scale or laboratory operations, lab coats or equivalent protection is required. Disposable Tyvek or other dust impermeable suit should be considered based on procedure or level of exposure. Use of additional PPE such as shoe coverings, gauntlets, hood, or head covering may be necessary. Consult your site safety staff for guidance. In large-scale or manufacturing operations, disposable Tyvek or other dust impermeable suit is recommended and based on level of exposure. Use of additional PPE such as shoe coverings, gauntlets, hood, or head covering may be necessary. Consult your site safety staff for guidance.

EXPOSURE LIMIT VALUES

INGREDIENT	CAS NUMBER	ACGIH TLV (TWA)	OSHA PEL (TWA)
Mineral Oil	8012-95-1	5 mg/m^3	5 mg/m^3

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

FORM: Oily Suspension
COLOR: White to off-white
ODOR: Odorless
VAPOR DENSITY: 0.8-0.9 g/mL
SOLUBILITY:
Water: Not determined

See Section 5 for flammability/explosivity information.

SECTION 10. STABILITY AND REACTIVITY

STABILITY/ REACTIVITY:
Stable under normal conditions.

INCOMPATIBLE MATERIALS / CONDITIONS TO AVOID:
None known.

HAZARDOUS DECOMPOSITION PRODUCTS / REACTIONS:
No dangerous decomposition is expected if used according to manufacturer's specifications.

SECTION 11. TOXICOLOGICAL INFORMATION

The information presented below is for this material unless otherwise indicated.

ACUTE TOXICITY DATA

INHALATION:
Mometasone furoate did not cause mortality but did result in rales, ano-genital staining, emaciation and body weight losses in rats at 0.68 mg/l (maximum attainable concentration).

Ethene homopolymer: Practically not toxic.

SKIN:
ORBIMAX Otic Suspension: Dermal LD50: > 2000 mg/kg (rat)

There were no deaths and no signs of systemic toxicity noted in an acute dermal toxicity study in rats.

ORBIMAX Otic Suspension: Skin Irritation: Not irritating (rabbit)
Very slight erythema was noted in animals (rabbits) 1 hour after application. No edema was noted in animals 24 hours after application. The primary irritation index (PII) was 0.2 (0-8 scale).

EYE:
ORBIMAX Otic Suspension: Eye Irritation: Practically not irritating (rabbit)
Caused conjunctival redness, chemosis and/or discharge in all animals 1 and 24 hour postinstillation, which was resolved by 72 hours postinstillation.

ORAL:
ORBIMAX Otic Suspension: Oral LD50: > 2000 mg/kg (rat)
There were no deaths and no signs of systemic toxicity noted in an acute oral toxicity study in rats.

DERMAL AND RESPIRATORY SENSITIZATION:
ORBIMAX Otic Suspension: Skin Sensitization: Not sensitizing (guinea pig)

REPEAT DOSE TOXICITY DATA

SUBCHRONIC / CHRONIC TOXICITY:
Orbifloxacin was studied in rats, dogs, and cats at doses ranging from 7.5 to 360 mg/kg/day in subchronic oral studies ranging from 10 to 90 days. In rats, folicular hyperplasia was observed in the spleen of rats treated with 80 mg/kg/day. Dose-dependent effects including histopathological renal changes, vacuolation of hepatocytes, renal lymphoid infiltrates, testicular degeneration, and nephritis were observed at doses of 250 mg/kg/day or greater. Effects observed in dogs were similar to those identified with fluoroquinolone antimicrobial agents (e.g. articular cartilage and joint changes). Other organs affected included the testes, kidney, liver spleen, bone marrow, and heart. At higher dose levels, 250 mg/kg/day and greater, mortality was observed in dogs preceded by ataxia and convulsions. Decreased body weight and food consumption, emesis, and transient diarrhea were observed in dogs and cats secondary to the antimicrobial effects on intestinal flora. The no observed effect levels (NOELs) were 20 mg/kg/day (rat), 15 mg/kg/day (dog), and 7.5 mg/kg/day (cat).

Several repeat dose studies have been performed with mometasone furoate (MF) using rodents and dogs. The systemic effects observed after treatment with MF are fairly consistent across species and exposure routes.

One-month oral toxicity studies in rats and dogs showed changes in the thymus, mesenteric lymph nodes, liver, adrenals, and skin with a reported NOEL of 5 mcg/kg in rats and LOEL of 500 mcg/kg in dogs.

Short- and long-term inhalation studies in rats, mice and dogs were performed using doses of MF ranging from 0.02 mcg/L to 16 mcg/L. Common clinical signs observed across species included changes in body weights, adrenal glands, lungs, thymus, lymph nodes, spleen, trachea, bone marrow, kidney, and liver.

In one month rat diet studies, posaconazole caused decreases in mean body weight and food consumption at 45 mg/kg/day in both sexes. Serum chemistry and histopathological changes were consistent with those seen in other animal species. Rats in mid-and high-dose groups also had evidence of accumulation of vacuolated macrophages in skin. Posaconazole altered calcium homeostasis in rats.

In another study, six-week old male and female rats were administered posaconazole at doses of 5, 15 and 45 mg/kg/day for six months. Toxicity observed was similar to that of other studies with posaconazole. High-dose recovery animals showed persistent lesions in lungs, adrenal glands and ovaries after eight weeks postexposure. Generally, lesions that were observed in these organs were more severe or in greater incidence in treated females. Following recovery, histopathologic changes were reduced in severity and/or incidence demonstrating reversibility. [LOEL: 5 mg/kg/day].

An intravenous formulation of posaconazole (phospholipid-coated particlulate suspension) has also been evaluated in one-month studies in rats and monkeys. The toxicity findings in these studies were similar to those seen after oral dosing. In addition, Kupffer cell hypertrophy, pulmonary thrombi or thrombo-emboli were also seen following intravenous injecton. One-hour daily infusion of 40 mg/kg in monkeys caused mild to moderate increases in arterial pressure that persisted up to 5 days after dosing.

Repeated administration of posaconazole in a number of animal species for months or years produced clear evidence of phospholipidosis, findings related to blocked steroid synthesis, disseminated intravascular coagulation, QT interval prolongation, myocarditis, bone loss with fractures, and tumor development in the adrenal gland and liver.

Cynomolgus monkeys were administered single daily oral doses of posaconazole at 15, 45, 90 or 180 mg/kg for one month. Monkeys receiving 180 mg/kg/day showed hematologic evidence of regenerative anemia with other serum chemistry changes. Male monkeys given the high dose of posaconazole had increased liver, heart and adrenal weights. In treated monkeys, histopathologic findings consistent with phospholipidosis were observed in the lungs, lymph nodes, bone marrow, spleen and liver [LOEL: 15 mg/kg/day]. In a 12-month study in cynomolgus monkeys given posaconazole by oral gavage at 180 mg/kg/day, clinical pathological findings included decreased red blood cell counts, decreased hemoglobin and hematocrit, increased lymphocyte counts, decreased cholesterol, decreased alkaline phosphatase and lower serum calcium in males. Additionally, treated females showed increased fibrinogen values. No mortality was observed. After a 6 or 12 month study in monkeys, posaconazole produced mild histopathological effects including minimal accumulation of macrophages within the small intestine and mild vacuolation of macrophages in the spleen or gut-associated lymphoid tissue (GALT). Most treatment-related histopathological changes were reversible and absent after the three-month recovery period.

Dogs were administered posaconazole by oral gavage at doses of 0, 3, 10 or 30 mg/kg/day for as long as 56 weeks. In a 6-month study, dose-dependent mortality with disseminated intravascular disorder was observed with both sexes. In addition to the vascular difficulties produced at mid and high doses, dogs administered 30 mg/kg/day showed neuropathic change in the brain, spinal cord and small intestine. The adrenal glands of high-dose dogs were also affected and changes in lungs, liver and lymphoid tissues were found in all doses tested. Microscopic evidence of phospholipidosis was reported. Findings in the one-year toxicity study in dogs were similar to those reported in the 6-month study. Other posaconazole-related changes reported in the 56-week study included increased urine calcium content and volume (decreased osmolarity), sternal bone marrow hypercellularity, testicular atrophy, and sloughing of cells in the epididymis and tubular basophilia in the renal cortex. The same low effect level was reported in both studies [LOEL: 3 mg /kg/day]. Female rats received mineral oil in the diet at dosages up to 20,000 ppm for 90 days. Effects observed included increased liver, kidney, and spleen weights, and enlargement of the lymph nodes together with granulomatous lipoid granules.

Animals received mineral oil in the diet at high concentrations. Effects observed included increased liver, kidney, and spleen weights and enlargement of the lymph nodes together with granulomatous lipoid granules.

REPRODUCTIVE / DEVELOPMENTAL TOXICITY:
In a dietary two-generation study in rats with orbifloxacin, no effects on reproductive capabilities, and neonatal viability, growth and development were seen in animals treated with 20 to 50 mg/kg/day. Parental toxicity was indicated in the 150 mg/kg/day group by decreased body weights and/or body weight gains. Prenatal and/or neonatal toxic effects included decreased pup vialbility and litter size, decreased pup weight gain, and increased incidence of pups which were pale, cool to touch and edematous were observed at 150 mg/kg/day. (NOAEL: 50 mg/kg/day)

In developmental toxicity studies, rats and rabbits were treated with orbifloxacin at dosages ranging from 20 to 1000 mg/kg/day. In rabbits, maternal toxicity (decreased body weight and/or body weight gains) was observed at all dose levels (20 to 120 mg/kg/day). Developmental toxicity was apparent at a dose level of 120 mg/kg/day by an increased incidence of structural malformations; however, because it was in the presence of maternal toxicity, orbifloxacin did not result in selective effects on the development of the embryo/fetus. There was no evidence of teratogenicity in rats.

Corticosteroids are known teratogens in rodent species with some teratogenic effects having been observed in non-human primates. They are generally teratogenic in laboratory animals when administered systemically at low dosages.

Developmental toxicity studies were conducted with mometasone furoate in rats, rabbits, and mice using subcutaneous, topical dermal, and oral administration. Developmental or teratogenic effects were observed in all animals (rats, mice, and rabbits) treated with dosages of mometasone furoate between 15-2800 mcg/kg.

Mometasone furoate (MF) caused cleft palate in mice given subcutaneous doses of greater than or equal to 60 mcg/kg. Offspring survival was reduced when mice were treated with 180 mcg/kg (NOEL 20 mcg/kg). No effect on fertility in rats was seen following subcutanteous administration of doses up to 15 mcg MF/kg; however, prolonged gestation, prolonged and difficult labor, reduced offspring survival and reduced maternal body weight gain were observed at 15 mcg MF/kg. Similar effects were seen in rabbits and rats following topical dermal doses of greater than or equal to 150 mcg MF/kg including: reductions in maternal body weight gain, cleft lip/palate, protruding bowel, brain and umbilical hernias and effects on fetal growth (lower fetal body weights and/or delayed ossification).

Oral doses of 700 mcg MF/kg in rabbits caused increased incidences of resorptions, cleft palate and head malformations. Following oral doses of 2800 mcg MF/kg, rabbits failed to become pregnant (resorptions).

In reproductive and developmental studies, posaconazole increases gestation duration, causes fetotoxicity (reduced number of live pups and decreased mean pup weights), and causes increases in skeletal variations and malformations.

Male rats were administered posaconazole by oral gavage at doses of 0, 45, 90 or 180 mg/kg for 63 days prior to mating with untreated females. No signs of male reproductive toxicity were observed at any of the doses tested based on precoital time, male mating index and male fertility index [NOEL for male fertility: > 180 mg/kg].

Female rats were administered posaconazole by oral gavage at doses of 0, 5, 15 or 45 mg/kg/day for 14 days prior to mating and throughout the cohabitation period until day 7 after mating. No signs of female reproductive toxicity or changes in the rodent estrous cycle were observed at any of the doses tested [NOEL for female fertility: > 45 mg/kg/day].

Pregnant rats were administered posaconazole by oral gavage at doses of 0, 3, 9 or 27 mg/kg/day on days 6 through 15 of gestation. Except for food consumption in the high-dose group, no mortality, clinical signs of toxicity, or body weight changes were noted for posaconazole-treated dams. A low incidence of significant malformations, including missing ribs and major cranial malformations, were observed in 2/32 fetuses born to posaconazole-treated dams at 27 mg/kg/day. The total fetal incidence of skeletal variations was also slightly increased at this dose level [maternal and developmental NOEL: 9 mg/kg/day].

In a two-generation reproductive study in rats, posaconazole was administered by oral gavage to dams (F0 generation) at doses of 0, 6, 18 or 36 mg/kg/day from gestation Day 7 through lactation Day 20. Oral administration of posaconazole at 18 or 36 mg/kg/day increased the duration of gestation compared to concurrent controls. Among F0 females, there were five deaths due to posaconazole-induced dystocia with the majority in the high dose group. Total litter loss was observed in two F0 females at 18 and 36 mg posaconazole/kg/day. At necropsy, high-dose F0 females had reddened and/or enlarged adrenal glands. F1 generation pups had reduced live-litter size and pup survival in 18 and 36 mg/kg/day dose groups. At 36 mg/kg/day, F1 generation pups had reduced body weights pre-weaning but normal behavioral development; however, at maturity, F1 females had normal body weights and reproductive performance. F2 pups were unaffected by F0 posaconazole administration at all dose levels. [NOEL for maternal (F0), reproductive (F0) and neonatal (F1) toxicity: 6 mg/kg/day].

Pregnant New Zealand white rabbits were administered posaconazole by oral gavage at doses of 0, 20, 40 or 80 mg/kg/day on days 7 through 19 of gestation. High-dose dams showed a slight decrease in weight gain and evidence of blood in the litter pan. At 80 mg/kg/day posaconazole produced pregnancy failure in most animals and fetuses that were produced had lower fetal body weights. Mid-dose dams also showed increased resorptions compared to controls. There were no posaconazole-related malformations in any dose group but the incidence of skeletal variations was increased at 40 and 80 mg/kg/day [maternal NOEL: 40 mg/kg/day, developmental NOEL: 20 mg/kg/day].

MUTAGENICITY / GENOTOXICITY:
Orbifloxacin was positive in a mouse lymphoma assay (high concentrations without activation) and in an in vitro assay in human peripheral blood lymphocytes (concentrations exceeding the solubility in the assay medium). Orbifloxacin was negative in a hepatocyte DNA repair assay in rats and in a mouse micronucleus assay. There was both negative and positive findings in a bacterial mutagenicity assay (Ames).

Mometasone furoate was negative in the Ames bacterial mutagenicity assay, mouse-lymphoma assay, rat bone marrow clastogenicity assay, Chinese hamster lung chromosome aberration assay, and male germ cell clastogenicity assay. At cytotoxic doses, mometasone furoate produced an increase in chromosome aberrations in vitro but not in the presence of microsomal activation (rat liver S9 fraction).

Posaconazole was negative in the Salmonella/mammalian microsome and Escherichia/mammalian microsome reverse mutation assays and the hypoxanthine-guanine phosphoribosyl transferase (HGPRT)/Chinese hamster ovary cell (CHO) assay. In the mouse micronucleus assay, bone marrow toxicity was observed in male and female mice indicating that posaconazole can reach and affect the bone marrow; however, increases in micronucleus frequency was not observed in test animals at any dose administered.

CARCINOGENICITY:
Inhalation studies ranging from 19 months to 2 years with mometasone furoate in mice and rats did not produce statistically significant increases in tumor formation at doses of 67 and 160 mcg MF/day respectively.

Posaconazole caused an increase in adrenal gland tumors in rats and an increase in hepatocellular adenomas in mice, after two-year exposures [NOEL for adrenal tumors in male rats: 5 mg/kg/day and in female rats: 10 mg/kg/day; NOEL for liver tumors in mice: 30 mg/kg/day].

The 2-year toxicity and carcinogenicity of posaconazole has been evaluated in rats and mice. Many of the toxicity findings previously described in six-month and one-year studies in rats and dogs were also found in rats fed posaconazole in diet for 2 years. Many of these findings occurred with greater severity and/or incidence with lifetime administration. In rats phospholipidosis of the lungs, thinning of bones and adrenal gland tumors (benign and malignant) were the main toxic endpoints.

There was no evidence of carcinogenicity in animals exposed to mineral oil mist at 100 mg/m^3 or higher for as long as two years.

SECTION 12. ECOLOGICAL INFORMATION

There are no data for the final product or its formulation(s). The information presented below pertains to the following ingredient(s).

ECOTOXICITY DATA

INGREDIENT ECOTOXICITY

Posaconazole: 96-hr EC50 (rainbow trout): >0.95 mg/L
Posaconazole: 96-hr EC50 (algae): >0.119 mg/L (growth rate)
Posaconazole: 48-hr EC50 (daphnid): 0.276 mg/L

ENVIRONMENTAL DATA

PRODUCT / CHEMICAL NAME: Orbifloxacin

Dissociation Constant Results: 5.95 and 9.01

OTHER INGREDIENT ENVIRONMENTAL DATA:

Posaconazole: n-Octanol/Water Partition Coefficient (log Pow): 0.591 mg/L
Posaconazole is not readily biodegradable (1.6% ready biodegradability).

SECTION 13. DISPOSAL CONSIDERATIONS

MATERIAL WASTE:
Disposal must be in accordance with applicable federal, state/provincial, and/or local regulations. Incineration is the preferred method of disposal, when appropriate. Operations that involve the crushing or shredding of waste materials or returned goods must be handled to meet the recommended exposure limit(s).

PACKAGING AND CONTAINERS:
Disposal must be in accordance with applicable federal, state/provincial, and/or local regulations.

SECTION 14. TRANSPORT INFORMATION

This material is not subject to the transportation regulations of DOT, IATA, IMO, and the ADR.

SECTION 15. REGULATORY INFORMATION

TSCA LISTING

INGREDIENT	TSCA
Mineral Oil	X
Ethene Homopolymer (Polyethylene)	X

Substances not included in the table above are TSCA exempt or not regulated under TSCA.

U.S. STATE REGULATIONS

INGREDIENT	California Proposition 65	CARTK	NJRTK	CTRTK	MARTK
Mineral Oil		X	1437		X

INGREDIENT	PARTK	MNRTK	MIRTK	RIRTK
Mineral Oil	X	X		X

Fields in the above tables that do not contain data indicate that those materials have not been listed by local regulations.

X: Listed on applicable state hazardous substance or right-to-know lists.

SECTION 16. OTHER INFORMATION

Although reasonable care has been taken in the preparation of this document, we extend no warranties and make no representations as to the accuracy or completeness of the information contained therein, and assume no responsibility regarding the suitability of this information for the user's intended purposes or for the consequence of its use. Each individual should make a determination as to the suitability of the information for their particular purpose(s).

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MERCK MSDS HELPLINE:	(800) 770-8878 (US and Canada) (908) 473-3371 (Worldwide) Monday to Friday, 9am to 5pm (US Eastern Time)
MSDS CREATION DATE:	24-May-2000
SUPERSEDES DATE:	19-Feb-2010
SIGNIFICANT CHANGES (US SUBFORMAT):	Conversion, Hazard classification, OEG, Supplier Address, [M]SDS Name Change, OEB