Merck & Co., Inc.
One Merck Dr.
Whitehouse Station, NJ 08889

MATERIAL SAFETY DATA SHEET

Merck 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: **Temozolomide Capsules (100 - 250 mg/capsule)**

SYNONYM(S):
Temozolomide Capsules (100 - 250 mg/capsule)
ASTROMIDE Capsules, 100-250 mg/capsule
TEMODAL Capsules, 100 - 250 mg/capsule
TEMODAL Capsulas, 100 - 250 mg/capsula
TEMODAR Capsules, 100 - 250 mg/capsule
TEMOXOL Capsules, 100 - 250 mg/capsule

MSDS NUMBER: SP001314

EMERGENCY NUMBER(S):
(908) 423-6000 (24/7/365) English Only
Emergencies - CHEMTREC:
(800) 424-9300 (Inside Continental USA)
(703) 527-3887 (Outside Continental USA)

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

Powder
White to tan or light pink
Odor unknown
Toxic if swallowed.
Prolonged exposure may cause serious health effects.
May be irritating to skin and eyes.
Mutagen.
May cause cancer.
May cause allergic reactions in susceptible individuals.
Causes birth defects.
Causes impaired fertility.
Causes effects to:
gastrointestinal tract
blood
bone marrow
immune system
male reproductive system
fetus
May cause effects to:
eye
skin
liver
respiratory system
Harmful to aquatic organisms.
May cause long-term adverse effects in the aquatic environment.

POTENTIAL HEALTH EFFECTS:

Only information about the ingredients that are expected to contribute significantly to the potential health hazard profile of the formulation(s) are presented.

Temozolomide is an alkylating chemotherapeutic agent of the imidazotetrazine class. As a class, alkylating antitumor agents cause DNA damage and are associated with a risk of birth defects, mutagenicity, cancer, and cytotoxicity to the blood, lymphatic, gastrointestinal, and reproductive systems.

In clinical use, the most common adverse effects reported for temozolomide in patients are mild to moderate nausea and vomiting, weight loss, alopecia, rash, headache, constipation, and fatigue. Hair loss has been reported with temozolomide use and is common for patients given drugs in this class. Overdoes have been reported. One patient had taken 10,000 mg (total dose in a single cycle, over 5 days) resulting in pancytopenia, pyrexia, multi-organ failure and death. in other cases with prolonged treatment of more than 5 days, up to 64 days, have reported bone marrow suppression, infections, and death.

In laboratory animals, temozolomide is moderately toxic by ingestion, slightly irritating to the skin and eyes, and non-sensitizing. Repeated administration of temozolomide to animals produced toxicity to the immune system and blood (e.g. bone marrow, thymus, spleen, lymphnodes), gastrointestinal tract, thyroid, and male reproductive system. These effects are common with materials in this pharmacological class and may be expected in humans. Temozolomide causes genetic damage and may cause cancer. Temozolomide has also been shown to produce toxicity to the fetus, skeletal variations, and malformations in animals.

Additional adverse reactions during clinical use have been reported, although because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to the drug exposure. Allergic reactions to Temozolomide capsules have been reported, including anaphylaxis, and erythema multiforme which resolved after discontinuation and in some cases recurred upon re-administration. Cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have also been reported. There have been reported cases of hepatotoxicity including elevations of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis. Cases of interstitial pneumonitis/pneumonitis, alveolitis, and pulmonary fibrosis have been reported. Prolonged pancytopenia, which may result in aplastic anemia, has been reported, and in some cases has resulted in a fatal outcome.

Lactose is not expected to produce significant toxicity with workplace exposure. Lactose may cause irritation to the eyes, skin, and mucous membranes from mechanical action. Lactose may cause abdominal pain, bloating and diarrhea if ingested in large amounts or in lactose-intolerant individuals. Lactose may cause allergic reactions in sensitive individuals.

LISTED CARCINOGENS

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

PRODUCT USE: Drug 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.

The information presented in this MSDS is for the powder formulation in the capsule.

CHEMICAL COMPOSITION

INGREDIENT	CAS NUMBER	PERCENT
Temozolomide	85622-93-1	33.3-55.6
Lactose	63-42-3	30-60
Sodium Starch Glycolate	9063-38-1	<10
Stearic Acid	57-11-4	<10
Tartaric Acid	87-69-4	<10

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 unless under the direction of a qualified medical professional or Poison Control Center. IMMEDIATELY consult a physician. Do not attempt to give anything by mouth to a seizing, drowsy or unconscious person. If alert, rinse mouth and drink a glass of water.

NOTE TO PHYSICIAN: This material is a chemotherapeutic alkylating agent.

SECTION 5. FIRE FIGHTING MEASURES

FLAMMABILITY DATA:

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

DUST EXPLOSIVITY DATA:

Deflagration Index (Kst):	234 bar.m/s (Temozolomide Capsules, 33.3%) 247 bar.m/s (Temozolomide, 100%)
Maximum Explosion Pressure (PMAX):	7.7 bar (Temozolomide Capsules, 33.3%) 9.0 bar (Temozolomide, 100%)
Minimum Ignition Energy (MIE):	30-50 mJ (Temozolomide Capsules, 33.3%) < 3 mJ (Temozolomide, 100%)
Minimum Ignition Temperature (MIT):	540-560 deg C (Temozolomide Capsules, 33.3%) 720-740 deg C (Temozolomide, 100%)
Hazard Classification:	Based on dust explosivity testing, this material is considered a weak/moderate explosion hazard.

EXPLOSION HAZARDS:
The information presented below is for the 33% temozolomide formulation. Both the 33% formulation and 100% temozolomide are moderate dust deflagration hazards. However, 100% temozolomide is particularly sensitive to ignition by electrostatic discharges; whereas, the 33% formulation is susceptible to ignition by moderately energetic electrostatic discharges.

Under normal conditions of use, this material does not present a significant fire or explosion hazard. This material has been shown by standard laboratory testing to present a moderate dust deflagration hazard. This hazard may exist where sufficient quantities of finely divided material are (or may become) suspended in air during typical process operations. An assessment of each operation should be conducted and suitable deflagration prevention and protection techniques employed.

This material has been shown to be susceptible to ignition by moderately energetic electrostatic discharges. All conductive plant items and operations personnel handling this material should be suitably grounded.

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:
Avoid generation of dust during clean-up. 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.

ENVIRONMENTAL PRECAUTIONS:
This product is harmful to aquatic organisms. Do not allow product to reach ground water, water course, sewage or drainage systems.

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 double lined plastic in fiberboard or other appropriate containers. Store in a cool, dry, well ventilated area.

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

SECTION 8. EXPOSURE CONTROLS AND PERSONAL PROTECTION

The following guidance applies to the handling of the active ingredient(s) in this formulation. The end-user should perform an appropriate risk assessment when handling other forms or formulations of this active ingredient.

OCCUPATIONAL EXPOSURE BAND (OEB):
OEB 5: <1 mcg/m^3. Materials in an OEB 5 category are considered extreme health hazards. The OEB is a range of airborne concentrations expressed as an 8-hour Time Weighted Average (8-hr. TWA) and is intended to be used with Industrial Hygiene Risk Assessment to assist with industrial hygiene sampling and selection of proper controls for worker protection. Consult your site safety and industrial hygiene staff for guidance on handling and control strategies.

INTERNAL OCCUPATIONAL EXPOSURE LIMIT (8-hr TWA):
0.6 mcg/ m3 for Temozolomide

Wipe Limit:
6 mcg/100 cm2 for Temozolomide

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

See Occupational Exposure Guideline (OEG) listed above.

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

FORM: Powder
COLOR: White to tan or light pink
ODOR: Odor unknown
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:
Heat. Oxidizers. Strong acids and bases.

HAZARDOUS DECOMPOSITION PRODUCTS / REACTIONS:
Carbon oxides (COx). Nitrogen oxides (NOx).

SECTION 11. TOXICOLOGICAL INFORMATION

The information presented below pertains to the following individual ingredients, and not to the mixture(s).

ACUTE TOXICITY DATA

SKIN:
Temozolomide was mildly irritating to the skin of rabbits. Irritation cleared within 24 hours.

EYE:
Temozolomide produced slight eye irritation in rabbits. One hour after test substance instillation, all treated eyes exhibited corneal opacity, conjunctivitis, and iritis. All animals were free of ocular irritation within 24 hours. The maximum mean total score was 16.0.

ORAL:
In dogs temozolomide was highly to moderately toxic, having an oral LD50 of greater than 400 mg/m2 (20 mg/kg). In rats and mice, temozolomide was moderately toxic in single-dose, oral studies. In rats, the LD50 was 1,937 mg/m2 (328 mg/kg). The acute oral LD50 for mice was 891 mg/m2 (297 mg/kg) and 1,072 mg/m2 (357 mg/kg) in males and female, respectively. LD50 values for rats and mice by the intraperitoneal route of exposure were similar to oral exposure values.

Lactose: Oral LD50: > 10g/kg (rat)

DERMAL AND RESPIRATORY SENSITIZATION:
Temozolomide was not sensitizing on the skin of guinea pigs when tested by the closed-patch technique.

REPEAT DOSE TOXICITY DATA

SUBCHRONIC / CHRONIC TOXICITY:
Temozolomide repeated-dose toxicity has been evaluated in dogs and rats. All repeated-dosing studies utilized a 1-month cycle design (five consecutive dosing days and 23 days of non-dosing). Target organs in dogs and rats were consistent with alkylating agents and include bone marrow, thymus, spleen, lymph nodes, gastrointestinal tract, thyroid gland, and testes. Additionally, high doses caused retinal changes in the eyes of both species tested. Thyroid and mammary gland effects were specific to rats.

Single-cycle, three-cycle, and six-cycle oral toxicity studies were conducted in dogs at doses ranging from 25 to 1000 mg/m2 (1.3 to 50 mg/kg). In single-cycle studies at doses above 125 mcg/m2 (6.3 mg/kg), animals experienced severe toxicity within two weeks of study initiation, and all dogs died or were euthanized in poor condition by day 20. Significant toxicity included lymphoid depletion in the thymus and spleen and increases in testicular cellularity and immature sperm. Doses at or below 50 mcg/m2 (2.5 mg/kg) were well-tolerated. In dogs, target organs for cycled temozolomide exposures included hematopoietic and lymphoreticular systems, bone marrow, thymus, spleen, lymph nodes, gastrointestinal tract, and testes. The hematopoietic, lymphoreticular and alimentary systems recovered by day 29. With the exception of emesis, the no effect level (NOEL) in these studies was 50 mg/m2 (2.5 mg/kg).

Temozolomide toxicity was also studied in rats in single-cycle, three-cycle, and six-cycle studies at doses ranging from 25 to 800 mg/m2 (4 to 136 mg/kg). In single- and three-cycle studies, mortality and severe morbidity were observed at doses of 400 mg/m2 (68 mg/kg) or higher. Alopecia was noted during each dosing cycle. Temozolomide was moderately well tolerated at 200 mg/m2 (34 mg/kg). A high incidence of mammary masses was observed in female rats administered 200 mg/m2 (34 mg/kg). Two high-dose male rats had subcutaneous masses (NOEL 50 mg/m2 or 8.5 mg/kg). The lowest NOEL for these studies was 50 mg/m2 (8.5 mg/kg).

In a six-cycle study in rats, mammary gland carcinoma was found in all groups of exposed female rats and in two high-dose males. The occurrence of neoplasia in mesenchymal tissue was also significantly increased in males and females administered 125 mg/m2 (21 mg/kg) temozolomide. Based on these findings, a NOEL was not identified for female rats; the NOEL for temozolomide in male rats was 25 mg/m2 (4 mg/kg).

REPRODUCTIVE / DEVELOPMENTAL TOXICITY:
No direct tests to determine the effect of temozolomide on fertility have been completed. However, repeated-dose toxicity studies in dogs and rats show clear adverse effects to the male reproductive system (increases in testicular cellularity and immature sperm) at doses of 50 mg/m2/day or greater (2.5 mg/kg to 8.5 mg/kg in dogs and rats, respectively).

Developmental toxicity has been evaluated in rabbits and rats and these studies demonstrate adverse effects to the fetus at doses of 50 mg/m2 or greater. A developmental toxicity study with temozolomide was conducted with pregnant rats. All dams treated with temozolomide by oral gavage at doses of 25, 50 and 75 mg/m2/day (4 to 13 mg/kg/day) for gestation days 8-12 survived until the end of the study and no treatment-related toxicity to dams was observed (dam body weight changes were attributed to in utero effects). A slightly higher incidence of resorptions was observed at mid- and high-dose levels. Mean fetal weights were significantly lower at 50 mg/m2 (8.5 mg/kg) and 75 mg/m2 (13 mg/kg) dosages. Fetal malformations, including malformations of the limbs and digits, were observed at the high dose. Soft-tissue and skeletal variations were observed at both 50 and 75 mg/m2. Taken together the findings show that the maternal NOEL was 75 mg/m2 (13 mg/kg), and the developmental NOEL was 25 mg/m2 (4 mg/kg).

MUTAGENICITY / GENOTOXICITY:
Temozolomide tested positive in a bacterial reverse mutation assay (Ames), a chromosome aberration study in cultured human lymphocytes, and a mouse bone marrow micronucleus study.

CARCINOGENICITY:
Two-year oncogenicity studies of temozolomide have not been conducted. However, the results of the six-cycle study in rats can be used to evaluate the carcinogenic potential of temozolomide. In this study mammary tumors developed rapidly and at all dose levels (25, 125 and 200 mg/m2; 4-34 mg/kg). Rat mammary tissue may be more sensitive than human mammary tissue to the tumorogenic effects of temozolomide. No carcinogenic effects were observed in the six-cycle dog study at doses as high as 125 mg/m2 (6 mg/kg).

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

Temozolomide: 96-hr LC50 (rainbow trout): > 100 mg/L; NOEC = 100 mg/L
Temozolomide: 72-hr EC50 - Biomass (algae): 75 mg/L; NOEC = 40 mg/L
Temozolomide: 48-hr EC50 (daphnid): > 100 mg/L; NOEC = 10 mg/L

ENVIRONMENTAL DATA

OTHER INGREDIENT ENVIRONMENTAL DATA:

Temozolomide is not readily biodegradable. Temozolomide did not meet the 10-day window to meet the criteria for ready biodegradability, but did degrade 79% by day 28. Temozolmide did hydrolyze, within 2 hours, into AIC the primary degradation product in the environment and the human body.

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.

SPECIAL ENVIRONMENTAL HANDLING PROCEDURES:
This product contains materials that are harmful to the environment. Do not allow product to reach ground water, water courses, sewage or drainage systems.

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
Lactose	X
Sodium Starch Glycolate	X
Stearic Acid	X
Tartaric Acid	X

U.S. STATE REGULATIONS

Check state requirements for ingredient listing.

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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