

Purdue Pharma L.P.

Material Safety Data Sheet

Ryzolt[®] 100, 200, and 300 mg (tramadol hydrochloride extended release tablets)

Version: 19-Mar-09

1. CHEMICAL PRODUCT/COMPANY IDENTIFICATION

Material Identification: Ryzolt[®] extended-release 100, 200, and 300 mg tablets

Chemical Name: Mixture, not applicable

Active Ingredient: RR,SS-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

Synonyms: (±) *cis*-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

tramadol hydrochloride, tramadol, Contramal Uno, Dolpar, Durotram, Monoalgie, Monotramal, Noax Uno, Ryzolt[®], Tradorec, TramaConti, Tramadex, Tramadol Contramid Once a Day (OAD), Tramadol Labopharm, Tramador, Tridural, Unitrama

Molecular Formula: Mixture

Molecular Weight: Mixture

Active Ingredient: C₁₆H₂₅NO₂·HCl

Active Ingredient: 299.8

CAS Number: Mixture, N/A

Active Ingredient: 22204-88-2

Product Use: Synthetic opioid analgesic.

Company Identification:

Responsible Party

Purdue Pharma L.P.
One Stamford Forum
201 Tresser Boulevard
Stamford, CT 06901-3431
Telephone: (888) 726-7535

EMERGENCY CONTACT

Chemtrec (800) 424- 9300. For all international transportation emergencies, call Chemtrec collect at (703) 527-3887.

2. HAZARDOUS COMPONENTS

<u>Material</u>	<u>CAS Number</u>	<u>%</u>
-----------------	-------------------	----------

Purdue Pharma L.P.

Tramadol hydrochloride (100 mg)	22204-88-2	28.6
Tramadol hydrochloride (200 mg)	22204-88-2	37.0
Tramadol hydrochloride (300 mg)	22204-88-2	41.4

3. Hazards Identification

Emergency Overview

Ryzolt[®] is an extended-release tablet product. It does not pose a hazard under normal workplace handling conditions.

The active ingredient of Ryzolt[®] is tramadol hydrochloride, an orally active opioid analgesic. If Ryzolt[®] tablets are broken or crushed, workplace exposure to tramadol hydrochloride in dust may occur. The following information is provided for those circumstances where uncontrolled exposure to tramadol hydrochloride from Ryzolt[®] may occur due to breakage or crushing of the tablet.

Tramadol hydrochloride

May be fatal if ingested.

Harmful by inhalation.

Harmful by skin absorption.

May cause skin and eye irritation.

May cause skin and/or respiratory sensitization.

Target organs: central nervous system, gastrointestinal tract, cardiovascular system.

Acute overdosage with tramadol is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and, possibly, death.

Potential Health Effects

Tramadol hydrochloride is a synthetic opioid analgesic.

Tramadol hydrochloride may cause eye and skin irritation. Tramadol hydrochloride may be absorbed through the skin.

Repetitive exposure to tramadol hydrochloride may cause skin and/or respiratory allergies.

Acute overdosage with tramadol hydrochloride is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension and, possibly, death.

Repetitive exposure to tramadol hydrochloride during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn.

Purdue Pharma L.P.

Neonatal seizures, neonatal withdrawal syndrome, fetal death, and stillbirth have been reported during post-marketing clinical surveillance of tramadol immediate-release products.

Conditions that may be aggravated by exposure to tramadol include chronic obstructive lung disease, asthma, and hypotension.

Carcinogenicity Information

Tramadol hydrochloride is not listed by IARC, NTP, OSHA, or ACGIH as a carcinogen.

4. First Aid Measures

First Aid

INHALATION

If dusts are inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician (see notes to physician below). If allergic reactions occur (e.g., stuffy, runny or itchy nose, itchy throat, sneezing, watery/itchy eyes, etc.) see a physician.

SKIN CONTACT

Remove contaminated clothing. Flush skin with plenty of water and wash thoroughly with soap and water. If irritation (redness, itching, swelling) develops, seek medical attention. Wash contaminated clothing before reuse.

EYE CONTACT

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. If easy to do, remove contact lenses. See a physician.

INGESTION

If swallowed, immediately give 2 glasses of water and induce vomiting under the direction of medical personnel. Never give anything by mouth to an unconscious person. Call a physician.

Notes to Physicians

Tramadol hydrochloride is an opioid agonist. Naloxone is a specific antidote against respiratory depression from opioid overdose. Naloxone will reverse some (but not all) symptoms of overdose with tramadol but the risk of seizures is also increased with naloxone administration. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to tramadol overdose.

In cases of overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose

Purdue Pharma L.P.

as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

If ingested and the patient is conscious, induction of emesis may be indicated. Gastric lavage may be indicated if the patient is unconscious under the direction of a physician.

5. Fire Fighting Measures

Flammable Properties

Tramadol hydrochloride is not considered flammable. However, concentrated dust from broken or crushed tablets may pose a dust explosion hazard. Eliminate sources of ignition.

Extinguishing Media

Water spray, carbon dioxide, dry chemical powder, or foam as appropriate for the surrounding material.

Fire Fighting Instructions

Evacuate personnel to a safe area. Keep personnel removed and upwind of fire. Wear self-contained breathing apparatus. Wear full protective equipment.

NFPA

H=2; F=1; R=0

6. Accidental Release Measures

Safeguards (Personnel)

NOTE: Review FIRE FIGHTING MEASURES and HANDLING (PERSONNEL) sections before proceeding with clean-up. Use appropriate PERSONAL PROTECTIVE EQUIPMENT during clean-up to minimize exposure to this material. Evacuate personnel from the area.

Initial Containment

Prevent material from entering sewers, waterways, or low areas. Dike area for later disposal.

Spill Clean-up

Tramadol hydrochloride is regulated in the United States in Kentucky and Arkansas as a schedule IV controlled substance. Tramadol hydrochloride is not classified as a controlled substance by the U.S. Drug Enforcement Agency. Wear suitable protective clothing to prevent exposure. Sweep up intact tablets carefully to avoid generation of dust. If available, use HEPA vacuum to collect broken or crushed tablets. In states where tramadol is regulated as a schedule IV controlled substance, refer to applicable agency statutes for disposal and/or reconciliation requirements. Thoroughly wash area with detergent and water. Dispose of all

Purdue Pharma L.P.

solid waste and wash and rinse water in accordance with federal, state, and local regulations.

7. Handling and Storage

Handling (Personnel)

Avoid procedures that will generate dust. Local exhaust is recommended to avoid generation of significant airborne dust levels. Avoid contact with eyes, skin, or clothing. Wash thoroughly after handling. Wash contaminated clothing after use.

Handling (Physical Aspects)

Close container after each use. Do not generate dust.

Storage

Keep containers tightly closed. Protect from light. Store at 25°C (77°F) and control temperature excursions to between 15-30°C (59-86°F).

8. Exposure Controls/Personal Protection

Engineering Controls

Handle material under adequate ventilation. Keep container tightly closed.

Personal Protective Equipment

Wear chemical goggles if exposure to dust is possible. Wear impervious clothing such as gloves, lab coat, shoe covers, apron, or jumpsuit, as appropriate, to prevent skin exposure to broken or crushed tablets, powder, and dust. Wear approved respiratory protection when the possibility exists for respiratory exposure. Consult the site safety professional for additional guidance, as needed.

Exposure Guidelines

Exposure Limits

Tramadol hydrochloride

PEL (OSHA): None established.

TLV (ACGIH): None established.

Occupational Exposure Guideline (Purdue Pharma L.P.): Not established.

Exposure Guideline Comments

May be absorbed through skin; repetitive exposure may cause skin and/or respiratory sensitization.

9. Physical and Chemical Properties

Ryzolt® tablets

Odor: Odorless.

Form: White to off-white, plain, bevelled-edge, round, biconvex tablets.

Purdue Pharma L.P.

Tramadol hydrochloride

Odor:	Odorless.
Form:	Powder.
Color:	White to off-white.
Vapor Pressure:	No information available.
Melting Point:	180-184°C.
Solubility:	Freely soluble in water, ethanol, and methanol. Slightly soluble in isopropanol.
pH:	5.5-7.0 (1% aqueous solution).
pKa:	8.3
Kow	1.35 (pH 7).

10. Stability and Reactivity

Chemical Stability

Stable under normal conditions of use.

Incompatibility with Other Materials

Strong oxidizers, acids, bases.

Oxidizing materials may increase the risk of fire and explosion (e.g., potassium perchlorate, potassium nitrate).

Conditions to Avoid

Strong oxidizers, bases or acids, static charge, sparks, generation of dust, and elevated temperatures.

Decomposition

Will not decompose under conditions of handling.

Polymerization

Material will not polymerize.

11. Toxicological Information

Relevant Data for Tramadol Hydrochloride

Skin/Eyes

Tramadol has not been evaluated in skin and eye irritation studies in animals. It is expected that Tramadol may produce mild skin irritation and eye irritation.

Acute Toxicity

Species	Oral LD ₅₀ Values (mg/kg)	s.c.	i.v.
Mouse*	328-785	197-265	47-68
Rat	151-572	240-293	56

Purdue Pharma L.P.

Rabbit	300-450	–	20-40
Guinea pig	850-897	23-250	–
Dog	100-450	–	>50 < 100

s.c. = subcutaneous; i.v. = intravenous

*Signs of toxicity of tramadol in male mice: sedation at low doses followed by hypermotility, straub tail, slight tremor, exophthalmos, clonic convulsions, cyanosis.

Subchronic Toxicity

Tramadol hydrochloride was orally administered to male and female mice for 3 months at dosages of 0, 30, 60, 125, and 250 mg/kg/day (free base). Mortalities were observed in both male and female mice in the 250 mg/kg/day groups. Clinical signs in the 250 mg/kg/day groups were stained fur, unkempt appearance, hunched posture, increased activity, wobbly gait, tremors, and salivation. No other observations were considered related to tramadol hydrochloride treatment. The no observed adverse effect level in the study was 125 mg/kg/day for the males and 30 mg/kg/day for the females.

Male and female rats were orally administered tramadol hydrochloride at dosage levels of 0, 12.5, 25, 50, and 100 mg/kg/day (free base) for 3 months. Nearly all the female rats at 100 mg/kg/day but no males died. At 100 mg/kg/day, salivation, hunched posture, twitching, tremors, increased activity, and convulsions were observed especially in female rats. Inconsistent, transient decreases in body weights/weight gains or food consumption were also more pronounced in the female rats. Hyperplasia in the urinary bladder epithelium and lymphocytosis in the thymus were observed in male and female rats at 50 and 100 mg/kg/day. The no observed adverse effect level in the study was 25 mg/kg/day.

Tramadol hydrochloride was orally administered to male and female dogs at dosages of 0, 2.5, 6, 15, and 40 mg/kg/day (free base) for three months. There were no mortalities in the study but convulsions, intermittent tremors, slight to moderate salivation, diarrhea, soft stools, and emesis. No other observations were considered related to treatment with tramadol hydrochloride.

Carcinogenicity

A slight, but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study. Mice were dosed orally up to 30 mg/kg (90 mg/m² or 0.5 times the maximum daily human dosage of 185 mg/m²) for approximately two years, although these dosages were not maximally tolerated. This finding is not believed to suggest a carcinogenic risk in humans. Tramadol was not carcinogenic in rats (dosing orally as high as 30 mg/kg – 180 mg/m² equal to the maximum daily human dosage of tramadol).

Mutagenicity/Genotoxicity

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay, (in the absence of metabolic activation), dominant lethal mutation tests in

Purdue Pharma L.P.

mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Positive mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats.

Impairment of Fertility

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (300 mg/m²) in male rats and 75 mg/kg (450 mg/m²) in female rats. These dosages are 1.6- and 2.4-times the maximum daily human dosage of 185 mg/m², respectively.

Developmental/Reproductive Toxicity

At maternally toxic dosages tramadol has been shown to be embryo and fetotoxic in mice, (120 mg/kg or 360 mg/m²), rats (\geq 25 mg/kg or 150 mg/m²) and rabbits (\geq 75 mg/kg or 900 mg/m²), but was not teratogenic at these dose levels. These dosages on a mg/m² basis are 1.9-, 0.8- and 4.9-times the maximum daily human dosage (185 mg/m²) for mouse, rat and rabbit, respectively.

No tramadol-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420 mg/m²), rats (up to 80 mg/kg or 480 mg/m²) or rabbits (up to 300 mg/kg or 3600 mg/m²). The dosages listed for mouse, rat and rabbit are 2.2-, 2.6- and 19.4-times the maximum daily human dosage (185 mg/m²), respectively.

Tramadol was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m² or 1.6-times the maximum daily human Ryzolt[®] dosage) or greater had decreased body weights and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m² or 2.6-times the maximum daily human dosage).

Tramadol has been shown to cross the placenta, and has also been found in breast milk of women following a single IV 100 mg dose of tramadol.

There are no adequate and well-controlled studies in pregnant women. Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported during post-marketing clinical surveillance of tramadol immediate-release products.

12. Ecological Information

Relevant Data for Tramadol

Ecotoxicological Information

Classification: Not easily degradable.

Evaluation Test: Difficult to eliminate from water.

Acute fish toxicity (Golden orfe):

LC (0') 5.0 mg/l/96h

Purdue Pharma L.P.

LC (50')	6.2 mg/l/96h
LC(100')	7.5 mg/l/96h

13. Disposal Considerations

This material is not listed under US RCRA. It is regulated as a Schedule IV drug in Kentucky and Arkansas. Disposal of this material must be in accordance with federal, state/provincial, and local regulations.

14. Transportation Information

This material is non-hazardous under US DOT.

15. Regulatory/Statutory Information

Tramadol is regulated in Kentucky and Arkansas as a schedule IV controlled substance. Tramadol is not classified as a controlled substance by the U.S. Drug Enforcement Agency.

16. Other Information

The information contained in this Material Safety Data Sheet is believed to be accurate and represents the best information available at the time of preparation. However, no warranty, express or implied, with respect to such information, is made. The data in this Material Safety Data Sheet relate only to the specific material designated herein and does not relate to use in combination with any other material. The data in this Material Safety Data Sheet are subject to revision as additional knowledge and experience are gained.

This MSDS was prepared for Purdue Pharma L.P., by the Occupational and Environmental Assessment and the Environment, Health and Safety Sections of Purdue.