

MATERIAL SAFETY DATA SHEET

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
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Product name
APTIVUS® Capsules

DATE ISSUED: June 23, 2005

EMERGENCY TELEPHONE NUMBER

CHEMTREC - 24 hours

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1. SUBSTANCE IDENTIFICATION

CHEMICAL NAME: {R-(R*,R*)}-N-{3-{1-{5,6-Dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl}propyl}phenyl}-5-trifluoromethyl)-2-pyridinesulfonamide

GENERIC NAME: Tipranavir

MOLECULAR FORMULA: C₃₁H₃₃F₃N₂O₅S

TRADEMARK:

MOLECULAR WEIGHT: 602.68

CHEMICAL FAMILY:

CAS NUMBER: 174484-41-4

PRODUCT USE: Non nucleotide inhibitor

SYNONYMS: PNU-140690

2. COMPONENTS PER UNIT DOSE

MATERIAL	WEIGHT mg/capsule	EXPOSURE LIMITS
Active Ingredient:	250.0	TWA: 0.1 mg/m ³ (BIEL)**
Inert Ingredients:		
\Dehydrated alcohol, USP, EP	100.0	TWA: 1000 ppm (*ACGIH TLV 2002)
Propylene Glycol, USP, EP	73.0	
Polyoxyl 35 Castor Oil, NF, EP	455.0	
Mono/Diglycerides of Caprylic/Caproic Acid	75.0	
Tromethamine, USP, EP	15.0	
Purified Water, USP	30.0	
Propyl Gallate, NF/FCC	2.0	

**BIEL is the BI Exposure Control Level. Where lower governmentally imposed occupational exposure limits exist, such limits should take precedence.

3. HAZARD IDENTIFICATION

EMERGENCY OVERVIEW

Combustible liquid filled capsule.

PRIMARY ROUTE(S) OF EXPOSURE: Skin contact, eye contact, ingestion and inhalation.

ADVERSE REACTIONS TO PRODUCT: Adverse events reported during clinical studies were primarily gastrointestinal tract related including diarrhea, nausea, dyspepsia, eructation, vomiting, decreased appetite, cramping, and pain. Fever, fatigue, headache, bronchitis, depression, and rash also occurred

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: The active ingredient (Tipranavir) is metabolized by cytochrome P450 3A and is also an inducer of the enzyme. Drug-drug interactions may take place when the drug is co-administered with drugs that undergo metabolism by this enzyme (phenobarbital, carbamazepine, dexamethasone and a variety of other compounds).

APTIVUS co-administered with 200 mg ritonavir has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity.

CONTRAINDICATIONS: APTIVUS, a sulfa-containing drug, should be used with caution in patients with a known sulfa allergy. Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported in subjects receiving APTIVUS/r.

4. EMERGENCY FIRST AID PROCEDURES

INHALATION: Remove from area to fresh air. Seek medical attention if respiratory irritation develops or if breathing becomes difficult.

INGESTION: Get medical attention to determine whether vomiting or evacuation of stomach is necessary. Do not give anything by mouth to an unconscious or convulsing person.

SKIN CONTACT: Remove contaminated clothing. Wash affected areas with plenty of water and soap for several minutes. Seek medical attention if irritation or rash develops and persists.

INJECTION: In case of accidental injection, wash and thoroughly disinfect, get medical attention.

EYE CONTACT: Flush eyes with large amounts of running water for 15 minutes. Hold eyelids open. Get immediate medical attention.

5. FIRE AND EXPLOSION HAZARD DATA

Flash Point
120 °F

Flammable Limits
Upper
N/D
Lower
N/D

FIRE EXTINGUISHING MEDIA: Water, carbon dioxide, or dry chemical.

SPECIAL FIRE FIGHTING PROCEDURES: NIOSH approved SCBA and full protective gear for firefighters is recommended if product is involved in a fire.

UNUSUAL FIRE AND EXPLOSION HAZARDS: None for the finished product.

HAZARDOUS COMBUSTION PRODUCTS: Carbon monoxide, carbon dioxide, nitrogen oxides, sulfur oxides & hydrogen fluoride.

6. SPILL AND ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN THE EVENT OF A SPILL OF COMPROMISED LIQUID CAPSULES: Wear approved respirator, eye protection, personal protective coverings and gloves. Do not allow product to reach sewer system or any body of water. Absorb liquid with non combustible absorbent. Place spillage in

appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area and wash spill site.

7. PRECAUTIONS FOR SAFE HANDLING AND USE

HANDLING AND STORAGE PRECAUTIONS: Store in tight container. Store away from foodstuffs. This material should be handled and stored as per label and other instructions to ensure product integrity. Keep product refrigerated for drug efficacy requirements.

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED FROM CAPSULES: Remove ignition sources; control the generation of vapors; provide respiratory, skin and eye protection to prevent overexposure. Keep out of drains; prevent entry to surface water, groundwater and soil. Absorb liquid with non combustible absorbent. Place in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area and wash spill site.

OTHER PRECAUTIONS HANDLING BROKEN CAPSULES: Avoid contact with eyes, skin or clothing. Avoid breathing vapor. Use with adequate local ventilation. Wash hands thoroughly after handling. Wear fresh clothing daily.

8. CONTROL MEASURES

ENGINEERING CONTROLS: Not generally required when handling containers or capsules. (See section 2 for exposure limits.)

RESPIRATORY PROTECTION: Not generally required when handling containers or capsules. The need for respiratory protection should be determined by an industrial hygiene survey. (See Section 2 for exposure limits.) NIOSH/MSHA approved respirators for protection should be used if respirators are found to be necessary.

VENTILATION: General ventilation should be adequate. If general ventilation is not sufficient, local exhaust is recommended.

PERSONAL PROTECTIVE EQUIPMENT: Not generally required when handling containers. If containers are compromised or exposure to the active ingredient or mixture is likely wear:

Eye Protection: Safety glasses w/ sideshields or goggles

Hand Protection: Neoprene or nitrile gloves

Protective Clothing: Laboratory coats

Other: Eye wash

WORK/HYGIENIC PRACTICES: Keep away from foodstuffs, beverages and feed. Immediately remove all soiled and contaminated clothing. Wash hands before breaks and at the end of work.

9. PHYSICAL/CHEMICAL CHARACTERISTICS

Appearance: **Liquid Capsule** Odor: **Slight**

Boiling Point: NA

Specific Gravity: NA

Vapor Pressure (mm Hg): Not known

Melting Point: Not known

Vapor Density: Not known

Mol Wgt: 602.68

Water Solubility: Soluble

10. REACTIVITY DATA

PHYSICAL CONDITIONS TO AVOID: Not established

INCOMPATIBILITY WITH OTHER MATERIALS: Not established

HAZARDOUS DECOMPOSITION PRODUCTS: Carbon monoxide, carbon dioxide, nitrogen oxides, sulfur oxides & hydrogen fluoride.

HAZARDOUS POLYMERIZATION: Does not occur.

STABILITY: Stable.

11. TOXICOLOGICAL INFORMATION

FOR ACTIVE INGREDIENT

ACUTE STUDIES:

EYE IRRITATION (RABBIT): Minimally irritating to the unrinsed eye. Practically non-irritating to the rinsed eye. In addition, the compound appeared to cause cumulative irritation after multiple instillations.

SKIN IRRITATION (RABBIT): Nonirritating to intact skin. Mildly irritating to abraded skin.

ORAL TOXICITY (MONKEY): In a 2-week oral toxicity study, male cynomolgus monkeys were administered 20, 80 or 320 mg/kg/day in two equally divided doses. The no observed adverse effect level (NOAEL) was 320 mg/kg/day.

ORAL TOXICITY (DOG): In a four-week toxicity study with a four-week recovery phase with tipranavir disodium, dogs received 0, 30, 75, 160 or 320 mg/kg/day (free base equivalent) in equally divided doses and was well tolerated up to 160 mg/kg/day. The NOAEL was 160 mg/kg/day. The target organs were the gastrointestinal tract and liver.

ORAL TOXICITY (RAT): In an oral toxicity study, 64, 126, 250, 500 and 1000 mg/kg/day administered in two equally divided doses for 14 days was well tolerated. Minimal to mild toxicity was noted in the 500 and 1000 mg/kg/day dose levels based on suppressed body weight gain in males, changes in coagulation indices, increases in liver weight, and hypertrophic cellular changes in the liver and thyroids in both sexes. The liver and thyroids are the target organs of toxicity. The no-observed-adverse effect level (NOAEL) was 250 mg/kg/day. In a four-week toxicity study with a four-week recovery phase with tipranavir disodium, rats received equally divided doses of 0, 40, 125, 400, 1000 (females only) or 1250 (males only) mg/kg/day (free base equivalent). The NOAEL was 40 mg/kg/day. The primary target organ was the liver.

ORAL LD50 (RAT): > 5,000 MG/KG

SUBCHRONIC/CHRONIC STUDIES: In a 26-week oral toxicity study in the rat followed by a 13-week recovery period with tipranavir disodium, the NOAEL was 40 mg/kg/day for males and 20 mg/kg/day for females. The primary target organ was the liver. In a 39-week oral toxicity study in the dog followed by a 9-week recovery period, tipranavir disodium was administered at doses of 0, 20, 75 or 320 mg/kg/day (free base equivalents). The NOAEL was 20 mg/kg/day.

OTHER STUDIES:

GENOTOXICITY: UDS Assay - Negative

Ames Assay - Negative.

In-vivo micronucleus test in mouse bone marrow – Negative.

In-vitro chromosome aberration assay in human peripheral lymphocytes - Negative.

AS52/XPRT Assay, CHO cells: Negative.

TERATOGENICITY: In an embryo-fetal development study in rats there was no evidence of treatment-related embryo-lethality or teratogenicity at any dose. The NOAEL for both maternal and developmental toxicity was 40 mg/kg/day. None of the postweaning functions examined in F1 offspring (including reproductive ability) were compromised at any dose. The NOAEL for both dams and offspring was 40 mg/kg/day.

CARCINOGENICITY: Ingredient(s) are not listed as carcinogenic by IARC, NTP or OSHA.

12. ECOLOGICAL INFORMATION

No information available

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

14. TRANSPORT INFORMATION

Not regulated for transportation by the DOT, IMO, or IATA.

15. REGULATORY INFORMATION

No information available

16. OTHER INFORMATION

ABBREVIATIONS:

BIPI - Boehringer Ingelheim Pharmaceuticals, Inc.

N/A - Not applicable

N/D - Not determined

PREPARATION INFORMATION

Prepared by: Environmental Affairs & Safety

Date Prepared: 6/23/05

Replaces: New

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