

# MATERIAL SAFETY DATA SHEET

Boehringer Ingelheim Pharmaceuticals, Inc.  
900 Ridgebury Rd  
Ridgefield, CT 06877

Product name: Aptivus® Oral Solution

DATE ISSUED: November 17, 2008

EMERGENCY TELEPHONE NUMBER  
(203) 798-5521

## 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

MOLECULAR FORMULA: C<sub>31</sub>H<sub>33</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S

GENERIC NAME: Tipranavir

MOLECULAR WEIGHT: 602.68

CHEMICAL FAMILY:

CAS NUMBER: 174484-41-4

PRODUCT USE: Protease inhibitor

SYNONYMS:

## 2. COMPONENTS PER UNIT DOSE

MATERIAL	Function	Exposure Limits
<b>Active Ingredient</b>		
Tipranavir	Drug Substance	500 µg/M <sup>3</sup>
<b>Excipients</b>		
Ascorbic Acid	Anti-oxidant	N/E
Butter Toffee PHL-135461	Flavor	N/E
Buttermint 24020	Flavor	N/E
Mono/Diglycerides of Caprylic/Capric Acid	Lipid Phase	N/E
Polyethylene Glycol 400	Solvent	10 mg/M <sup>3</sup> as AIHA WEELs
Propylene Glycol	Solvent	10 mg/M <sup>3</sup> as AIHA WEELs
Purified Water	Solvent	N/E
Sucralose	Sweetening Agent	N/E

\*ECL: BIPI Exposure Control Limit. Where lower governmentally imposed limits are in effect, such limits should take precedence. Category 3A default banding control limits 10 - <100ug/m3.

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### 3. HAZARD IDENTIFICATION

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#### EMERGENCY OVERVIEW

- Clear yellow viscous butter mint-butter toffee flavored liquid containing 100 mg tipranavir in each mL.
- The solution is supplied in a unit of use amber glass bottle providing 95 mL of solution with a 5 mL plastic oral dispensing syringe

ROUTES OF ENTRY: Inhalation, ingestion, eye and skin contact.

TARGET ORGANS: Liver

CONTRAINDICATIONS: This product should not be taken by individuals who have a history of moderate to severe (Child-Pugh Class B or C, respectively) hepatic impairment. In addition, this product should not be taken by individuals who are prescribed medications that are dependant on CYP 3A for clearance or are potent CYP 3A inducers, e.g.: Antiarrhythmics; Antimycobacterials; Ergot derivatives; CI Motility Agents; Herbal Products; HMG CoA reductase inhibitors; Neuroleptic; and Sedatives/hypnotics.

ADVERSE REACTIONS TO PRODUCT: diarrhea, nausea, pyrexia, vomiting, fatigue, headache, and abdominal pain.

**WARNING:**

The use of use of APTIVUS®/ritonavir in treatment-naïve patients is not recommended. Genotypic or Phenotypic testing and/or treatment history should guide the use of APTIVUS®/ritonavir. Use caution when prescribing APTIVUS®/ritonavir to patients with elevated transaminases, hepatitis B or C co-infection, or patients with mild hepatic impairment. The drug-drug interaction potential of APTIVUS®/ritonavir when co-administered with other drugs must be considered.

SIGNS AND SYMPTOMS OF EXPOSURE: Hepatic Impairment and Toxicity; Intracranial Hemorrhage; Rash;

ACUTE EXPOSURE: Tiredness; general ill feeling or “flu-like” symptoms; loss of appetite; nausea; yellowing of the skin or whites of the eye; dark colored urine; pale stools; pain, ache, or sensitivity beneath the ribs on the right side of the body.

CHRONIC EXPOSURE: Not known

MEDICAL CONDITIONS POTENTIALLY AGGRAVATED BY EXPOSURE: Hepatic Impairment and Toxicity; Intracranial Hemorrhage; preexisting hypersensitivity to any of the products' components; Sulfonamide allergies; drug-drug interactions; diabetes mellitus, and elevated blood lipid levels.

CARCINOGENICITY: Not listed as carcinogen or potential carcinogen by NTP, IARC Monographs or OSHA

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## 4. EMERGENCY FIRST AID PROCEDURES

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

**INGESTION:** Give 3-4 glasses of water, but **DO NOT** induce vomiting. If vomiting occurs, give fluids again. 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 if available, 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. Get immediate medical attention.

**OVERDOSAGE:** There is no known antidote for APTIVUS® overdose. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. If indicated, elimination of unabsorbed tipranavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid the removal of unabsorbed drug. Since tipranavir is highly protein bound, dialysis is unlikely to provide significant removal of the drug.

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## 5. FIRE AND EXPLOSION HAZARD DATA

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Flash Point	Flammable Limits	
	Upper	Lower
ND	ND	ND

**FIRE EXTINGUISHING MEDIA:** Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.

**SPECIAL FIRE FIGHTING PROCEDURES:** As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing. Use water spray to keep fire-exposed containers cool and protect against all exposures.

**UNUSUAL FIRE AND EXPLOSION HAZARDS:** As with all organic liquids, this material presents a flammable hazard. It can burn in a fire, producing acrid fumes including acid gases (Hydrofluoric and Nitric Acid) and oxides of carbon, nitrogen, and sulfur.

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## 6. SPILL AND ACCIDENTAL RELEASE MEASURES

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**STEPS TO BE TAKEN IN THE EVENT OF A SPILL:** Wear approved respirator, eye protection and chemically compatible gloves if containers have been compromised. Absorb liquid spillage or pick or sweep up spilled (undamaged) containers. Avoid creating any mists. Place spillage in appropriate container for waste disposal. Wash any contaminated clothing before reuse. If necessary, ventilate area; wash down spill site; and control any wash water.

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## 7. PRECAUTIONS FOR SAFE HANDLING AND USE

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### HANDLING AND STORAGE PRECAUTIONS:

Store in a tight container and store away from foodstuffs. This material should be handled and stored as per label and other instructions to ensure product integrity. Avoid contact with eyes, skin or clothing. Avoid breathing dust or mist.

APTIVUS Oral Solution must be stored between 15°C (59°F) and 30°C (86°F). **Do not refrigerate or freeze** APTIVUS® Oral Solution. KEEP OUT OF REACH OF CHILDREN. The solution must be used within 60 days after first opening the bottle.

OTHER PRECAUTIONS: Wash hands thoroughly after handling. Wear fresh clothing daily. Wash contaminated clothing before re-use.

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## 8. CONTROL MEASURES

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ENGINEERING CONTROLS: Not generally required when handling containers. (See section 2 for exposure limits.) Use appropriate respiratory protection based upon an industrial hygiene survey.

RESPIRATORY PROTECTION: 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 to maintain exposure levels below recommended established limits for final product. If general ventilation is not sufficient, local exhaust is recommended.

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

**Eye Protection:** Safety glasses with side shields or goggles

**Hand Protection:** Gloves

**Protective Clothing:** Laboratory coats

**Other:** Eye wash & safety shower

WORK/HYGIENIC PRACTICES: Do not permit eating, drinking or smoking near this material.

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## 9. PHYSICAL/CHEMICAL CHARACTERISTICS

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APPEARANCE AND ODOR: Clear yellow viscous butter mint-butter toffee flavored liquid

Boiling Point: N/A

Specific Gravity: N/A

Vapor Pressure (mm Hg): N/A

Melting Point: N/A

Vapor Density: N/A

Evaporation Rate: N/A

Water Solubility: Soluble

Volatiles, %: N/A

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## 10. REACTIVITY DATA

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STABILITY: Stable

CONDITIONS TO AVOID: None Known

INCOMPATIBLE MATERIALS: None Known

HAZARDOUS DECOMPOSITION OR BY-PRODUCTS: When heated to decomposition or under fire conditions, material emits: acrid fumes including acid gases (Hydrofluoric and Nitric Acid) and oxides of carbon, nitrogen, and sulfur.

HAZARDOUS POLYMERIZATION: N/A

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## 11. TOXICOLOGICAL INFORMATION

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### ACUTE TOXICITY:

In preclinical studies in rats, tipranavir treatment induced dose-dependent changes in coagulation parameters (increased prothrombin time, increased activated partial thromboplastin time and decrease in some vitamin K dependent factors). In some rates, these changes led to bleeding in multiple organs and death. The co-administration of vitamin E in the form of TPGS (d-alpha-tocopherol polyethylene glycol 1000 succinate) with tipranavir resulted in a significant increase in effects on coagulation parameters, bleeding events and death.

In preclinical studies of tipranavir in dogs, an effect on coagulation parameters was not seen. Co-administration of tipranavir and vitamin E has not been studied in dogs. Clinical evaluations of coagulation effects on HIV-1-infected patients demonstrated no tipranavir plus ritonavir effect and no effect of the vitamin E-containing oral solution on coagulation parameters.

### NOAEL:

Animal	Study Duration	Effect Level	Effects Considered
Rat	26 Weeks	20 mg/kg/day	None listed
Mouse	13 Weeks	40 mg/kg/day	Gross loss of general condition in some animals
Beagle	4 Weeks	160 mg/kg/day	Emesis, diarrhea, soft stool, hepatocellular hypertrophy
Cynomolgus Monkey	2 Weeks	320 mg/kg/day	Emesis, diarrhea, soft stool, increased fibrinogen

### TERATOGENICITY:

Pregnancy Category C – There are no adequate and well controlled studies for the treatment of HIV-1 infection.

No teratogenicity was detected in reproductive studies in pregnant rats and rabbits up to dose levels of 1000mg/kg/day and 150 mg/kg/day tipranavir, respectively, at exposure levels approximately 1.1 fold and 0.1 fold human exposure. At 400 mg/kg/day and above in rats, fetal toxicity (decreased sternebrae ossification and body weights) was observed, corresponding to an AUC of 1310  $\mu\text{M}\cdot\text{h}$  or approximately 0.8 fold human exposure at the recommended dose. In rats and rabbits, fetal toxicity, was not noted at 40 mg/kg/day and 150 mg/kg/day, respectively, corresponding accordingly to  $C_{\text{max}}/\text{AUC}_{0-24\text{h}}$  levels of 30.4  $\mu\text{M}/340\mu\text{M}\cdot\text{h}$  and 8.4  $\mu\text{M}/120\mu\text{M}\cdot\text{h}$ . These exposure levels (AUC) are approximately 0.2 fold and 0.1 fold the exposure in humans at the recommended dose.

In pre and post development studies in rats, tipranavir showed no adverse effects at 40 mg/kg/day (~0.2 fold human exposure), but cause growth inhibition in pups and maternal toxicity at dose levels of 400 mg/kg/day (~0.8 fold human exposure). No post weaning functions were affected at any dose level.

**NURSING MOTHERS:** The Center for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Because of both the potential for HIV-1 transmission and any possible adverse effects of APTIVUS®, mothers should be instructed not to breastfeed if they are receiving APTIVUS®.

#### CARCINOGENESIS:

Long term carcinogenicity studies in mice and rats have been conducted with tipranavir. Mice were administered 30, 150, or 300 mg/kg/day tipranavir, 150/40 mg/kg/day tipranavir/ritonavir in combination, or 40 mg/kg/day ritonavir. The incidences of benign hepatocellular adenomas and combined adenomas/carcinomas were increased in females of all groups except the low dose of tipranavir. The clinical relevance of the carcinogenic finding in mice is unknown.

Female rats administered 300 mg/kg/day tipranavir, the highest dose, had an increased incidence follicular cell adenomas of the thyroid gland. This finding is probably not relevant to humans, because thyroid follicular cell adenomas are considered a rodent-specific effect secondary to enzyme induction.

#### MUTAGENICITY:

Tipranavir showed no evidence of mutagenicity or clastogenicity in a battery of five *in vitro* and *in vivo* tests including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, unscheduled DNA synthesis in rat hepatocytes, induction of gene mutation in Chinese hamster ovary cells, a chromosome aberration assay in human peripheral lymphocytes, and a micronucleus assay in mice.

#### IMPAIRMENT OF FERTILITY:

Tipranavir had no effect on fertility or early embryonic development in rats at dose levels up to 1000 mg/kg/day, equivalent to a  $C_{\text{max}}$  of 258  $\mu\text{M}$  in females. Based on  $C_{\text{max}}$  levels in these rats, as well as an exposure (AUC) of 1670  $\mu\text{M}\cdot\text{h}$  in pregnant rats from another study, this exposure was approximately equivalent to the anticipated exposure in humans at the recommended dose level of 500/200 mg APTIVUS/ritonavir BID.

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## 12. ECOLOGICAL INFORMATION

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There is no data on the ecotoxicity of this product.

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## 13. DISPOSAL CONSIDERATIONS

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**WASTE DISPOSAL CONSIDERATIONS:** Dispose of in accordance with local, state and federal regulations. Recommended method is incineration.

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## 14. TRANSPORT INFORMATION

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D.O.T. Proper Shipping Name:	Not Regulated
Hazard Class:	N/A
Identification Number:	N/A
Packing Group:	N/A
Label:	N/A
Emergency Response Guidebook:	N/A

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## 15. REGULATORY INFORMATION

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This material is **not** listed on the US TSCA Inventory. Therefore, it can only be used for TSCA exempt purposes such as R&D or drug use.

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## 16. OTHER INFORMATION

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### ABBREVIATIONS:

N/E: Not Established  
N/A: Not Applicable  
N/D: Not Determined

Prepared by: Environmental Health & Safety  
Date Prepared: November 17, 2008  
Replaces: New  
Sections Revised:

### NOTICE:

The opinions expressed herein are those of qualified experts within Boehringer Ingelheim Pharmaceutical, Inc. (BIPI). We believe that the information contained within the MSDS is current as of the date issued. Since the use of this information and these opinions and the conditions of use of this material are not within the control of BIPI, it is the user's obligation to determine the conditions of safe use of this material. BIPI urges the users of this product to study the MSDS and become aware of any hazards associated with this material. In the interests of safety, the information contained in this MSDS should be made available to your employees, agents, and contractors who handle this material.

### SEE CURRENT PACKAGE INSERT FOR FURTHER INFORMATION

### REFERENCES:

Tipranavir Oral Solution 100 mg/mL MSDS date July 30, 2004  
Highlights of Prescribing Information for APTIVUS Document – dated 6/2008  
Physician's Desk Reference – Electronic Version