MATERIAL SAFETY DATA SHEET

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

Product name: **Twynsta ® Tablets**

DATE ISSUED: October 22, 2009

EMERGENCY TELEPHONE NUMBER
(203) 798-5521

1. SUBSTANCE IDENTIFICATION

CHEMICAL NAME: Telmisartan – (4'-[(1,4'-dimethyl—2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]—2-carboxylic acid

Amlodipine – 3-ethyl-5-methyl (±)-2[2-aminoethoxy]methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate,monobenzenesulphonate

MOLECULAR FORMULA: Telmisartan – $C_{33}H_{30}N_4O_2$
Amlodipine – $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$

GENERIC NAME: TWYNSTA Tablets

MOLECULAR WEIGHT: Telmisartan – 514.63
Amlodipine – 566.51

CHEMICAL FAMILY:

CAS NUMBER:

PRODUCT USE: antihypertensive agent

SYNONYMS: telmisartan/amlodipine tablets

2. COMPONENTS PER UNIT DOSE

MATERIAL	Function	Exposure Limits
Active Ingredient		
Telmisartan	Drug Substance	100 µg/M^3
Amlodipine besylate	Drug Substance	N/E
Excipients		
Colloidal Silicon Dioxide	Inactive Ingredient	10 mg/M^3 Particulates NOC
Corn Starch	Inactive Ingredient	10 mg/M^3
FD&C blue #1	Inactive Ingredient	N/E
Ferric oxide black	Inactive Ingredient	N/E
Ferric oxide yellow	Inactive Ingredient	10 mg/M^3
Magnesium stearate	Inactive Ingredient	10 mg/M^3 (as stearate)
Meglumine	Inactive Ingredient	N/E
Microcrystalline cellulose	Inactive Ingredient	15 mg/M^3 (as total dust) 5 mg/M^3 (as respirable fraction)
Povidone	Inactive Ingredient	N/E
Sodium Hydroxide	Inactive Ingredient	2 mg/M^3 Ceiling
Sorbitol	Inactive Ingredient	N/E

3. HAZARD IDENTIFICATION

EMERGENCY OVERVIEW

- Non-scored, multilayer tablets of oval, biconvex shape.
- Tablets are White to Off-white on one side and blue on the other side.
- White side is debossed with BOEHRINGER INGELHEIM symbol and with either A1, A2, A3 or A4 for the 40/5 mg, 40/10 mg, 80/5 mg, and 80/10 (telmisartan/amlodipine) strengths, respectively.

- **WARNING – AVOID USE IN PREGNANCY**

- When pregnancy is detected, discontinue TWYNSTA as soon as possible. Drugs that act directly on the rennin-agiotensin system can cause injury and even death to the developing fetus.

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

TARGET ORGANS: Liver, Kidney, Heart, and rennin-agiotensin system

CONTRAINDICATIONS: None.

ADVERSE REACTIONS TO PRODUCT: peripheral edema, dizziness, clinically meaningful orthostatichypotension, and back pain. Peripheral edema is a known, dose-dependant adverse reaction of amlodipine, but not telmisartan. During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated). Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including telmisartan.

ACUTE EXPOSURE: Limited data are available with regard to telmisartan in humans. The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Overdosage with regard to amlodipine might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited.

SIGNS AND SYMPTOMS OF EXPOSURE: Hypotension, dizziness, elevated heart rate

CHRONIC EXPOSURE: Not known

MEDICAL CONDITIONS POTENTIALLY AGGRAVATED BY EXPOSURE: Kidney, Liver and Heart Conditions.

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

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: 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 TWYNSTA Tablet overdose. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status.

Telmisartan
Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan tablets would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Amlodipine
Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on an mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae was noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

5. FIRE AND EXPLOSION HAZARD DATA

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 (Hydrochloric, Nitric and sulfuric Acid) and oxides of carbon, nitrogen, and sulfur.

6. SPILL AND ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN THE EVENT OF A SPILL: Wear approved respirator, eye protection and chemically compatible gloves if containers have been compromised. Pick or sweep up spilled (undamaged) containers. Avoid creating any dust. 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. Dispose in accordance with local regulations.

7. PRECAUTIONS FOR SAFE HANDLING AND USE

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.

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature]. Do not remove from blisters until immediately before administration. Protect from moisture and light.

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

8. CONTROL MEASURES

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
Protective Clothing: Laboratory coats
Hand Protection: Gloves
Other: Eye wash & safety shower

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

9. PHYSICAL/CHEMICAL CHARACTERISTICS

APPEARANCE AND ODOR: TWYNSTA tablets are non-scored, white–off-white/blue, multilayer tablets of oval, biconvex shape. White side is debossed with BOEHRINGER INGELHEIM symbol and with either A1, A2, A3 or A4 for the 40/5 mg, 40/10 mg, 80/5 mg, and 80/10 (telmisartan/amlodipine) strengths, respectively

Boiling Point: N/A
Vapor Pressure (mm Hg): N/A
Vapor Density: N/A
Water Solubility: Soluble
Specific Gravity: N/A
Melting Point: N/A
Evaporation Rate: N/A
Volatiles, %: N/A

10. REACTIVITY DATA

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: acid gases (Hydrochloric, Nitric and sulfuric Acid) and oxides of carbon, nitrogen, and sulfur.
HAZARDOUS POLYMERIZATION: N/D

11. TOXICOLOGICAL INFORMATION

TERATOGENICITY:

TWYNSTA is Pregnancy Category C (first trimester) and D (second and third trimesters). When pregnancy is detected, discontinue TWYNSTA use as soon as possible

Telmisartan

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on an mg/m2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on an mg/m2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the maximum recommended human dose [MRHD] of 10 mg amlodipine on a mg/m2 basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg.) However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) for rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

CARCINOGENESIS:

Telmisartan

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m2 basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on an mg/m2 basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.)

MUTAGENICITY:

Telmisartan

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

Amlodipine

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

IMPAIRMENT OF FERTILITY:

Telmisartan

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on an mg/m2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Amlodipine

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on an mg/m2 basis).

12. ECOLOGICAL INFORMATION

There is no data on the ecotoxicity of this product.

13. DISPOSAL CONSIDERATIONS

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

14. TRANSPORT INFORMATION

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

15. REGULATORY INFORMATION

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.

16. OTHER INFORMATION

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

Prepared by: Environmental Health & Safety
Date Prepared: October 22, 2009
Replaces: New
Sections Revised:

NOTICE:

The opinions expressed herein are those of qualified experts within Boehringer Ingelheim Pharmaceuticals, 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:
4
Highlights of Prescribing Information for TWYNSTA Document – dated 10/2009