Bristol-Myers Squibb Company

Material Safety Data Sheet

1. PRODUCT AND COMPANY IDENTIFICATION

Product Information	
Product name	BARACLUDE® (entecavir) Tablets, 0.5 mg and 1.0 mg
Version	2.0, 12/18/2013
Jurisdiction	This Safety Data Sheet was prepared for the Globally Harmonized System (GHS).
Synonyms	Entecavir Tablets, 0.5 mg, 1.0 mg
Intended Uses	This material is a finished drug product for patient use. It is used for treatment of hepatitis B virus infection.
Company/Undertaking Identification	
Address	**Bristol-Myers Squibb Australia Pty Ltd** 4 Nexus Court, Mulgrave, Victoria 3170, Australia
Emergency Phone Number	CHEMTREC Australia (Sydney): +(61)-290372994

2. HAZARDS IDENTIFICATION

UN Globally Harmonized System (GHS)

Classification

Mild Eye Irritation - Category 2B
Carcinogenicity - Category 2
Toxic To Reproduction - Male Reproductive Toxicity - Category 2
Toxic To Reproduction - Female Reproductive Toxicity - Category 2
Toxic To Reproduction - Developmental Toxicity - Category 2
Specific Target Organ Systemic Toxicity (Single Exposure) - Category 3
Specific Target Organ Systemic Toxicity (Repeated Exposure) - Category 1

Symbol

Signal Word

Danger

Hazard Statements

Causes eye irritation.
Suspected of causing cancer.
May cause respiratory irritation
Suspected of damaging fertility or the unborn child. (female reproductive toxicity, male reproductive toxicity, Developmental Toxicity) .
Causes damage to organs (liver, spleen, thymus, prostate, muscle, bone marrow, testes, lymph nodes, gastrointestinal tract, kidney, heart, lungs, pancreas, blood) through prolonged or repeated exposure.

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2. HAZARDS IDENTIFICATION

Precautionary Statements	Avoid breathing dust. Use only outdoors or in a well-ventilated area. Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Use personal protective equipment as required. Do not eat, drink or smoke when using this product. Wash thoroughly after handling.

3. COMPOSITION/INFORMATION ON INGREDIENTS

Components	Concentration	CAS-No.
Hazardous components		
Entecavir Monohydrate	0.24 %	209216-23-9
Microcrystalline Cellulose	> 10 %	9004-34-6
Titanium Dioxide	> 1.16 - <1.3 %	13463-67-7
Other ingredients		
Non-Hazardous Ingredients	<70 %	Not available
Magnesium Stearate	<1 %	557-04-0

4. FIRST AID MEASURES

Eye contact	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If exposed or concerned: Get medical attention/advice.
Skin contact	Take off contaminated clothing and shoes immediately. Wash off immediately with plenty of water for at least 15 minutes. Obtain medical attention. Discard contaminated clothing or wash before re-use. If exposed or concerned: Get medical attention/advice.
Inhalation	Move to fresh air. Oxygen or artificial respiration if needed. IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing. Call a POISON CENTER or doctor/physician if you feel unwell. If exposed or concerned: Get medical attention/advice.
Ingestion	Do NOT induce vomiting. Never give anything by mouth to an unconscious person. If exposed or concerned: Get medical attention/advice.
Notes to Physician	Refer to Section 11. Pregnant or nursing women should avoid exposure.
Medical Surveillance	The need for a pre-placement physical examination and history for employees with potential exposure to this compound is to be evaluated by a physician that is thoroughly knowledgeable about both the toxicity of this compound and the extent of work place exposure. Baseline testing would include: a complete blood count with differential, a blood test for liver function, a blood test for kidney function, lung function test. Based on opportunity for exposure and duration of exposure a periodic follow-up examination may be considered. Employees who are pregnant, are breast-feeding, or who are concerned with other reproductive issues should be encouraged to consult with the occupational health physician monitoring worker's health. Pregnant or nursing women should avoid exposure.

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5. FIRE-FIGHTING MEASURES

Flammable Properties	Not available
Extinguishing Media	Suitable extinguishing media: Dry chemical, Water spray, Foam Unsuitable extinguishing media: Do NOT use water jet.
Protection of Firefighters	Specific hazards: Reproductive toxicant Developmental toxicant Irritating to respiratory tract. Protective equipment: Use personal protective equipment. In the event of fire, wear self-contained breathing apparatus. Hazardous Combustion Products: carbon oxides (COx), nitrogen oxides (NOx)
Other information:	Decontaminate protective clothing and equipment before reuse. Avoid generating dust; fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions	Refer to protective measures listed in sections 7 and 8. Use personal protective equipment. Examples include tightly fitting safety goggles, lab coat and impervious gloves. Wear respiratory protection. Depending on the nature of the spill (quantity and extent of spill) additional protective clothing and equipment such as a self-contained breathing apparatus may be needed.
Environmental precautions	Prevent release to drains and waterways. Prevent release to the environment.
Containment Methods	Wet down any dust to prevent generation of aerosols, if appropriate. Cover with suitable material.
Cleanup Methods	Contain and collect spillage and place in container for disposal according to local regulations (see Section 13). Handle waste materials, including gloves, protective clothing, contaminated spill cleanup material, etc., as appropriate for chemically and pharmacologically similar materials. Spill prevention procedures and a spill response procedure should be implemented.

7. HANDLING AND STORAGE

Handling Precautions	Avoid exposure - obtain special instructions before use. Avoid formation of dust and aerosols. When handling broken or crushed tablets or capsules, ensure worker exposure is below the recommended exposure limit. Keep away from heat and sources of ignition. Prevent release to drains and waterways.
Storage Conditions	Store at controlled room temperature of 15 - 30°C. Avoid moisture. Do not freeze.
Container Requirements	Store in the original primary packaging as provided.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

COMPONENT EXPOSURE LIMIT(S)

Exposure limit(s)	Company Guideline	ACGIH	OSHA	NIOSH
Entecavir Monohydrate	2 µg/m3	--	--	--

Continued

8. EXPOSURE CONTROLS / PERSONAL PROTECTION				
Microcrystalline Cellulose	--	10 mg/m3 TWA	--	10 mg/m3 TWA 5 mg/m3 TWA
Magnesium Stearate	--	10 mg/m3 TWA	--	--
Titanium Dioxide	--	10 mg/m3 TWA	--	5,000 mg/m3 IDLH

Exposure Control Band	Entecavir Monohydrate ***4*** -- The established company exposure guideline falls within Exposure Control Band 4 (range 1 - <10 µg/m3).
Bristol-Myers Squibb Exposure Guidelines Summary	Entecavir Monohydrate Materials require particular care and handling. Adherence to this guideline should protect employees from experiencing the therapeutic and/or adverse effects of this drug.
Recommended Industrial Hygiene Monitoring Methods	A specific exposure sampling method is not available. Contact the Bristol-Myers Squibb AIHA accredited Industrial Hygiene Laboratory at 732-227-6338.
EXPOSURE CONTROLS / PERSONAL PROTECTION FOR MATERIAL AS SUPPLIED	
This mixture contains material(s) with the exposure limit(s) noted above. The mixture as supplied should be controlled during handling to limit total airborne exposure to the limit noted below or less.	
Exposure Control Band - For Operations Using Material as Supplied	BARACLUDE® (entecavir) Tablets, 0.5 mg and 1.0 mg ***2*** -- Material is assigned to Exposure Control Band 2 (range 100 - 1000 µg/m3).
Engineering Controls and Ventilation	When handling small quantities in a clinical setting, good room ventilation is desirable. Specific engineering controls should not be needed. When handling broken or crushed tablets or capsules, ensure worker exposure is below the recommended exposure limit. If significant dust is generated, use process enclosures, containment technology, or other engineering controls to keep airborne levels below recommended exposure limit.
Respiratory protection	Use the indicated respiratory protection if the occupational exposure limit is exceeded and/or in case of product release (dust). Use and selection of respiratory protection is based upon engineering controls in use and potential for aerosol generation. When engineering controls are not sufficient to control exposure, wear an approved respirator with NIOSH Class 100 or high efficiency particulate (HEPA) filters or cartridges when exposures are up to 10 times the exposure control guideline. Wear a loose-fitting (Tyvek or helmet type) HEPA powered-air purifying respirator (PAPR) when exposures are 10-25 times the exposure control guideline. Wear a full facepiece negative pressure respirator with Class 100 or HEPA filters when exposures are 25-50 times the exposure control guideline. Wear a tight-fitting, full facepiece HEPA PAPR when exposures are 50-100 times the exposure control guideline. Wear a hood-shroud HEPA PAPR or full facepiece supplied air respirator operated in a pressure demand or other positive pressure mode when exposures are 100-1000 times the exposure control guideline.
Eye protection	Normally not required for handling a small number of tablets/capsules.
Hand protection	Impervious nitrile, rubber and latex gloves are recommended. Please note that employees who are allergic to natural rubber latex should use nitrile gloves.

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8. EXPOSURE CONTROLS / PERSONAL PROTECTION	
Skin and body protection	It is recommended that a laboratory coat be worn when handling product.
Hygiene	Wash hands before breaks and immediately after handling the product.

9. PHYSICAL AND CHEMICAL PROPERTIES	
Appearance	
Physical State	solid
Color	white to off-white or pink
Form	tablet
Other information	
Molecular Weight	Not applicable
Molecular formula	Not applicable
Bulk density	Not available
Evaporation rate	Not available
Hydrolysis/Photolysis	Not available
Hygroscopicity	Not available
Log Octanol/Water Partition Coefficient [log Kow]	Not available
Surface Tension	Not available
Odor	Not available
Odor Threshold	Not available
pH	Not available
pKa	Not available
Particle Size	Not available
Solubility, Water	Not available
Specific Gravity/ Relative density	Not available
Viscosity	Not available
Thermal/Stability properties	
Autoignition temperature	Not available
Boiling Point	Not available
Thermal decomposition	Not available
Explosive Limits, LEL	Not available
Explosive limits, UEL	
Explosiveness	Not available
Flammability	Not available
Flash point	Not available
Melting Point	Not available
Oxidizing Potential	Not available
Vapor Properties	
Vapor Density	Not available
Vapor Pressure	Not available
Saturated Vapor Concentration	Not available

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10. STABILITY AND REACTIVITY	
Stability	
Chemical Stability	Stable under normal conditions.
Conditions to avoid	Not available
Incompatible products	Not available
Hazardous decomposition products	Hazardous decomposition products formed under fire conditions.: carbon oxides (COx), nitrogen oxides (NOx)
Hazardous reactions	None known.

11. TOXICOLOGICAL INFORMATION	
Routes of Entry	Ingestion, inhalation, Eye contact, Skin contact
Eye Irritation	Microcrystalline Cellulose Mildly and/or transiently irritating to eyes Titanium Dioxide Dust may cause mechanical irritation.
Skin Irritation	Microcrystalline Cellulose Not irritating to skin. Titanium Dioxide Dust may cause mechanical irritation.
Respiratory Irritation	Microcrystalline Cellulose Respiratory Irritant Titanium Dioxide Irritating to respiratory tract.
Sensitization	Microcrystalline Cellulose Not a dermal sensitizer Titanium Dioxide Not a dermal sensitizer

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11. TOXICOLOGICAL INFORMATION

Acute Toxicity Study

Acute Oral

Entecavir

LD50 (rat, males): > 1,000 - < 5,000 mg/kg High exposure effects include: fecal changes, mortality.

LD50 (mouse, males and females): > 1,000 mg/kg low exposure effects include: decreased body weight. High exposure effects include: hypoactivity, abnormal posture, mortality.

Microcrystalline Cellulose

LD50 (rat, males and females): > 5,000 mg/kg

Titanium Dioxide

LD50 (rat): > 10,000 mg/kg

Acute Dermal

Microcrystalline Cellulose

LD50 (rat, males and females): > 2,000 mg/kg

Titanium Dioxide

LD50 (rabbit): > 10,000 mg/kg

Acute inhalation toxicity

Microcrystalline Cellulose

LC50 (rat, males and females): > 5350 mg/m3/4 H

Titanium Dioxide

LC50 (rat): > 2.29 mg/l/4 H/4 H

Acute toxicity (other routes of administration)

Microcrystalline Cellulose

LD50 (rat, males, intraperitoneal): > 3,160 mg/kg

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11. TOXICOLOGICAL INFORMATION

Repeated Dose Toxicity	Entecavir 2 Weeks oral (daily) rat study : LOAEL = 20 mg/kg (males and females). Low dose effects include (< 100 mg/kg): death, decreased body weight, decreased food consumption, increased urine volume, changes in red blood cell parameters, decreased white blood cell count, decreased platelets, decreased organ weights included:, thymus, spleen, prostate, uterus/cervix. 6 months oral (daily) rat study : LOAEL = 0.02 mg/kg (males and females). Microscopic changes were observed in the following organs: liver centrilobular region, muscle. 3 months dietary (daily) rat study : LOAEL = 1 mg/kg (males and females). Low dose effects include (< 100 mg/kg): decreased body weight, increase in blood cholesterol, death, increased platelets, changes in white blood cell parameters, decreased food consumption, gastrointestinal tract toxicity, degeneration of skeletal muscle, increased organ weights included:, spleen, decreased organ weights included:, testes, uterus/cervix. Microscopic changes were observed in the following organs: gastrointestinal tract, thymus, lymph nodes, testes, heart, lungs, kidney, muscle, bone marrow, spleen. 2 Weeks oral (daily) dog study : NOAEL = 1 mg/kg (males and females). Low dose effects include (< 100 mg/kg): death, vomiting, decreased body weight, decreased food consumption, changes in clinical pathology parameters, decreased organ weights included:, testes. Microscopic changes were observed in the following organs: testes, bone marrow, lymph nodes, gastrointestinal tract, thymus, spleen, kidney. 3 months oral (daily) dog study : LOAEL = 0.3 mg/kg (males and females). Low dose effects include (< 100 mg/kg): central nervous system toxicity, decreased body weight, decreased food consumption, decreased white blood cell count, decreased platelets, decreased organ weights included:, testes, prostate, ovary. Microscopic changes were observed in the following organs: pancreas, testes, prostate, bone marrow, kidney, liver, lymph nodes. 1 Years oral (daily) monkey study : NOAEL = 40 mg/kg (males and females). Microscopic changes were observed in the following organs: blood. Titanium Dioxide **Assessment Repeat Dose Toxicity** Several studies were conducted. See "Human Experience".
Genetic Toxicity	Entecavir **In vitro** Ames reverse-mutation assay -- negative Chromosome aberration test in vitro -- positive Forward gene mutation assay -- negative **in vivo** 3 Days oral, Mutagenicity (micronucleus test) (rat) -- negative oral, DNA repair assay (rat) -- negative **Mutagenicity Assessment** Not considered a mutagen according to 29 CFR 1910, 67/348/EC or Canadian Controlled Products Regulations. Microcrystalline Cellulose **Mutagenicity Assessment** This material was negative in a battery of in vivo and in vitro genotoxicity assays. Titanium Dioxide

Continued

11. TOXICOLOGICAL INFORMATION

Mutagenicity Assessment
This material was negative in a battery of in vivo and in vitro genotoxicity assays.

Carcinogenicity

Entecavir
2 Years oral (daily) mouse study : Tumor NOAEL = 0.004 mg/kg (males and females). [tumor organs: lungs, cardiovascular, liver] Effects include: increase in food consumption, death, decreased weight gain, decreased body weight. Effects considered species specific and may not be relevant for humans include:, lung toxicity, The relevance for human risk assessment is unknown.
2 Years oral (daily) rat study : Tumor NOAEL = 0.2 mg/kg (males and females). [tumor organs: liver, brain, skin, uterus/cervix] Effects include: decreased body weight. Microscopic changes were observed in the following organs: pancreas, kidney, testes.
Carcinogenicity Assessment
This material has limited evidence of carcinogenic potential. Several studies were conducted. It is carcinogenic in rodents after long term chronic exposure. The relevance to humans is unknown.

Microcrystalline Cellulose
Carcinogenicity Assessment
This material did not show carcinogenic potential in animal studies. Not classifiable as to its carcinogenicity to humans.

Titanium Dioxide
Carcinogenicity Assessment
Tumors were observed at high dose in animal studies by inhalation and intratracheal administration. Tumors were not observed by other routes.

Carcinogenicity	ACGIH	OSHA	NTP	IARC
Entecavir	--	--	--	--
Microcrystalline Cellulose	--	--	--	--
Titanium Dioxide	A4	--	--	2B

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11. TOXICOLOGICAL INFORMATION

Reproductive Toxicity	Entecavir 33 - 42 Days oral (daily) Study of Fertility and Early Embryonic Development (rat) (males) LOAEL = 10 mg/kg Paternal effects include: decreased body weight, decreased weight gain. No effects were found on mating or fertility. No effects were observed in the fetus/embryo. 2 - 3 Weeks oral (daily) Study of Fertility and Early Embryonic Development (rat) (females) NOAEL = 30 mg/kg No effects were found on mating or fertility. No effects were observed in the fetus/embryo. **Assessment Reproductive Toxicity** No effects were found on mating or fertility. Compound may cause injury to male reproductive organs. (only at high doses) Microcrystalline Cellulose **Assessment Reproductive Toxicity** Data indicate that this compound is not a reproductive hazard.
Developmental Toxicity	Entecavir 10 Days oral (daily) exposure time = 15 Days Study of Embryo-Fetal Development (rat) (embryo/fetus, females) NOAEL = 2 mg/kg Fetal effects include: decreased body weight, malformations, death. Maternal effects include: decreased weight gain, decreased body weight, decreased food consumption, fecal changes, death. Teratogenic effects occur only at doses which also produce adverse effects in the maternal animal. 15 Days oral (daily) Study of Pre- and Postnatal Development (rat) (parent, F1 offspring, females) NOAEL = 3 mg/kg Maternal effects include: decreased weight gain. No effects were observed in the fetus/embryo. 13 Days oral (daily) exposure time = 24 Days Study of Embryo-Fetal Development (rabbit) (embryo/fetus, females) NOAEL = 4 mg/kg Fetal effects include: developmental delay, malformations, death. No adverse maternal effects were observed. Selective developmental toxicant **Developmental Toxicity Assessment** Birth defects were observed in animal studies. Microcrystalline Cellulose **Developmental Toxicity Assessment** Available data do not indicate a potential for selective developmental toxicity.
Human experience	**Experiences with Human Exposure** Entecavir oral Clinical trial(s) (daily) 100 mg. low exposure - long term exposure effects include: headache, dizziness, vision changes, increase in body temperature, cough, shortness of breath, abdominal pain, nausea, diarrhoea, sensitivity to light, nasal inflammation, fatigue, vomiting, sleep disturbances, pain, increased liver enzymes, changes in blood clotting parameters, changes in serum chemistry, acidosis, death. Titanium Dioxide Incident report(s) worker exposure low exposure - acute effects include: cough,

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11. TOXICOLOGICAL INFORMATION

	breathing difficulties, rhinitis, Irritating to respiratory system..
Target Organs	Entecavir liver, spleen, thymus, prostate, muscle, bone marrow, testes, lymph nodes, gastrointestinal tract, kidney, heart, lungs, pancreas, blood Titanium Dioxide lungs
Symptoms	Entecavir See "Human Experience". Microcrystalline Cellulose labored respiration, noisy respiration, chest pain, breathing difficulties, shortness of breath, lung inflammation
Pharmacokinetics/ Toxicokinetics	Not available
Other Toxicity Information	Not available

12. ECOLOGICAL INFORMATION

Ecotoxicological Information (Aquatic)

Acute Toxicity to Fish

Entecavir

NOEC (Oncorhynchus mykiss (rainbow trout), 96 H) : 110 mg/l.

Acute Toxicity to Aquatic Invertebrates

Entecavir

EC50 (Daphnia, 48 H) : 72 mg/l.

NOEC (Daphnia, 48 H) : 14 mg/l.

Toxicity to microorganisms

Entecavir

Respiration inhibition, EC50 (Activated Sludge, 0.2 H) : > 500 mg/l

Chronic toxicity to aquatic invertabrates

Entecavir

NOEC (Daphnia magna (Water flea), 21 Days) : 1.6 mg/l (reproduction rate)

Ecotoxicological Information (Terrestrial) Not available

Chemical fate information

Biodegradation

Entecavir

Ready biodegradation (28 D) : 1.62 % ; Not Readily Biodegradable - unlikely to undergo rapid biodegradation in the environment According to the results of tests of biodegradability this product is not readily biodegradable.

Inherent biodegradation (4 D) : 84 % ; Inherently biodegradable - biodegrades in the environment. Inherently biodegradable.

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12. ECOLOGICAL INFORMATION

Entecavir
Koc (Activated Sludge) : 260 - 401 Moderate mobility in soil
Kd (Activated Sludge) : 169 Moderate mobility in soil

Summary Statements

Aquatic toxicity

Entecavir
Harmful to aquatic organisms.

Chemical Fate

Entecavir
Inherently biodegradable - biodegrades in the environment. Moderate mobility in soil
Entecavir

13. DISPOSAL CONSIDERATIONS

Advice On Disposal And Packaging	Disposal should be in accordance with applicable regional, national and local laws and regulations. Local regulations may be more stringent than regional or national requirements.

14. TRANSPORT INFORMATION

This material is not a dangerous good for the purpose of transportation in all modes.

15. OTHER REGULATORY INFORMATION

United States of America

OSHA Hazard Classification	Respiratory Irritant Reproductive Toxicity Developmental Toxicity Target Organs
313 Toxic Release Inventory	No components listed on the SARA 313 inventory.
TSCA Inventory	Not listed. Food, drug and cosmetic products are exempt from TSCA.

International

Canada

WHMIS	Finished medicinal products are not classified under WHMIS, but using the classification criteria this material would be considered: D2A: Very Toxic Material Causing Other Toxic Effects
DSL/NDSL	Entecavir Not listed.

Mexico

Mexico Classification	Health classification - Moderate Hazard 2 - Substances that may cause temporary disability or residual harm under emergency conditions Reproductive Toxicity Developmental Toxicity Possible Carcinogen

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15. OTHER REGULATORY INFORMATION

Europe

EINECS/ELINCS/Number	Microcrystalline Cellulose: 232-674-9 Magnesium Stearate: 209-150-3 Titanium Dioxide: 236-675-5
Symbol(s)	Not applicable
S-phrase(s)	S22: Do not breathe dust. S24/25: Avoid contact with skin and eyes. S36/37/39: Wear suitable protective clothing, gloves and eye/face protection. S38: In case of insufficient ventilation, wear suitable respiratory equipment. S45: In case of accident or if you feel unwell, seek medical advice immediately (show label where possible). S53: Avoid exposure - obtain special instructions before use.
Other information	Medicinal products are exempt from classification and labeling requirements under EU Preparations Directive 1999/45/EC.

16. OTHER INFORMATION

SDS preparation information

Prepared by	Research and Development Environment, Health and Safety 1-732-227-7380
Prepared on	12/18/2013
	This Safety Data Sheet has been revised. This data sheet contains changes from the previous version in section(s): 1, and 16.

The information contained in this SDS is believed to be accurate and represents the best information reasonably available at the time of preparation. However, we make no warranty, express or implied, with respect to such information. and we assume no liability from its use.

End of Safety Data Sheet