Bristol-Myers Squibb Company

Material Safety Data Sheet

1. PRODUCT AND COMPANY IDENTIFICATION	
Product Information	
Product name	BARACLUDE® Oral Solution
Version	2.1, 11/17/2011
Jurisdiction	This Material Safety Data Sheet was prepared for the jurisdiction USA.
Synonyms	Entecavir Oral Solution
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 Company** P.O. Box 191 New Brunswick, New Jersey 08903 United States of America 1-732-227-7380
Emergency Phone Number	CHEMTREC 1-800-424-9300. For all international transportation emergencies call CHEMTREC at 1-703-527-3887. Collect calls accepted.

2. COMPOSITION/INFORMATION ON INGREDIENTS		
Components	Concentration	CAS-No.
Hazardous components		
Entecavir Monohydrate	0.005 %	209216-23-9
Other ingredients		
Non-Hazardous Ingredients	> 95 %	Not available
Other information: Sodium hydroxide and/or hydrochloric acid are used for pH adjustment.		

3. HAZARDS IDENTIFICATION	
Emergency Overview	
Appearance	liquid : clear , colourless to light yellow ; aqueous solution
Signal Word	Danger
Hazard Statements	Suspected of damaging fertility. Suspected of damaging the unborn child. Causes damage to organs through prolonged or repeated exposure. Target Organs: liver, spleen, thymus, prostate, muscle, bone marrow, testes, lymph nodes, gastrointestinal tract, kidney, heart, lungs, pancreas, blood.
Precautionary Measures	Do not breathe dust/fume/gas/mist/vapours/spray. Do not eat, drink or smoke when using this product. Wash thoroughly after handling. Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Use personal protective equipment as required. Store locked up.
OSHA Regulatory Status	This material is classified as hazardous under OSHA regulations.
Potential Health Effects	

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3. HAZARDS IDENTIFICATION	
Eyes	Not available
Skin	Not available
Ingestion	Not available
Inhalation	Not available
Target Organs	liver, spleen, thymus, prostate, muscle, bone marrow, testes, lymph nodes, gastrointestinal tract, kidney, heart, lungs, pancreas, blood
Signs and Symptoms	Refer to Section 11.
Environmental Effects	Not available

4. FIRST AID MEASURES	
Eye contact	Rinse immediately with plenty of water for at least 15 minutes. Keep eye wide open while rinsing. Obtain medical attention.
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.
Inhalation	Move to fresh air. Oxygen or artificial respiration if needed. Obtain medical attention.
Ingestion	Do NOT induce vomiting. Never give anything by mouth to an unconscious person. Get medical attention/advice if you feel unwell.
Notes to Physician	Refer to Section 11. Pregnant or nursing women should avoid exposure.
Medical Surveillance	A pre-placement physical examination and history for employees with potential exposure to this compound is recommended. Baseline testing would include: a blood test for liver function, a complete blood count with differential, 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. This exam should be overseen by a physician thoroughly knowledgeable about both the toxicity of this compound and the extent of work place exposure. It is recommended that the content be similar to the pre-placement exam. 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.

5. FIRE-FIGHTING MEASURES	
Flammable Properties	Material is an aqueous solution. Not expected to be flammable.
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 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.

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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	Contain spillage, and then collect with non-combustible absorbent material, (e.g. sand, earth, diatomaceous earth, vermiculite) and place in container for disposal according to local / national regulations (see section 13).
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. Soluble in water.Clean spill area thoroughly with detergent and water followed by water rinse.

7. HANDLING AND STORAGE	
Handling Precautions	Avoid exposure - obtain special instructions before use. Avoid inhalation of vapour or mist. 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. Store in original container. Avoid freezing and refrigeration.
Container Requirements	Store in original container.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

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

Exposure Control Band	***4*** -- The established company exposure guideline falls within Exposure Control Band 4 (range 1 - <10 µg/m3).
Bristol-Myers Squibb Exposure Guidelines Summary	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	Contact the Bristol-Myers Squibb AIHA accredited Industrial Hygiene Laboratory at 732-227-6338. See Section 4 "Notes to Physician" for information on medical surveillance.
EXPOSURE CONTROLS / PERSONAL PROTECTION FOR MATERIAL AS SUPPLIED	
Exposure Control Band - For Operations Using Material as Supplied	***1*** -- Material is assigned to Exposure Control Band 1 (range 1,000 - 10,000 µg/m3).

Continued

8. EXPOSURE CONTROLS / PERSONAL PROTECTION	
Engineering Controls and Ventilation	If significant aerosol (mist) is generated, use process enclosures, containment technology, or other engineering controls to keep airborne levels below recommended exposure limit. When handling quantities up to 1.5 grams, a standard laboratory with general laboratory dilution ventilation (e.g. 6-12 air changes per hour) is appropriate. When handling quantities from 1.5 grams to 1 kilogram, work in a standard laboratory using a fume hood; biological safety cabinet(Class II, all types), approved vented enclosure; specific local exhaust. Quantities exceeding 1 kilogram should be handled in a designated laboratory. A laminar flow/powder containment booth is recommended for handling >1 kilograms of active substance. When handling solutions with low energy operations (pipette transfers, pouring, low velocity stirring, fraction collection, etc.) use protective shielding to limit the spread of splash or splatter. When handling quantities up to 150 milligrams, a standard laboratory with general laboratory dilution ventilation (e.g. 6-12 air changes per hour) is appropriate.
Respiratory protection	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	Safety glasses with side-shields are recommended. Face shields or chemical safety goggles may be required if splash potential exists or if corrosive materials are present. Note: Choice of eye protection may be influenced by the type of respirator which is selected.
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.
Skin and body protection	Wear a laboratory coat when handling quantities up to 1 kilogram. For quantities over 1 kilogram, wear laboratory coat or coverall of low permeability.
Hygiene	Wash hands and face before breaks and immediately after handling the product.

9. PHYSICAL AND CHEMICAL PROPERTIES	
Appearance	
Physical State	liquid
Color	clear , colourless to light yellow
Form	aqueous solution
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 Coeff [log Kow]	Not available
Surface Tension	Not available
Odor	Not available
Odor Threshold	Not available

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9. PHYSICAL AND CHEMICAL PROPERTIES	
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	Not available
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

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. Stable under normal conditions.

11. TOXICOLOGICAL INFORMATION	
Routes of Entry	Ingestion, Inhalation, Eye contact, Skin contact
Eye Irritation	Not available
Skin Irritation	Not available
Respiratory Irritation	Not available
Sensitization	Not available

Continued

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.
Repeated Dose Toxicity	Entecavir 2 Weeks Oral (daily) Rat Study : LOAEL = 20 mg/kg (males and females). Low dose effects include: 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: 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: 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: 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.
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.

Continued

11. TOXICOLOGICAL INFORMATION

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.

Carcinogenicity	**ACGIH**	**OSHA**	**NTP**	**IARC**
Entecavir	--	--	--	--

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)

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.

Human experience

Experiences with Human Exposure

Entecavir

Oral Clinical trial(s) (daily) 100 mg. low exposure - long term exposure effects include:

Continued

11. TOXICOLOGICAL INFORMATION

	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.
Target Organs	Entecavir liver, spleen, thymus, prostate, muscle, bone marrow, testes, lymph nodes, gastrointestinal tract, kidney, heart, lungs, pancreas, blood
Symptoms	Entecavir See "Human Experience".
Pharmacokinetics/Toxicokinetics	Entecavir Absorption: Not available Distribution: Not available Metabolism: Not available Elimination: Half-life = 138 hours (Human).
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 aquatic plants

Entecavir

NOEC (Pseudokirchneriella subcapitata (formerly Selenastrum capricornutum), Algae biomass, 72 H) : 110 mg/l

NOEC (Pseudokirchneriella subcapitata (formerly Selenastrum capricornutum), Algae growth rate, 72 H) : 110 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.

Continued

12. ECOLOGICAL INFORMATION

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

sorption/desorption

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

Summary Statements

Aquatic toxicity

BARACLUDE® Oral Solution
Harmful to aquatic organisms.
Entecavir
Harmful to aquatic organisms.

Chemical Fate

BARACLUDE® Oral Solution
Inherently biodegradable - biodegrades in the environment. Moderate mobility in soil
Entecavir
Inherently biodegradable - biodegrades in the environment. Moderate mobility in soil

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.
Other information	This information presented only applies to the material as supplied. Disposal by incineration is recommended.

14. TRANSPORT INFORMATION

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

15. REGULATORY INFORMATION

United States of America

OSHA Hazard Classification	Reproductive Toxicity Developmental Toxicity Target Organs	
CERCLA/SARA RQ	Hydrochloric Acid	RQ = 5,000 lb
	Hydrochloric Acid	RQ = 2,270 kg
	Sodium Hydroxide	RQ = 1,000 lb
	Sodium Hydroxide	RQ = 454 lb
	Sodium Hydroxide	RQ = 1,000 lb
	Sodium Hydroxide	RQ = 454 lb
313 Toxic Release Inventory. Listed Chemicals/Compounds	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:

Continued

15. REGULATORY INFORMATION

D2A: Very Toxic Material Causing Other Toxic Effects

DSL/NDSL — Entecavir Sodium Citrate Anhydrous Not listed.

Mexico

Mexico Classification — Reproductive Toxicity
Developmental Toxicity

Europe

EINECS/ELINCS/Registration Number — Methylparaben: 202-785-7
Propylparaben: 202-307-7
Maltitol: 209-567-0
Citric Acid Anhydrous: 201-069-1
Water: 231-791-2
Sodium Hydroxide: 215-185-5
Hydrochloric Acid: 231-595-7

Other information — Medicinal products are exempt from classification and labeling requirements under EU Preparations Directive 1999/45/EC.

UN Globally Harmonized System (GHS)

Classification — 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 (Repeated Exposure) - Category 1

Symbol

Signal Word — Danger

Hazard Statements — Suspected of causing cancer.
Suspected of damaging fertility or the unborn child. (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.

Precautionary Statements — Refer to HAZARDS IDENTIFICATION section.

16. OTHER INFORMATION

MSDS preparation information

Prepared by	Research and Development Environment, Health and Safety 1-732-227-7380
Prepared on	11/17/2011
	This Safety Data Sheet has been revised. This data sheet contains changes from the previous version in section(s): 2, and 16.

Other information

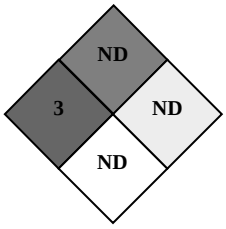
HMIS

Health	3*
Flammability	1
Reactivity	Not Determined (ND)
Personal protective equipment	See Section 8.

Continued

NFPA

Health	3
Fire	ND
Reactivity	ND
Special	ND



The information contained in this MSDS 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