Pioglitazone Hydrochloride

sc-204848

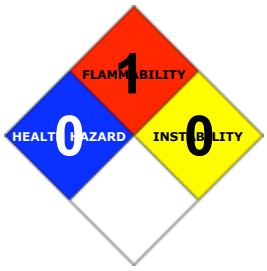
Material Safety Data Sheet

Hazard Alert Code Key:	EXTREME	HIGH	MODERATE	LOW

Section 1 - CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME
Pioglitazone Hydrochloride

STATEMENT OF HAZARDOUS NATURE
CONSIDERED A HAZARDOUS SUBSTANCE ACCORDING TO OSHA 29 CFR 1910.1200.

NFPA


SUPPLIER
Santa Cruz Biotechnology, Inc.
2145 Delaware Avenue
Santa Cruz, California 95060
800.457.3801 or 831.457.3800
EMERGENCY:
ChemWatch
Within the US & Canada: 877-715-9305
Outside the US & Canada: +800 2436 2255
(1-800-CHEMCALL) or call +613 9573 3112

SYNONYMS
C19-H20-N2-O3-S.HCl, "5-[4-(2-(5-ethyl-2-pyridyl)ethoxy)benzyl]-2, 4-thiazolidinedione", hydrochloride, "(+/-)-5-[(4-(2-(5-ethyl-2-pyridinyl)ethoxy)phenyl]-2, 4-", thiazolidinedione, hydrochloride, "(+/-)-5-[p-(2-ethyl-2-pyridyl)ethoxy)benzyl]-2, 4-thiazolidinedione", chloride, AD-4833, heteroaromatic, "ether heterocyclic amide", "insulin sensitiser", antidiabetic, glitazone, ACTOS

Section 2 - HAZARDS IDENTIFICATION

CHEMWATCH HAZARD RATINGS

		Min	Max
Flammability:	1		
Toxicity:	2		
Body Contact:	0		
Reactivity:	1		
Chronic:	2		

Min/Nil=0
Low=1
Moderate=2
High=3
Extreme=4

CANADIAN WHMIS SYMBOLS

EMERGENCY OVERVIEW

RISK

Possible risk of harm to the unborn child.

POTENTIAL HEALTH EFFECTS

ACUTE HEALTH EFFECTS

SWALLOWED

■ Accidental ingestion of the material may be damaging to the health of the individual.

■ An adverse clinical effect was reported for 7% of the exposures to thiazolidinediones, the most frequent of which were hypoglycaemia (2%), hyperglycaemia (1%), and drowsiness (1%).

In patients receiving thiazolidinedione therapy, serious adverse events with or without a fatal outcome, potentially related to volume expansion (e.g., congestive heart failure, pulmonary oedema, and pleural effusions) have been reported.

Thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.

Symptoms of thiazolidinedione therapy may include:

· swelling or fluid retention, especially in the ankles or legs (peripheral oedema)

· shortness of breath or trouble breathing, especially when lying down

· an unusually fast increase in weight

· unusual tiredness

Oedema is a common adverse event associated with thiazolidinedione therapy. The potential for mild-to-moderate peripheral oedema with thiazolidinedione is known, especially in patients who have heart failure or use insulin.

Vary rarely, reports of new onset or worsening (diabetic) macular oedema with decreased visual acuity have been published following the use of thiazolidinediones. It is unknown whether or not there is a causal relationship between these antidiabetic drugs and macular oedema. Physicians should consider the possibility of macular oedema if a patient reports decreased visual acuity. Most patients had peripheral oedema at the time macular edema was diagnosed. Some patients had improvement in their macular oedema after discontinuation of their thiazolidinedione.

Subcutaneous benign adipose tissue tumours (lipomas) have been observed in rats treated with thiazolidinedione drugs, and are probably related to the pharmacodynamic activity of this drug class. Urinary bladder tumours were probably secondary to formation of urinary calculi, and are unlikely to pose a carcinogenic risk in humans.

EYE

■ Although the material is not thought to be an irritant, direct contact with the eye may cause transient discomfort characterized by tearing or conjunctival redness (as with windburn). Slight abrasive damage may also result.

SKIN

■ The material is not thought to produce adverse health effects or skin irritation following contact (as classified using animal models). Nevertheless, good hygiene practice requires that exposure be kept to a minimum and that suitable gloves be used in an occupational setting.

■ Open cuts, abraded or irritated skin should not be exposed to this material.

■ Entry into the blood-stream, through, for example, cuts, abrasions or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected.

INHALED

■ The material is not thought to produce either adverse health effects or irritation of the respiratory tract following inhalation (as classified using animal models). Nevertheless, adverse effects have been produced following exposure of animals by at least one other route and good hygiene practice requires that exposure be kept to a minimum and that suitable control measures be used in an occupational setting.

■ Persons with impaired respiratory function, airway diseases and conditions such as emphysema or chronic bronchitis, may incur further disability if excessive concentrations of particulate are inhaled.

CHRONIC HEALTH EFFECTS

■ Results in experiments suggest that this material may cause disorders in the development of the embryo or fetus, even when no signs of poisoning show in the mother.

Limited evidence suggests that repeated or long-term occupational exposure may produce cumulative health effects involving organs or biochemical systems.

Long term exposure to high dust concentrations may cause changes in lung function i.e. pneumoconiosis; caused by particles less than 0.5 micron penetrating and remaining in the lung.

Exposure to small quantities may induce hypersensitivity reactions characterized by acute bronchospasm, hives (urticaria), deep dermal wheals (angioneurotic edema), running nose (rhinitis) and blurred vision . Anaphylactic shock and skin rash (non-thrombocytopenic purpura) may occur.

A two-year carcinogenicity study in mice showed no drug-related increases in tumour incidences at oral doses up to 91 mg/kg/day. Rats dosed orally with pioglitazone at 0.9-57 mg/kg/day for two years showed increased incidences of subcutaneous benign adipose tissue tumours (lipomas) and urinary bladder transitional cell tumours. Systemic exposure (plasma AUC0-24h) to total active compounds at the highest dose in both studies was 8 times greater than that in humans at the maximum recommended dose. The no-effect doses were not

established for either tumour site. Subcutaneous benign adipose tissue tumours (lipomas) have been observed in rats treated with other thiazolidinedione drugs, and are probably related to the pharmacodynamic activity of this drug class. Urinary bladder tumours were probably secondary to formation of urinary calculi, and are unlikely to pose a carcinogenic risk in humans.
Pioglitazone was not mutagenic in a battery of tests for gene mutation in bacteria and mammalian cells in vitro, in assays for chromosomal damagein vitro and in vivo, and in an assay for DNA damage (unscheduled DNA synthesis in rat hepatocytes in vitro).
No adverse effects on fertility were observed in male and female rats at oral doses up to 40 mg/kg/day. Systemic exposure (plasma AUC0-24h) to total active compounds at the highest dose was about 7 times greater than that in humans at the maximum recommended dose.
A study in pregnant rats showed that pioglitazone and its metabolites cross the placenta. Pioglitazone was not teratogenic in rats or rabbits at oral doses up to 80 and 160 mg/kg/day respectively. Systemic exposure (plasma AUC0-24h) to total active compounds at the highest dose was about 12 times (rats) and 7 times (rabbits) greater than that in humans at the maximum recommended dose.
Embryotoxicity (increased post-implantation loss) was observed in both animal species, and foetotoxic effects (reduced foetal weight and retarded development) were seen in rats. Administration of pioglitazone during the period of organogenesis also caused suppression of postnatal growth in rats.
Administration of pioglitazone to rats throughout gestation and lactation caused retardation in postnatal growth and development, and impaired fertility of the offspring. The no-effect dose for retardation of postnatal growth and development in rats was 3 mg/kg/day and systemic exposure to total active compounds at this dose was similar to that in humans. There are no adequate and
well controlled studies in pregnant women. The substance should be used during pregnancy only if the potential benefits justify the potential risk to the foetus.

Section 3 - COMPOSITION / INFORMATION ON INGREDIENTS

NAME	CAS RN	%
pioglitazone hydrochloride	112529-15-4	>98

Section 4 - FIRST AID MEASURES

SWALLOWED
· If swallowed do NOT induce vomiting. · If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration.

EYE
■ If this product comes in contact with the eyes: · Wash out immediately with fresh running water. · Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids.

SKIN
■ If skin or hair contact occurs: · Flush skin and hair with running water (and soap if available). · Seek medical attention in event of irritation.

INHALED
· If dust is inhaled, remove from contaminated area. · Encourage patient to blow nose to ensure clear passage of breathing. · If irritation or discomfort persists seek medical attention.

NOTES TO PHYSICIAN
■ Treat symptomatically.
Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Steady state is achieved after 4-7 days of dosing. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption. The absolute bioavailability following oral administration is approximately 83%.
Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following intravenous administration is 0.25 L/kg of body weight.
Protein Binding: Pioglitazone is extensively bound to plasma protein (> 99 %), principally to serum albumin. The free fraction is less than 2% and independent of concentration in the range of 34-2000 ng/mL (which includes the therapeutic concentration range).
Metabolism: Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 and 3A4. Three of the six metabolites formed are active. The major circulating metabolite is M-IV (1-hydroxyethyl pioglitazone), which accounts for most of the drug-related material in human plasma and probably accounts for much of the therapeutic efficacy.
Pioglitazone did not inhibit P450 activity when incubated with human P450 liver microsomes.
Elimination: Following oral administration of radiolabelled pioglitazone to humans, recovered label was mainly in faeces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or faeces. The mean plasma elimination half-life of unchanged pioglitazone in man is 5 - 6 hours and for its total active metabolites 16 - 23 hours.
Special Populations
Renal insufficiency: In patients with renal impairment, plasma concentrations of pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but with similar oral clearance of parent drug. Thus free (unbound) pioglitazone concentration remains unchanged. Dose adjustment in patients with renal dysfunction is not recommended. No information is available for patients on dialysis therefore ACTOS should not be used in such patients.
Hepatic insufficiency: In subjects with impaired hepatic function, total plasma concentration of pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is therefore reduced, coupled with a higher unbound fraction of pioglitazone. Therapy should not be initiated in patients with increased baseline liver enzyme levels (ALT >2.5 times the upper limit of normal).

Elderly: No clinically significant differences between elderly and young subjects were observed.
Paediatric: Pharmacokinetic data in the paediatric population is not available.
Gender: The mean Cmax and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin or insulin, treatment improved glycaemic control in both males and females. In controlled clinical trials, haemoglobin A1c (HbA1c) decreases from baseline were generally greater for females than for males (average mean difference in HbA1c 0.5%).
Since therapy should be individualised for each patient to achieve glycaemic control, dose adjustment is not recommended based on gender alone.

Section 5 - FIRE FIGHTING MEASURES

Vapour Pressure (mmHG):	Negligible
Upper Explosive Limit (%):	Not Available
Specific Gravity (water=1):	Not Available
Lower Explosive Limit (%):	Not Available

EXTINGUISHING MEDIA
· Foam.
· Dry chemical powder.

FIRE FIGHTING
· Alert Emergency Responders and tell them location and nature of hazard.
· Wear breathing apparatus plus protective gloves.

GENERAL FIRE HAZARDS/HAZARDOUS COMBUSTIBLE PRODUCTS
· Combustible solid which burns but propagates flame with difficulty.
· Avoid generating dust, particularly clouds of dust in a confined or unventilated space as dusts may form an explosive mixture with air, and any source of ignition, i.e. flame or spark, will cause fire or explosion. Dust clouds generated by the fine grinding of the solid are a particular hazard; accumulations of fine dust may burn rapidly and fiercely if ignited.
Combustion products include: carbon monoxide (CO), carbon dioxide (CO_2), hydrogen chloride, phosgene, nitrogen oxides (NOx), sulfur oxides (SOx), other pyrolysis products typical of burning organic material.
May emit poisonous fumes.

FIRE INCOMPATIBILITY
■ Avoid contamination with oxidizing agents i.e. nitrates, oxidizing acids,chlorine bleaches, pool chlorine etc. as ignition may result.

PERSONAL PROTECTION
Glasses:
Chemical goggles.
Gloves:
Respirator:
Particulate

Section 6 - ACCIDENTAL RELEASE MEASURES

MINOR SPILLS
· Clean up waste regularly and abnormal spills immediately.
· Avoid breathing dust and contact with skin and eyes.
· Wear protective clothing, gloves, safety glasses and dust respirator.
· Use dry clean up procedures and avoid generating dust.
· Vacuum up or sweep up. NOTE: Vacuum cleaner must be fitted with an exhaust micro filter (HEPA type) (consider explosion-proof machines designed to be grounded during storage and use).
· Dampen with water to prevent dusting before sweeping.
· Place in suitable containers for disposal.
MAJOR SPILLS
■ Moderate hazard.
· CAUTION: Advise personnel in area.
· Alert Emergency Responders and tell them location and nature of hazard.

Section 7 - HANDLING AND STORAGE

PROCEDURE FOR HANDLING
· Avoid all personal contact, including inhalation.
· Wear protective clothing when risk of exposure occurs.
Empty containers may contain residual dust which has the potential to accumulate following settling. Such dusts may explode in the presence of an appropriate ignition source.
· Do NOT cut, drill, grind or weld such containers.

· In addition ensure such activity is not performed near full, partially empty or empty containers without appropriate workplace safety authorisation or permit.

RECOMMENDED STORAGE METHODS

■ Glass container.
· Polyethylene or polypropylene container.
· Check all containers are clearly labelled and free from leaks.

STORAGE REQUIREMENTS

· Store in original containers.
· Keep containers securely sealed.

Section 8 - EXPOSURE CONTROLS / PERSONAL PROTECTION

EXPOSURE CONTROLS

The following materials had no OELs on our records

• pioglitazone hydrochloride: CAS:112529-15-4

PERSONAL PROTECTION



RESPIRATOR

Particulate
Consult your EHS staff for recommendations

EYE

■ When handling very small quantities of the material eye protection may not be required.
For laboratory, larger scale or bulk handling or where regular exposure in an occupational setting occurs:
· Chemical goggles
· Face shield. Full face shield may be required for supplementary but never for primary protection of eyes
· Contact lenses may pose a special hazard; soft contact lenses may absorb and concentrate irritants. A written policy document, describing the wearing of lens or restrictions on use, should be created for each workplace or task. This should include a review of lens absorption and adsorption for the class of chemicals in use and an account of injury experience. Medical and first-aid personnel should be trained in their removal and suitable equipment should be readily available. In the event of chemical exposure, begin eye irrigation immediately and remove contact lens as soon as practicable. Lens should be removed at the first signs of eye redness or irritation - lens should be removed in a clean environment only after workers have washed hands thoroughly. [CDC NIOSH Current Intelligence Bulletin 59].

HANDS/FEET

■ Suitability and durability of glove type is dependent on usage. Important factors in the selection of gloves include: such as:
· frequency and duration of contact,
· chemical resistance of glove material,
· glove thickness and
· dexterity
Select gloves tested to a relevant standard (e.g. Europe EN 374, US F739).
· When prolonged or frequently repeated contact may occur, a glove with a protection class of 5 or higher (breakthrough time greater than 240 minutes according to EN 374) is recommended.
· When only brief contact is expected, a glove with a protection class of 3 or higher (breakthrough time greater than 60 minutes according to EN 374) is recommended.
· Contaminated gloves should be replaced.
Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturiser is recommended.
· Rubber gloves (nitrile or low-protein, powder-free latex). Employees allergic to latex gloves should use nitrile gloves in preference.
· Double gloving should be considered.
· PVC gloves.
· Protective shoe covers.
· Head covering.
Experience indicates that the following polymers are suitable as glove materials for protection against undissolved, dry solids, where abrasive particles are not present.
· polychloroprene
· nitrile rubber
· butyl rubber
· fluorocaoutchouc

· polyvinyl chloride
Gloves should be examined for wear and/ or degradation constantly.

OTHER

· For quantities up to 500 grams a laboratory coat may be suitable.
· For quantities up to 1 kilogram a disposable laboratory coat or coverall of low permeability is recommended. Coveralls should be buttoned at collar and cuffs.
· For quantities over 1 kilogram and manufacturing operations, wear disposable coverall of low permeability and disposable shoe covers.
· For manufacturing operations, air-supplied full body suits may be required for the provision of advanced respiratory protection.
· Eye wash unit.
· Ensure there is ready access to an emergency shower.
· For Emergencies: Vinyl suit.

ENGINEERING CONTROLS

■ Enclosed local exhaust ventilation is required at points of dust, fume or vapor generation.
HEPA terminated local exhaust ventilation should be considered at point of generation of dust, fumes or vapors.

Section 9 - PHYSICAL AND CHEMICAL PROPERTIES

PHYSICAL PROPERTIES

Does not mix with water.

State	Divided Solid	Molecular Weight	392.9
Melting Range (°F)	377.6- 383	Viscosity	Not Applicable
Boiling Range (°F)	Not Applicable	Solubility in water (g/L)	Immiscible
Flash Point (°F)	Not Available	pH (1% solution)	<7
Decomposition Temp (°F)	Not Available	pH (as supplied)	Not Applicable
Autoignition Temp (°F)	Not Available	Vapour Pressure (mmHG)	Negligible
Upper Explosive Limit (%)	Not Available	Specific Gravity (water=1)	Not Available
Lower Explosive Limit (%)	Not Available	Relative Vapor Density (air=1)	Not Applicable
Volatile Component (%vol)	Negligible	Evaporation Rate	Not Applicable

APPEARANCE

White to off-white crystalline, odourless powder; does not mix with water. Soluble in 5N acetic acid and dimethylformamide (DMF)

Section 10 - CHEMICAL STABILITY

CONDITIONS CONTRIBUTING TO INSTABILITY

· Presence of incompatible materials.
· Product is considered stable.

STORAGE INCOMPATIBILITY

■ Avoid reaction with oxidizing agents.

For incompatible materials - refer to Section 7 - Handling and Storage.

Section 11 - TOXICOLOGICAL INFORMATION

PIOGLITAZONE HYDROCHLORIDE

TOXICITY AND IRRITATION

PIOGLITAZONE HYDROCHLORIDE:
■ No significant acute toxicological data identified in literature search.

Section 12 - ECOLOGICAL INFORMATION

No data

Section 13 - DISPOSAL CONSIDERATIONS

Disposal Instructions

All waste must be handled in accordance with local, state and federal regulations.
¦ Legislation addressing waste disposal requirements may differ by country, state and/ or territory. Each user must refer to laws operating in their area. In some areas, certain wastes must be tracked.
A Hierarchy of Controls seems to be common - the user should investigate:
· Reduction
· Reuse
· Recycling
· Disposal (if all else fails)
This material may be recycled if unused, or if it has not been contaminated so as to make it unsuitable for its intended use. Shelf life considerations should also be applied in making decisions of this type. Note that properties of a material may change in use, and recycling or reuse may not always be appropriate.
DO NOT allow wash water from cleaning equipment to enter drains. Collect all wash water for treatment before disposal.
· Recycle wherever possible.
· Consult manufacturer for recycling options or consult Waste Management Authority for disposal if no suitable treatment or disposal facility can be identified.

Section 14 - TRANSPORTATION INFORMATION

NOT REGULATED FOR TRANSPORT OF DANGEROUS GOODS: DOT, IATA, IMDG

Section 15 - REGULATORY INFORMATION

No data for pioglitazone hydrochloride (CAS: , 112529-15-4)

Section 16 - OTHER INFORMATION

Reasonable care has been taken in the preparation of this information, but the author makes no warranty of merchantability or any other warranty, expressed or implied, with respect to this information. The author makes no representations and assumes no liability for any direct, incidental or consequential damages resulting from its use. For additional technical information please call our toxicology department on +800 CHEMCALL.

■ Classification of the preparation and its individual components has drawn on official and authoritative sources as well as independent review by the Chemwatch Classification committee using available literature references.
A list of reference resources used to assist the committee may be found at:
www.chemwatch.net/references.

■ The (M)SDS is a Hazard Communication tool and should be used to assist in the Risk Assessment. Many factors determine whether the reported Hazards are Risks in the workplace or other settings. Risks may be determined by reference to Exposures Scenarios. Scale of use, frequency of use and current or available engineering controls must be considered.

Issue Date: Jul-21-2009

Print Date:Dec-28-2010