## SECTION-1: Identification of the substance / mixture and the company / undertaking

| | |
|---|---|
| **Catalogue Number** | CS-EG-01064 |
| **Product Name** | Metformin hydrochloride (M0605000) |
| **CAS No.** | 1115-70-4 |
| **Category** | EP Standards |
| **Synonyms** | Diabetosan; Biguanide, 1,1-dimethyl-, monohydrochloride; Glucaminol |
| **Brand** | Clearsynth Labs Ltd. |
| **Identified uses** | Laboratory Chemicals |
| **Uses advised against** | Not available |
| **Company** | Clearsynth Labs Ltd.<br>Mumbai, India |
| **Emergency Phone #** | +91-22-245045900 |
| **REACH No.** | Not available |

## SECTION 2: Hazards identification

**Disclaimer:** This is sample MSDS. Please email **sales@clearsynth.com** for more details.

### 2.1 Classification of the substance or mixture-Regulation (EC) No 1272/2008:

Skin irritation (Category 2)
Serious eye damage/eye irritation (Category 2)
Acute toxicity (Category 4)

### 2.2 Label Elements

**Signal Word:** Warning

**Hazard Statement(s)**

| Code | Statement |
|---|---|
| H302 | Harmful if swallowed. |
| H315 | Causes skin irritation. |

| | |
|---|---|
| H319 | Causes serious eye irritation. |
| H335 | Not available |
| H412 | Not available |

**Precautionary Statement(s)**

| Code | Statement |
|---|---|
| P261 | Avoid breathing dust/fume/gas/mist/vapours/spray. |
| P264 | Wash hands thoroughly after handling. |
| P264+P265 | Not available |
| P270 | Not available |
| P271 | Use only outdoors or in a well-ventilated area. |
| P273 | Not available |
| P280 | Wear protective gloves/protective clothing/eye protection/face protection. |
| P301+P317 | Not available |
| P302+P352 | IF ON SKIN: Wash with plenty of water and soap. |
| P304+P340 | IF INHALED: Remove person to fresh air and keep comfortable for breathing. |
| P305+P351+P338 | IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if presen |
| P319 | Get medical help if you feel unwell. |
| P321 | Specific treatment (see … on this label). |
| P330 | Not available |
| P332+P317 | If skin irritation occurs: Get medical help. |
| P337+P317 | If eye irritation persists: Get medical help. |
| P362+P364 | Take off contaminated clothing and wash it before reuse. |
| P403+P233 | Store in a well-ventilated place. Keep container tightly closed. |
| P405 | Store locked up. |
| P501 | Dispose of contents/container in accordance with local/regional/national/international regulatio |

## SECTION 3: Composition / information on ingredients

3.1 Substance

Component : Metformin hydrochloride (M0605000)
CAS Number : 1115-70-4

Molecular Formula : C4H12ClN5
Molecular Weight : 165.62
Parent Chemical : Metformin
Synonyms : Diabetosan; Biguanide, 1,1-dimethyl-, monohydrochloride; Glucaminol
Concentration : Not available

## SECTION 4: First aid measures

Not available

## SECTION 5: Firefighting measures

Not available

## SECTION 6: Accidental release measures

Not available

## SECTION-7: Handling and storage

Not available

## SECTION 8: Exposure controls / personal protection

Not available

## SECTION 9: Physical and chemical properties

### 9.1 Information on basic physical and chemical properties

| Test | Result |
|---|---|
| Appearance | No data available |
| IR spectrum | No data available |
| pH | No data available |
| Solubility | No data available |

| Property | Value |
|---|---|
| a) Physical State | No data available |
| b) Color | No data available |

| Property | Value |
|---|---|
| c) Odor | No data available |
| d) pH | No data available |
| e) Vapour Pressure | No data available |
| f) Viscosity | No data available |
| g) Initial Boiling Point and boiling range | No data available |
| h) Melting Point / Freezing Point | No data available |
| i) Auto Ignition Temperature | No data available |
| j) Flash Point | No data available |
| k) Explosion Limit, Lower | No data available |
| l) Explosion Limit, Upper | No data available |
| m) Decomposition Temperature | No data available |
| n) Loss on Drying | No data available |
| o) Relative Density | No data available |
| p) Solubility (in DMSO) | No data available |
| q) Oxidizing Properties | No data available |

## SECTION 10: Stability and reactivity

Not available

## SECTION 11: Toxicological information

11.1 Information on toxicological effects
- Acute toxicity: IDENTIFICATION AND USE: Metformin is antihyperglycemic, not hypoglycemic agent. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses. HUMAN EXPOSURE AND TOXICITY: Metformin is believed to work by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissue to insulin. It does not stimulate insulin secretion, which explains the absence of hypoglycemia. Metformin also has beneficial effects on the plasma lipid concentrations and promotes weight loss. Accumulation of metformin may occur in patients with renal impairment, and such accumulation rarely can result in lactic acidosis, a serious, potentially fatal metabolic disease. Lactic acidosis constitutes a medical emergency requiring immediate hospitalization and treatment; lactic acidosis is characterized by elevated blood lactate concentrations, decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. Lactic acidosis also may occur in association with a variety of pathophysiologic conditions, including diabetes mellitus, and whenever substantial tissue hypoperfusion and hypoxemia exist. Approximately 50% of cases of metformin-associated lactic acidosis have been reported to be fatal. No evidence of mutagenicity or chromosomal damage was observed in in vitro test systems, including human lymphocytes assay. ANIMAL

STUDIES: No evidence of carcinogenic potential was seen in a 104-week study in male and female rats receiving metformin hydrochloride dosages up to and including 900 mg/kg daily or in a 91-week study in male and female mice receiving metformin hydrochloride at dosages up to and including 1500 mg/kg daily. Cancer preventive effect of metformin (MF) has been studied in mice, rats and hamsters. In the majority of cases metformin treatment leads to inhibition of carcinogenesis. No evidence of impaired fertility was observed in rats following administration of metformin hydrochloride dosages of 600 mg/kg daily. Reproduction studies in rats and rabbits given metformin hydrochloride dosages of 600 mg/kg daily have not revealed teratogenicity. No evidence of mutagenicity or chromosomal damage was observed in vivo in a micronucleus test in mice or in in vitro test systems, including microbial (Ames test) and mammalian (mouse lymphoma) assays. Pretreatment of rat cerebellar granule neurons with metformin greatly enhanced cell viability against glutamate-induced neurotoxicity. In aged male mice fed high-fat diet supplemented with metformin for 6 months, metformin decreased body fat composition and attenuated declines in motor function induced by a high fat diet. Performance in the Morris water maze test of hippocampal based memory function, showed that metformin prevented impairment of spatial reference memory associated with the high fat diet. ECOTOXICITY STUDIES: Adult fathead minnows (Pimephales promelas) were chronically exposed to metformin for 4 wk, at 40 ug/L. Metformin treatment induced significant up-regulation of messenger ribonucleic acid (mRNA) encoding the egg-protein vitellogenin in male fish, an indication of endocrine disruption. Metformin's mechanisms of action differ from other classes of oral antihyperglycemic agents. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by metformin of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for metformin's inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. Metformin administration also increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake. The rare side effect, lactic acidosis, is thought to be caused by decreased liver uptake of serum lactate, one of the substrates of gluconeogenesis. In those with healthy renal function, the slight excess is simply cleared. However, those with severe renal impairment may accumulate clinically significant serum lactic acid levels. Other conditions that may precipitate lactic acidosis include severe hepatic disease and acute/decompensated heart failure.

- Skin corrosion/irritation: No data available.
- Serious eye damage/eye irritation: No data available.
- Respiratory or skin sensitization: No data available.
- Germ cell mutagenicity: IDENTIFICATION AND USE: Metformin is antihyperglycemic, not hypoglycemic agent. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses. HUMAN EXPOSURE AND TOXICITY: Metformin is believed to work by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissue to insulin. It does not stimulate insulin secretion, which explains the absence of hypoglycemia. Metformin also has beneficial effects on the plasma lipid concentrations and promotes weight loss. Accumulation of metformin may occur in patients with renal impairment, and such accumulation rarely can result in lactic acidosis, a serious, potentially fatal metabolic disease. Lactic acidosis constitutes a medical emergency requiring immediate hospitalization and treatment; lactic acidosis is characterized by elevated blood lactate concentrations, decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. Lactic acidosis also may occur in association with a variety of pathophysiologic conditions, including diabetes mellitus, and whenever substantial tissue hypoperfusion and hypoxemia exist. Approximately 50% of cases of metformin-associated lactic acidosis have been reported to be fatal. No evidence of mutagenicity or chromosomal damage was observed in in vitro test systems, including human lymphocytes assay. ANIMAL STUDIES: No evidence of carcinogenic potential was seen in a 104-week study in male and female rats receiving

metformin hydrochloride dosages up to and including 900 mg/kg daily or in a 91-week study in male and female mice receiving metformin hydrochloride at dosages up to and including 1500 mg/kg daily. Cancer preventive effect of metformin (MF) has been studied in mice, rats and hamsters. In the majority of cases metformin treatment leads to inhibition of carcinogenesis. No evidence of impaired fertility was observed in rats following administration of metformin hydrochloride dosages of 600 mg/kg daily. Reproduction studies in rats and rabbits given metformin hydrochloride dosages of 600 mg/kg daily have not revealed teratogenicity. No evidence of mutagenicity or chromosomal damage was observed in vivo in a micronucleus test in mice or in in vitro test systems, including microbial (Ames test) and mammalian (mouse lymphoma) assays. Pretreatment of rat cerebellar granule neurons with metformin greatly enhanced cell viability against glutamate-induced neurotoxicity. In aged male mice fed high-fat diet supplemented with metformin for 6 months, metformin decreased body fat composition and attenuated declines in motor function induced by a high fat diet. Performance in the Morris water maze test of hippocampal based memory function, showed that metformin prevented impairment of spatial reference memory associated with the high fat diet. ECOTOXICITY STUDIES: Adult fathead minnows (Pimephales promelas) were chronically exposed to metformin for 4 wk, at 40 ug/L. Metformin treatment induced significant up-regulation of messenger ribonucleic acid (mRNA) encoding the egg-protein vitellogenin in male fish, an indication of endocrine disruption. - Carcinogenicity: IDENTIFICATION AND USE: Metformin is antihyperglycemic, not hypoglycemic agent. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses. HUMAN EXPOSURE AND TOXICITY: Metformin is believed to work by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissue to insulin. It does not stimulate insulin secretion, which explains the absence of hypoglycemia. Metformin also has beneficial effects on the plasma lipid concentrations and promotes weight loss. Accumulation of metformin may occur in patients with renal impairment, and such accumulation rarely can result in lactic acidosis, a serious, potentially fatal metabolic disease. Lactic acidosis constitutes a medical emergency requiring immediate hospitalization and treatment; lactic acidosis is characterized by elevated blood lactate concentrations, decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. Lactic acidosis also may occur in association with a variety of pathophysiologic conditions, including diabetes mellitus, and whenever substantial tissue hypoperfusion and hypoxemia exist. Approximately 50% of cases of metformin-associated lactic acidosis have been reported to be fatal. No evidence of mutagenicity or chromosomal damage was observed in in vitro test systems, including human lymphocytes assay. ANIMAL STUDIES: No evidence of carcinogenic potential was seen in a 104-week study in male and female rats receiving metformin hydrochloride dosages up to and including 900 mg/kg daily or in a 91-week study in male and female mice receiving metformin hydrochloride at dosages up to and including 1500 mg/kg daily. Cancer preventive effect of metformin (MF) has been studied in mice, rats and hamsters. In the majority of cases metformin treatment leads to inhibition of carcinogenesis. No evidence of impaired fertility was observed in rats following administration of metformin hydrochloride dosages of 600 mg/kg daily. Reproduction studies in rats and rabbits given metformin hydrochloride dosages of 600 mg/kg daily have not revealed teratogenicity. No evidence of mutagenicity or chromosomal damage was observed in vivo in a micronucleus test in mice or in in vitro test systems, including microbial (Ames test) and mammalian (mouse lymphoma) assays. Pretreatment of rat cerebellar granule neurons with metformin greatly enhanced cell viability against glutamate-induced neurotoxicity. In aged male mice fed high-fat diet supplemented with metformin for 6 months, metformin decreased body fat composition and attenuated declines in motor function induced by a high fat diet. Performance in the Morris water maze test of hippocampal based memory function, showed that metformin prevented impairment of spatial reference memory associated with the high fat diet. ECOTOXICITY STUDIES: Adult fathead minnows (Pimephales promelas) were chronically exposed to metformin for 4 wk, at 40 ug/L. Metformin treatment induced significant up-regulation of messenger ribonucleic acid (mRNA) encoding the egg-protein vitellogenin in male fish, an indication of endocrine disruption. /LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity/ Long-term use of anti-diabetic agents has become commonplace as rates of obesity, metabolic syndrome and diabetes continue to escalate. Metformin, a commonly

used anti-diabetic drug, has been shown to have many beneficial effects outside of its therapeutic regulation of glucose metabolism and insulin sensitivity. Studies on metformin's effects on the central nervous system are limited and predominantly consist of in vitro studies and a few in vivo studies with short-term treatment in relatively young animals; some provide support for metformin as a neuroprotective agent while others show evidence that metformin may be deleterious to neuronal survival. In this study, we examined the effect of long-term metformin treatment on brain neurotrophins and cognition in aged male C57Bl/6 mice. Mice were fed control (C), high-fat (HF) or a high-fat diet supplemented with metformin (HFM) for 6 months. Metformin decreased body fat composition and attenuated declines in motor function induced by a HF diet. Performance in the Morris water maze test of hippocampal based memory function, showed that metformin prevented impairment of spatial reference memory associated with the HF diet. Quantitative RT-PCR on brain homogenates revealed decreased transcription of BDNF, NGF and NTF3; however protein levels were not altered. Metformin treatment also decreased expression of the antioxidant pathway regulator, Nrf2. The decrease in transcription of neurotrophic factors and Nrf2 with chronic metformin intake, cautions of the possibility that extended metformin use may alter brain biochemistry in a manner that creates a vulnerable brain environment and warrants further investigation.
- Reproductive toxicity: IDENTIFICATION AND USE: Metformin is antihyperglycemic, not hypoglycemic agent. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses. HUMAN EXPOSURE AND TOXICITY: Metformin is believed to work by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissue to insulin. It does not stimulate insulin secretion, which explains the absence of hypoglycemia. Metformin also has beneficial effects on the plasma lipid concentrations and promotes weight loss. Accumulation of metformin may occur in patients with renal impairment, and such accumulation rarely can result in lactic acidosis, a serious, potentially fatal metabolic disease. Lactic acidosis constitutes a medical emergency requiring immediate hospitalization and treatment; lactic acidosis is characterized by elevated blood lactate concentrations, decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. Lactic acidosis also may occur in association with a variety of pathophysiologic conditions, including diabetes mellitus, and whenever substantial tissue hypoperfusion and hypoxemia exist. Approximately 50% of cases of metformin-associated lactic acidosis have been reported to be fatal. No evidence of mutagenicity or chromosomal damage was observed in in vitro test systems, including human lymphocytes assay. ANIMAL STUDIES: No evidence of carcinogenic potential was seen in a 104-week study in male and female rats receiving metformin hydrochloride dosages up to and including 900 mg/kg daily or in a 91-week study in male and female mice receiving metformin hydrochloride at dosages up to and including 1500 mg/kg daily. Cancer preventive effect of metformin (MF) has been studied in mice, rats and hamsters. In the majority of cases metformin treatment leads to inhibition of carcinogenesis. No evidence of impaired fertility was observed in rats following administration of metformin hydrochloride dosages of 600 mg/kg daily. Reproduction studies in rats and rabbits given metformin hydrochloride dosages of 600 mg/kg daily have not revealed teratogenicity. No evidence of mutagenicity or chromosomal damage was observed in vivo in a micronucleus test in mice or in in vitro test systems, including microbial (Ames test) and mammalian (mouse lymphoma) assays. Pretreatment of rat cerebellar granule neurons with metformin greatly enhanced cell viability against glutamate-induced neurotoxicity. In aged male mice fed high-fat diet supplemented with metformin for 6 months, metformin decreased body fat composition and attenuated declines in motor function induced by a high fat diet. Performance in the Morris water maze test of hippocampal based memory function, showed that metformin prevented impairment of spatial reference memory associated with the high fat diet. ECOTOXICITY STUDIES: Adult fathead minnows (Pimephales promelas) were chronically exposed to metformin for 4 wk, at 40 ug/L. Metformin treatment induced significant up-regulation of messenger ribonucleic acid (mRNA) encoding the egg-protein vitellogenin in male fish, an indication of endocrine disruption. /LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Maternal obesity may program the fetus and increase the susceptibility of the offspring to adult diseases. Metformin crosses the placenta and has been associated with decreased inflammation and reversal of fatty liver in obese leptin-deficient mice. We investigated the

effects of metformin on maternal and fetal lipid metabolism and hepatic inflammation using a rat model of diet-induced obesity during pregnancy. Female Wistar rats (6-7 weeks old) were fed normal or high calorie diets for 5 weeks. After mating with normal-diet fed males, half of the high calorie-fed dams received metformin (300 mg/kg, daily); dams (8 per group) continued diets through gestational day 19. Maternal and fetal livers and fetal brains were analyzed for fatty acids and for fatty acid metabolism-related gene expression. Data were analyzed by ANOVA followed by Dunnett's post hoc testing. When compared to control-lean maternal livers, obesogenic-diet-exposed maternal livers showed significantly higher saturated fatty acids (14:0 and 16:0) and monounsaturated fatty acids (16:1n7 and 18:1n9) and lower polyunsaturated (18:2n6 and 20:4n6 [arachidonic acid]) and anti-inflammatory n3 polyunsaturated fatty acids (18:3n3 and 22:6n3 [docosahexaenoic acid]) ($p<0.05$). Metformin did not affect diet-induced changes in maternal livers. Fetal livers exposed to the high calorie diet showed significantly increased saturated fatty acids (18:0) and monounsaturated fatty acids (18:1n9 and 18:1n7) and decreased polyunsaturated fatty acids (18:2n6, 20:4n6 and 22:6n3) and anti-inflammatory n3 polyunsaturated fatty acids, along with increased gene expression of fatty acid metabolism markers (Fasn, D5d, D6d, Scd1, Lxra). Metformin significantly attenuated diet-induced inflammation and 18:1n9 and 22:6n3 in fetal livers, as well as n3 fatty acids ($p<0.05$). Prenatal obesogenic diet exposure significantly increased fetal liver IFNgamma levels ($p<0.05$), which was reversed by maternal metformin treatment ($p<0.05$). Consumption of a high calorie diet significantly affected maternal and fetal fatty acid metabolism. It reduced anti-inflammatory polyunsaturated fatty acids in maternal and fetal livers, altered gene expression of fatty acid metabolism markers, and induced inflammation in the fetal livers. Prenatal metformin attenuated some diet-induced fatty acid changes and inflammation in the fetal livers without affecting maternal livers, suggesting that maternal metformin may impact fetal/neonatal fatty acid/lipid metabolism.
- STOT-single exposure: No data available.
- STOT-repeated exposure: IDENTIFICATION AND USE: Metformin is antihyperglycemic, not hypoglycemic agent. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses. HUMAN EXPOSURE AND TOXICITY: Metformin is believed to work by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissue to insulin. It does not stimulate insulin secretion, which explains the absence of hypoglycemia. Metformin also has beneficial effects on the plasma lipid concentrations and promotes weight loss. Accumulation of metformin may occur in patients with renal impairment, and such accumulation rarely can result in lactic acidosis, a serious, potentially fatal metabolic disease. Lactic acidosis constitutes a medical emergency requiring immediate hospitalization and treatment; lactic acidosis is characterized by elevated blood lactate concentrations, decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. Lactic acidosis also may occur in association with a variety of pathophysiologic conditions, including diabetes mellitus, and whenever substantial tissue hypoperfusion and hypoxemia exist. Approximately 50% of cases of metformin-associated lactic acidosis have been reported to be fatal. No evidence of mutagenicity or chromosomal damage was observed in in vitro test systems, including human lymphocytes assay. ANIMAL STUDIES: No evidence of carcinogenic potential was seen in a 104-week study in male and female rats receiving metformin hydrochloride dosages up to and including 900 mg/kg daily or in a 91-week study in male and female mice receiving metformin hydrochloride at dosages up to and including 1500 mg/kg daily. Cancer preventive effect of metformin (MF) has been studied in mice, rats and hamsters. In the majority of cases metformin treatment leads to inhibition of carcinogenesis. No evidence of impaired fertility was observed in rats following administration of metformin hydrochloride dosages of 600 mg/kg daily. Reproduction studies in rats and rabbits given metformin hydrochloride dosages of 600 mg/kg daily have not revealed teratogenicity. No evidence of mutagenicity or chromosomal damage was observed in vivo in a micronucleus test in mice or in in vitro test systems, including microbial (Ames test) and mammalian (mouse lymphoma) assays. Pretreatment of rat cerebellar granule neurons with metformin greatly enhanced cell viability against glutamate-induced neurotoxicity. In aged male mice fed high-fat diet supplemented with metformin for 6 months, metformin decreased body fat composition and attenuated declines in motor function induced by a high fat diet. Performance in the Morris water maze test of hippocampal

based memory function, showed that metformin prevented impairment of spatial reference memory associated with the high fat diet. ECOTOXICITY STUDIES: Adult fathead minnows (Pimephales promelas) were chronically exposed to metformin for 4 wk, at 40 ug/L. Metformin treatment induced significant up-regulation of messenger ribonucleic acid (mRNA) encoding the egg-protein vitellogenin in male fish, an indication of endocrine disruption. /HUMAN EXPOSURE STUDIES/ The link between metformin and lactic acidosis in metformin therapy may be causal, associated or coincidental. Our objective was to investigate this link by studying and analyzing published reports of so-called 'metformin-associated lactic acidosis'. Systematically searched in the BIOSIS, DERWENT, EMBASE, MEDLINE, and PASCAL databases of the English language and non-English language literature for all reports of so-called 'metformin-associated lactic acidosis' published from May 1995 through January 2000. Reports related to metformin overdose or contrast media-induced renal failure /were not included/. Metformin accumulation and concurrent pathologies were critically reviewed as precipitating factors for metformin-associated lactic acidosis. Metformin accumulation was assessed in terms of the recorded measurement of metformin concentration in plasma or, if not available, by the presence of primary renal failure, i.e. renal failure that was not secondary to a shock syndrome. We found 21 reports describing a total of 26 patients. Criteria of lactic acidosis (lactate > 5 mmol/L, pH <or= 7.35) were not met in four patients. In the remaining 22 patients, plasma metformin concentration was determined in only four, of whom one had a normal value. In the 18 patients with lactic acidosis where plasma metformin concentration data was not available, the presence of primary renal failure was absent or unlikely in six patients, uncertain in two, and likely or proven in 14. With regard to these 14 patients, the precipitating factor was metformin in 12 patients (in the context of renal failure either chronic or acute) and intercurrent pathologies in two others. Overall, lactic acidosis was either absent (n = 4), precipitated by concurrent pathology (n = 8), precipitated by metformin without apparent associated pathology (n = 12) or of uncertain origin (n = 2). Death occurred 10 times but only once in the 12 patients with metformin-induced lactic acidosis and this was not related to metformin. While the term 'metformin-associated lactic acidosis' is commonly used to depict all situations of lactic acidosis in metformin therapy, true metformin-associated lactic acidosis, i.e. one which refers to metformin and concurrent pathologies as co-precipitating factors, was never observed in the studied reports ... /Salt not specified/
- Aspiration hazard: No data available.

Likely routes of exposure
- /SIGNS AND SYMPTOMS/ Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases.

Symptoms related to the physical, chemical and toxicological characteristics
- IDENTIFICATION AND USE: Metformin is antihyperglycemic, not hypoglycemic agent. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses. HUMAN EXPOSURE AND TOXICITY: Metformin is believed to work by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissue to insulin. It does not stimulate insulin secretion, which explains the absence of hypoglycemia. Metformin also has beneficial effects on the plasma lipid concentrations and promotes weight loss. Accumulation of metformin may occur in patients with renal impairment, and such accumulation rarely can result in lactic acidosis, a serious, potentially fatal metabolic disease. Lactic acidosis constitutes a medical emergency requiring immediate hospitalization and treatment; lactic acidosis is characterized by elevated blood lactate concentrations, decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. Lactic acidosis also may occur in association with a variety of pathophysiologic conditions, including diabetes mellitus, and whenever substantial tissue hypoperfusion and hypoxemia exist. Approximately 50% of cases of metformin-associated lactic acidosis have been reported to be fatal. No evidence of mutagenicity or chromosomal damage was observed in in vitro test systems, including human lymphocytes assay. ANIMAL STUDIES: No

evidence of carcinogenic potential was seen in a 104-week study in male and female rats receiving metformin hydrochloride dosages up to and including 900 mg/kg daily or in a 91-week study in male and female mice receiving metformin hydrochloride at dosages up to and including 1500 mg/kg daily. Cancer preventive effect of metformin (MF) has been studied in mice, rats and hamsters. In the majority of cases metformin treatment leads to inhibition of carcinogenesis. No evidence of impaired fertility was observed in rats following administration of metformin hydrochloride dosages of 600 mg/kg daily. Reproduction studies in rats and rabbits given metformin hydrochloride dosages of 600 mg/kg daily have not revealed teratogenicity. No evidence of mutagenicity or chromosomal damage was observed in vivo in a micronucleus test in mice or in in vitro test systems, including microbial (Ames test) and mammalian (mouse lymphoma) assays. Pretreatment of rat cerebellar granule neurons with metformin greatly enhanced cell viability against glutamate-induced neurotoxicity. In aged male mice fed high-fat diet supplemented with metformin for 6 months, metformin decreased body fat composition and attenuated declines in motor function induced by a high fat diet. Performance in the Morris water maze test of hippocampal based memory function, showed that metformin prevented impairment of spatial reference memory associated with the high fat diet. ECOTOXICITY STUDIES: Adult fathead minnows (Pimephales promelas) were chronically exposed to metformin for 4 wk, at 40 ug/L. Metformin treatment induced significant up-regulation of messenger ribonucleic acid (mRNA) encoding the egg-protein vitellogenin in male fish, an indication of endocrine disruption.

## SECTION 12: Ecological information

Not available

## SECTION 13: Disposal considerations

Not available

## SECTION 14: Transport information

Not available

## SECTION 15: Regulatory information

Not available

## SECTION 16: Other information

Not available

## DISCLAIMER

This MSDS is system-generated. Please verify and confirm all data, statements, and values with the Support Team before use or distribution.