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

Catalogue Number	CS-IP-00157
Product Name	Valproic acid for system suitability IPRS containing impurity K
CAS No.	99-66-1
Category	Impurity
Synonyms	Valeric acid, 2-propyl- (6CI, 7CI, 8CI); 2,2-Di-n-propylacetic acid; 2-Propylvaleric acid; 4-Heptanecarboxylic acid
Brand	Clearsynth Labs Ltd.
Identified uses	Laboratory Chemicals
Uses advised against	Not available
Company	Clearsynth Labs Ltd. 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.

H318	Causes serious eye damage.
H319	Causes serious eye irritation.
H335	Not available
H360	Not available
H336	Not available
H362	Not available
H370	Not available
H372	Not available

Precautionary Statement(s)

Code	Statement
P203	Not available
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.
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
P305+P354+P338	Not available
P317	Not available
P318	Not available
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
P260	Not available
P263	Not available
P308+P316	Not available

SECTION 3: Composition / information on ingredients

3.1 Substance

Component : Valproic acid for system suitability IPRS containing impurity K
CAS Number : 99-66-1
Molecular Formula : C8H16O2
Molecular Weight : 144.21
Parent Chemical : Valproic Acid
Synonyms : Valeric acid, 2-propyl- (6CI, 7CI, 8CI); 2,2-Di-n-propylacetic acid; 2-Propylvaleric acid; 4-Heptanecarboxylic acid
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
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: Valproic acid is a colorless to pale yellow viscous liquid. Valproic acid is an antiepileptic drug and is used solely or in combination with other anticonvulsants in the treatment of simple (petit mal) and complex absence seizures. Valproic acid may be effective against myoclonic and atonic seizures in young children. HUMAN EXPOSURE AND TOXICITY: After oral administration, the drug is rapidly absorbed from the gastrointestinal tract and metabolized in the liver. Fatal hepatic failure has been reported in patients on valproic acid therapy, especially those on chronic use. Pancreatitis has also been reported in patients receiving normal therapeutic dosage. Reports showed that acute toxicity is rare, and usually follows a benign course. The most commonly reported adverse effects are anorexia, nausea and vomiting. Central nervous system effects include drowsiness, possibly apathy and withdrawal, confusion, restlessness, hyperactivity. Less frequently, seizures and coma may occur. Sedative effects are more pronounced when drug is used together with other anti-epileptic agents. Hematopoietic system effects include thrombocytopenia, abnormal bleeding time and partial thromboplastin time with decreased fibrinogen levels and prolonged prothrombin time leading to bruising, petechiae, hematoma, and epistaxis. The drug can induce pruritic macular rashes and transient alopecia. Altered thyroid functions was described. Death is rare but if it occurs it results from cardiopulmonary arrest secondary to hepatic failure. Safe use of valproic acid during pregnancy has not been established. Although several reports suggest an association between the use of valproic acid in pregnant epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women, a causal relationship remains to be established. The drug crosses the placental barrier and has been found in breast milk. The mechanism of action of valproic acid is unknown. Effects of the drug may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter GABA. ANIMAL STUDIES: Animal studies have shown that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism. Results of one study indicate the drug inhibits neuronal activity by increasing potassium conductance. In animals, valproic acid protects against seizure induced by electrical stimulation, as well as those induced by pentylenetetrazol. In 2 year rat and chronic mouse studies, an increased incidence of subcutaneous fibrosarcoma occurred in male rats at the higher dosage level and a dose related trend for an increased incidence of benign pulmonary adenomas was observed in male mice. The importance of these findings to humans is not known. Adverse fetal effects have been observed in reproduction studies in rats and mice. Studies have not shown any evidence of mutagenic potential for the drug. Acute VPA toxicity can lead to central nervous system (CNS) depression, metabolic acidosis, hypernatremia, hypoglycemia, hyperammonemia, hepatotoxicity, pancreatitis, or multiorgan failure. Signs and Symptoms of Overdose CNS depression might manifest as drowsiness, confusion, ataxia, nystagmus, diplopia, dysarthria, tremor, or coma. Metabolic acidosis can present with tachypnea, hypotension, arrhythmias, or shock. Hypernatremia can manifest as thirst, dry mucous membranes, agitation, seizures, or coma. Hyperammonemia can manifest as lethargy, vomiting, ataxia, or encephalopathy. Hepatotoxicity can be evident through elevated liver enzymes. Management of Overdose Discontinuation of VPA: The initial step to managing VPA toxicity is discontinuing the medication. This will allow for the removal of the drug and decrease the risk of additional toxicity. Supportive care: Supportive care is crucial in managing VPA toxicity. This includes monitoring vital signs, maintaining airway patency, administering respiratory support when needed, and addressing fluid and electrolyte imbalances. Enhanced elimination: In cases of severe toxicity or significantly elevated VPA levels, procedures such as hemodialysis or hemoperfusion may be considered. These methods aid in expediting the removal of VPA from the bloodstream. Treatment: The patient might require transfer to the medical intensive care unit for ongoing monitoring and care. Stabilizing any life-threatening issues is the top priority. Initiate early intravenous (IV) access to administer fluids to patients experiencing hypotension. Administer isotonic crystalloid boluses intravenously to those with low blood

pressure. In severe cases, vasopressors might be required. Those experiencing significant respiratory depression could need endotracheal intubation and mechanical support for breathing. In cases of seizures resulting from valproate toxicity, benzodiazepines should be given. It has been reported naloxone administration, in doses between 0.8 mg and 2 mg, can counteract central nervous system depression in certain instances of valproate poisoning. If the patient arrives within 2 hours following a valproate overdose, a single dose of activated charcoal is used for gastrointestinal decontamination. The typical dosage for activated charcoal is 1 g/kg of patient weight. Do not administer to sedated patients when the airway can not be safeguarded. Since valproate comes in enteric-coated and extended-release forms that are absorbed slowly, activated charcoal may be administered after the 2-hour mark post-ingestion. Consider administering L-carnitine to patients who arrive with an acute valproic acid overdose accompanied by changes in mental status. The initial dose of L-carnitine should be 100 mg/kg, administered intravenously. The treatment regimen for L-carnitine then proceeds with doses of 50 mg/kg every 8 hours. It is also essential to concurrently monitor serum ammonia levels; L-carnitine treatment may be discontinued once these levels begin to decline. In cases of acute valproate overdose where patients are asymptomatic, a preventive oral dose of carnitine is recommended at 100 mg/kg/day, divided into four daily doses.
- 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: Valproic acid is a colorless to pale yellow viscous liquid. Valproic acid is an antiepileptic drug and is used solely or in combination with other anticonvulsants in the treatment of simple (petit mal) and complex absence seizures. Valproic acid may be effective against myoclonic and atonic seizures in young children. HUMAN EXPOSURE AND TOXICITY: After oral administration, the drug is rapidly absorbed from the gastrointestinal tract and metabolized in the liver. Fatal hepatic failure has been reported in patients on valproic acid therapy, especially those on chronic use. Pancreatitis has also been reported in patients receiving normal therapeutic dosage. Reports showed that acute toxicity is rare, and usually follows a benign course. The most commonly reported adverse effects are anorexia, nausea and vomiting. Central nervous system effects include drowsiness, possibly apathy and withdrawal, confusion, restlessness, hyperactivity. Less frequently, seizures and coma may occur. Sedative effects are more pronounced when drug is used together with other anti-epileptic agents. Hematopoietic system effects include thrombocytopenia, abnormal bleeding time and partial thromboplastin time with decreased fibrinogen levels and prolonged prothrombin time leading to bruising, petechiae, hematoma, and epistaxis. The drug can induce pruritic macular rashes and transient alopecia. Altered thyroid functions was described. Death is rare but if it occurs it results from cardiopulmonary arrest secondary to hepatic failure. Safe use of valproic acid during pregnancy has not been established. Although several reports suggest an association between the use of valproic acid in pregnant epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women, a causal relationship remains to be established. The drug crosses the placental barrier and has been found in breast milk. The mechanism of action of valproic acid is unknown. Effects of the drug may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter GABA. ANIMAL STUDIES: Animal studies have shown that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism. Results of one study indicate the drug inhibits neuronal activity by increasing potassium conductance. In animals, valproic acid protects against seizure induced by electrical stimulation, as well as those induced by pentylenetetrazol. In 2 year rat and chronic mouse studies, an increased incidence of subcutaneous fibrosarcoma occurred in male rats at the higher dosage level and a dose related trend for an increased incidence of benign pulmonary adenomas was observed in male mice. The importance of these findings to humans is not known. Adverse fetal effects have been observed in reproduction studies in rats and mice. Studies have not shown any evidence of mutagenic potential for the drug. /GENOTOXICITY/ Valproic acid (VPA) has been used as anticonvulsants, however, it induces hepatotoxicity such as microvesicular steatosis and necrosis in the liver. To explore the mechanisms of

VPA-induced steatosis, /this study/ profiled the gene expression patterns of the mouse liver that were altered by treatment with VPA using microarray analysis. VPA was orally administered as a single dose of 100 mg/kg (low-dose) or 1000 mg/kg (high-dose) to ICR mice and the animals were killed at 6, 24, or 72 hr after treatment. Serum alanine aminotransferase and aspartate aminotransferase levels were not significantly altered in the experimental animals. However, symptoms of steatosis were observed at 72 hr with low-dose and at 24 hr and 72 hr with high-dose. After microarray data analysis, 1910 genes were selected by two-way ANOVA ($P<0.05$) as VPA-responsive genes. Hierarchical clustering revealed that gene expression changes depended on the time rather than the dose of VPA treatment. Gene profiling data showed striking changes in the expression of genes associated with lipid, fatty acid, and steroid metabolism, oncogenesis, signal transduction, and development. Functional categorization of 1156 characteristically up- and down-regulated genes (cutoff >1.5-fold) revealed that 60 genes were involved in lipid metabolism that was interconnected with biological pathways for biosynthesis of triglyceride and cholesterol, catabolism of fatty acid, and lipid transport. This gene expression profile may be associated with the known steatogenic hepatotoxicity of VPA and it may provide useful information for prediction of hepatotoxicity of unknown chemicals or new drug candidates through pattern recognition.
- Carcinogenicity: /ALTERNATIVE and IN VITRO TESTS/ Human studies of neurodevelopment suggest that children exposed in utero to certain antiepileptic drugs (AEDs) suffer a variety of brain-behavior sequelae, such as neural tube defects, developmental delays, cognitive deficits, etc. Valproic acid (VPA), a commonly used AED, has greater risk for these side effects compared with other AEDs. However, the detailed molecular mechanisms underlying this developmental neurotoxicity of VPA is unclear despite previous research demonstrating that VPA could induce widespread apoptotic neurodegeneration in developing brains of animal models. This study characterizes the role of astrocytes in VPA-induced neurodegeneration. In developing brains, /this study/ evaluated the developmental neurotoxicity of VPA on differentiating neurons and astrocytes from neural progenitor cells cultured from the hippocampus of human fetuses. Exposure of a neuron-enriched culture to VPA at 250uM or 500uM did not cause neuronal apoptosis, but at 1mM and 7 days exposure, a slight increase in the percentage of apoptotic cells was observed. In contrast, VPA at 250 uM to 1mM, selectively induced neuronal apoptosis in a neuron-astrocyte mixed cell culture model. The VPA-treated astrocytes showed morphological changes, and the level of tumor necrosis factor-alpha (TNF-alpha) was elevated in the supernatant. Both neuronal apoptosis and TNF-alpha release from astrocytes increased with concentration and exposure time to VPA, suggesting a synergism between the two cell types. Treatment of the neuron-astrocyte mixed culture exposed to VPA with TNF-alpha antibody partly prevented neuronal apoptosis, while the addition of exogenous TNF-alpha induced apoptosis in both cultures. Moreover, this pro-apoptotic effect was specific to VPA, as another AED, valpromide, failed to mimic this pro-apoptotic effect, nor did an inhibitor of histone deacetylase (iHDAC), sodium butyrate (NaB). /This reports/ a novel finding that astrocytes participate in VPA induced neurodegeneration by releasing TNF-alpha. /HUMAN EXPOSURE STUDIES/ Valproic acid (VPA) inhibits histone deacetylase and has been reported to induce apoptosis in glioma. /This study reports on/ 44 heavily pretreated pediatric patients with high-grade glioma or diffuse intrinsic pontine glioma who received VPA as oral continues maintenance treatment with individual dose adaptation. The tumor status when starting the drug was: no measurable disease in 12, measurable but stable disease in 12, and measurable progressive disease in 22 patients. Average trough blood levels of VPA were 99 mg/L. The most frequent complaint was somnolence (three patients), but no severe toxicity was reported. One relapse patient responded, early progression of disease was observed in three frontline patients and in six relapsed patients. Median overall survival duration for all patients was 1.33 years, with large differences between first-line (5-year overall survival, 44%) and relapse therapy (5-year overall survival, 14%). This shows that valproate is safe in this patient population. The moderate tumor efficacy encourages studying the drug further as an element of multi-agent protocols.
- Reproductive toxicity: IDENTIFICATION AND USE: Valproic acid is a colorless to pale yellow viscous liquid. Valproic acid is an antiepileptic drug and is used solely or in combination with other anticonvulsants in the treatment

of simple (petit mal) and complex absence seizures. Valproic acid may be effective against myoclonic and atonic seizures in young children. HUMAN EXPOSURE AND TOXICITY: After oral administration, the drug is rapidly absorbed from the gastrointestinal tract and metabolized in the liver. Fatal hepatic failure has been reported in patients on valproic acid therapy, especially those on chronic use. Pancreatitis has also been reported in patients receiving normal therapeutic dosage. Reports showed that acute toxicity is rare, and usually follows a benign course. The most commonly reported adverse effects are anorexia, nausea and vomiting. Central nervous system effects include drowsiness, possibly apathy and withdrawal, confusion, restlessness, hyperactivity. Less frequently, seizures and coma may occur. Sedative effects are more pronounced when drug is used together with other anti-epileptic agents. Hematopoietic system effects include thrombocytopenia, abnormal bleeding time and partial thromboplastin time with decreased fibrinogen levels and prolonged prothrombin time leading to bruising, petechiae, hematoma, and epistaxis. The drug can induce pruritic macular rashes and transient alopecia. Altered thyroid functions was described. Death is rare but if it occurs it results from cardiopulmonary arrest secondary to hepatic failure. Safe use of valproic acid during pregnancy has not been established. Although several reports suggest an association between the use of valproic acid in pregnant epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women, a causal relationship remains to be established. The drug crosses the placental barrier and has been found in breast milk. The mechanism of action of valproic acid is unknown. Effects of the drug may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter GABA. ANIMAL STUDIES: Animal studies have shown that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism. Results of one study indicate the drug inhibits neuronal activity by increasing potassium conductance. In animals, valproic acid protects against seizure induced by electrical stimulation, as well as those induced by pentylenetetrazol. In 2 year rat and chronic mouse studies, an increased incidence of subcutaneous fibrosarcoma occurred in male rats at the higher dosage level and a dose related trend for an increased incidence of benign pulmonary adenomas was observed in male mice. The importance of these findings to humans is not known. Adverse fetal effects have been observed in reproduction studies in rats and mice. Studies have not shown any evidence of mutagenic potential for the drug. Valproic Acid binds to and inhibits GABA transaminase. This leads to increased brain concentrations of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the CNS. Acute poisoning by VPA can lead to severe CNS depression including coma, confusion, somnolence, dizziness or hallucinations. Hypotension, respiratory depression and hypo/hyperthermia are also common. VPA is also hepatotoxic, which is likely due to its mitochondrial toxicity. VPA appears to exert its mitochondrial toxicity by impairing mitochondrial functions leading to oxidative stress and cytochrome c expulsion, which leads to apoptosis (A15078). VPA is contraindicated in pregnancy due to its teratogenicity. VPA is a known folate antagonist, which can cause neural tube defects in developing fetuses. Thus, folic acid supplements in pregnant women may alleviate teratogenic problems associated with VPA use. VPA and its metabolites inhibit the biosynthesis of carnitine by decreasing the concentration of alpha-ketoglutarate (through direct inhibition of alpha-ketoglutarate dehydrogenase) and may contribute to carnitine deficiency. It is postulated that carnitine supplementation may increase the beta-oxidation of VPA, thereby limiting cytosolic omega-oxidation and the production of toxic metabolites that are involved in liver toxicity and ammonia accumulation. VPA-induced hepatotoxicity and hyperammonemic encephalopathy may be promoted either by a pre-existing carnitine deficiency or by deficiency induced by VPA per se. VPA has been shown to downregulate levels of superoxide dismutase (SOD), glutathione (GSH), histone deacetylase (HDAC) and folate. It has also been shown to upregulate H2O2 and homocysteine. Elevated levels of H2O2 negatively affect the NADPH reducing system for dihydrofolate reductase (DHFR) and methylene tetrahydrofolate reductase (MTHFR) (A15079).

- STOT-single exposure: No data available.
- STOT-repeated exposure: IDENTIFICATION AND USE: Valproic acid is a colorless to pale yellow viscous liquid. Valproic acid is an antiepileptic drug and is used solely or in combination with other anticonvulsants in the treatment of simple (petit mal) and complex absence seizures. Valproic acid may be effective against myoclonic and atonic

seizures in young children. HUMAN EXPOSURE AND TOXICITY: After oral administration, the drug is rapidly absorbed from the gastrointestinal tract and metabolized in the liver. Fatal hepatic failure has been reported in patients on valproic acid therapy, especially those on chronic use. Pancreatitis has also been reported in patients receiving normal therapeutic dosage. Reports showed that acute toxicity is rare, and usually follows a benign course. The most commonly reported adverse effects are anorexia, nausea and vomiting. Central nervous system effects include drowsiness, possibly apathy and withdrawal, confusion, restlessness, hyperactivity. Less frequently, seizures and coma may occur. Sedative effects are more pronounced when drug is used together with other anti-epileptic agents. Hematopoietic system effects include thrombocytopenia, abnormal bleeding time and partial thromboplastin time with decreased fibrinogen levels and prolonged prothrombin time leading to bruising, petechiae, hematoma, and epistaxis. The drug can induce pruritic macular rashes and transient alopecia. Altered thyroid functions was described. Death is rare but if it occurs it results from cardiopulmonary arrest secondary to hepatic failure. Safe use of valproic acid during pregnancy has not been established. Although several reports suggest an association between the use of valproic acid in pregnant epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women, a causal relationship remains to be established. The drug crosses the placental barrier and has been found in breast milk. The mechanism of action of valproic acid is unknown. Effects of the drug may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter GABA. ANIMAL STUDIES: Animal studies have shown that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism. Results of one study indicate the drug inhibits neuronal activity by increasing potassium conductance. In animals, valproic acid protects against seizure induced by electrical stimulation, as well as those induced by pentylenetetrazol. In 2 year rat and chronic mouse studies, an increased incidence of subcutaneous fibrosarcoma occurred in male rats at the higher dosage level and a dose related trend for an increased incidence of benign pulmonary adenomas was observed in male mice. The importance of these findings to humans is not known. Adverse fetal effects have been observed in reproduction studies in rats and mice. Studies have not shown any evidence of mutagenic potential for the drug. Valproic acid causes hyperammonemia, which can lead to brain damage. Rarely, it can cause blood dyscrasia, impaired liver function, jaundice, thrombocytopenia, and prolonged coagulation times. In about 5% of pregnant users, valproic acid will cross the placenta and cause congenital anomalies. Valproic acid may also cause acute hematological toxicities, especially in children, including rare reports of myelodysplasia and acute leukemia-like syndrome (L1132). May cause a potentially dangerous rash that may develop into Stevens Johnson syndrome, an extremely rare but potentially fatal skin disease. Acute overdoses of VPA can lead to hypo/hyperthermia, tachycardia, hypotension, respiratory depression, coma, confusion, somnolence, dizziness, headaches and cerebral edema. Extended use of VPA can cause hepatotoxicity. Allopecia, anorexia, renal failure, tremors and miosis are also associated with chronic toxicity. VPA is a known teratogen (due to folate antagonism). The teratogenicity of VPA is mostly found at genetic and somatic levels, causing teratogenesis involving neural tube defects (NTDs), anencephaly, lumbosacral meningomyelocele, and leg dysfunction due to spina bifida aperta.
- Aspiration hazard: No data available.

Likely routes of exposure
- Acute VPA toxicity can lead to central nervous system (CNS) depression, metabolic acidosis, hypernatremia, hypoglycemia, hyperammonemia, hepatotoxicity, pancreatitis, or multiorgan failure. Signs and Symptoms of Overdose CNS depression might manifest as drowsiness, confusion, ataxia, nystagmus, diplopia, dysarthria, tremor, or coma. Metabolic acidosis can present with tachypnea, hypotension, arrhythmias, or shock. Hypernatremia can manifest as thirst, dry mucous membranes, agitation, seizures, or coma. Hyperammonemia can manifest as lethargy, vomiting, ataxia, or encephalopathy. Hepatotoxicity can be evident through elevated liver enzymes. Management of Overdose Discontinuation of VPA: The initial step to managing VPA toxicity is discontinuing the medication. This will allow for the removal of the drug and decrease the risk of additional toxicity. Supportive care: Supportive care is crucial in managing VPA toxicity. This includes monitoring vital signs, maintaining airway patency,

administering respiratory support when needed, and addressing fluid and electrolyte imbalances. Enhanced elimination: In cases of severe toxicity or significantly elevated VPA levels, procedures such as hemodialysis or hemoperfusion may be considered. These methods aid in expediting the removal of VPA from the bloodstream. Treatment: The patient might require transfer to the medical intensive care unit for ongoing monitoring and care. Stabilizing any life-threatening issues is the top priority. Initiate early intravenous (IV) access to administer fluids to patients experiencing hypotension. Administer isotonic crystalloid boluses intravenously to those with low blood pressure. In severe cases, vasopressors might be required. Those experiencing significant respiratory depression could need endotracheal intubation and mechanical support for breathing. In cases of seizures resulting from valproate toxicity, benzodiazepines should be given. It has been reported naloxone administration, in doses between 0.8 mg and 2 mg, can counteract central nervous system depression in certain instances of valproate poisoning. If the patient arrives within 2 hours following a valproate overdose, a single dose of activated charcoal is used for gastrointestinal decontamination. The typical dosage for activated charcoal is 1 g/kg of patient weight. Do not administer to sedated patients when the airway can not be safeguarded. Since valproate comes in enteric-coated and extended-release forms that are absorbed slowly, activated charcoal may be administered after the 2-hour mark post-ingestion. Consider administering L-carnitine to patients who arrive with an acute valproic acid overdose accompanied by changes in mental status. The initial dose of L-carnitine should be 100 mg/kg, administered intravenously. The treatment regimen for L-carnitine then proceeds with doses of 50 mg/kg every 8 hours. It is also essential to concurrently monitor serum ammonia levels; L-carnitine treatment may be discontinued once these levels begin to decline. In cases of acute valproate overdose where patients are asymptomatic, a preventive oral dose of carnitine is recommended at 100 mg/kg/day, divided into four daily doses.

Symptoms related to the physical, chemical and toxicological characteristics
- IDENTIFICATION AND USE: Valproic acid is a colorless to pale yellow viscous liquid. Valproic acid is an antiepileptic drug and is used solely or in combination with other anticonvulsants in the treatment of simple (petit mal) and complex absence seizures. Valproic acid may be effective against myoclonic and atonic seizures in young children. HUMAN EXPOSURE AND TOXICITY: After oral administration, the drug is rapidly absorbed from the gastrointestinal tract and metabolized in the liver. Fatal hepatic failure has been reported in patients on valproic acid therapy, especially those on chronic use. Pancreatitis has also been reported in patients receiving normal therapeutic dosage. Reports showed that acute toxicity is rare, and usually follows a benign course. The most commonly reported adverse effects are anorexia, nausea and vomiting. Central nervous system effects include drowsiness, possibly apathy and withdrawal, confusion, restlessness, hyperactivity. Less frequently, seizures and coma may occur. Sedative effects are more pronounced when drug is used together with other anti-epileptic agents. Hematopoietic system effects include thrombocytopenia, abnormal bleeding time and partial thromboplastin time with decreased fibrinogen levels and prolonged prothrombin time leading to bruising, petechiae, hematoma, and epistaxis. The drug can induce pruritic macular rashes and transient alopecia. Altered thyroid functions was described. Death is rare but if it occurs it results from cardiopulmonary arrest secondary to hepatic failure. Safe use of valproic acid during pregnancy has not been established. Although several reports suggest an association between the use of valproic acid in pregnant epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women, a causal relationship remains to be established. The drug crosses the placental barrier and has been found in breast milk. The mechanism of action of valproic acid is unknown. Effects of the drug may be related, at least in part, to increased brain concentrations of the inhibitory neurotransmitter GABA. ANIMAL STUDIES: Animal studies have shown that valproic acid inhibits GABA transferase and succinic aldehyde dehydrogenase, enzymes which are important for GABA catabolism. Results of one study indicate the drug inhibits neuronal activity by increasing potassium conductance. In animals, valproic acid protects against seizure induced by electrical stimulation, as well as those induced by pentylenetetrazol. In 2 year rat and chronic mouse studies, an increased incidence of subcutaneous fibrosarcoma occurred in male rats at the higher dosage level and a dose related trend for an increased incidence of benign pulmonary adenomas was observed in

male mice. The importance of these findings to humans is not known. Adverse fetal effects have been observed in reproduction studies in rats and mice. Studies have not shown any evidence of mutagenic potential for the drug.

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.