HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DEHYDRATED ALCOHOL INJECTION safely and effectively. See full prescribing information for DEHYDRATED ALCOHOL INJECTION.

DEHYDRATED ALCOHOL INJECTION for intravenous use
Initial U.S. Approval: 1946

---------- INDICATIONS AND USAGE ----------

Dehydrated Alcohol Injection is a competitive alcohol dehydrogenase inhibitor indicated for the treatment of methanol poisoning in combination with hemodialysis in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Dilute Dehydrated Alcohol Injection to a 10% diluted dehydrated alcohol injection (10% ethanol) prior to intravenous administration. See full prescribing information for preparation and dilution instructions. (2.1)
- Administer 10% diluted Dehydrated Alcohol Injection (10% ethanol) intravenously as a loading dose followed by continuous infusion. (2.2)
- Recommended loading dose of 10% ethanol is 7.6 mL/kg administered over 1 hour. (2.3)
- See full prescribing information for recommended initial infusion rate and maintenance infusion rate for continuous infusion, as well as recommended ethanol concentration monitoring. (2.4, 2.5, 2.6)
- Discontinue 10% ethanol treatment when the patient is asymptomatic, has a normal arterial pH and methanol plasma or serum concentration lower than 20 mg/dL. (2.7)
- Pregnancy testing is recommended for females of reproductive potential prior to treatment with Dehydrated Alcohol Injection (2.8, 5.1).

---------- DOSAGE FORMS AND STRENGTHS ----------

Injection: ≥ 98% ethanol by volume in single-dose ampules (3)

----------CONTRAINDICATIONS----------

None (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Embryo-Fetal Toxicity: Dehydrated Alcohol Injection can cause fetal harm. However, treatment of methanol poisoning should not be delayed. If alternative treatments with less potential for embryo-fetal toxicity are available, avoid use of Dehydrated Alcohol Injection in pregnant females. (**Error! Reference source not found.**)
- Ethanol Toxicity: Ethanol toxicity may occur from treatment with Dehydrated Alcohol Injection. Symptoms of ethanol toxicity may overlap with methanol poisoning. Monitor plasma or serum concentrations of ethanol and methanol at frequent intervals throughout treatment. (5.1)
- Central Nervous System (CNS) and Respiratory Depression: Dehydrated Alcohol Injection can cause CNS and respiratory depression at high concentrations. Monitor for signs and symptoms and medically manage as needed. (5.3)
- Fluid Status Monitoring: Treatment with Dehydrated Alcohol Injection may cause fluid overload. Monitor intravascular and fluid volume status during treatment with Dehydrated Alcohol Injection. (5.4)
- Acetaldehyde Accumulation and Toxicity: Treatment with Dehydrated Alcohol Injection can cause acetaldehyde accumulation and toxicity. Patients with history of ethanol intolerance are at increased risk. Monitor for signs and symptoms of acetaldehyde toxicity. Avoid use of Dehydrated Alcohol Injection in patients with a history of ethanol intolerance. (5.5)
- Risk of QT Interval Prolongation: Dehydrated Alcohol Injection may prolong the QT interval. Monitor electrocardiograms during treatment. Consider alternative treatments if QT prolongation is present and/or arrhythmias develop. (5.6)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions are central nervous system depression, flushing, throbbing headache, nausea and vomiting, tachycardia, diaphoresis, dyspnea, hypotension, marked uneasiness and weakness, thirst, blurred vision, confusion, dry mouth, hypothermia, tremors, and respiratory depression. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Royal Pharmaceuticals, at 800-510-3401 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*

---------- DRUG INTERACTIONS ----------

- Disulfiram and Disulfiram-like Drugs: Avoid use if alternative treatments are available (7.1).
- Central Nervous System Depressants: Avoid use if alternative treatments are available. Monitor patients for signs of CNS and respiratory depression. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Breastfeeding is not recommended (0)
- Pediatric Use: The safety and effectiveness in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised 10/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Dehydrated Alcohol Injection is indicated for the treatment of methanol poisoning in combination with hemodialysis in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation and Dilution Instructions for Dehydrated Alcohol Injection

- Dehydrated Alcohol Injection is ≥ 98% ethanol by volume and must be diluted to a 10% diluted Dehydrated Alcohol Injection (referred to as "10% ethanol" in this section) prior to administration. Do not administer undiluted Dehydrated Alcohol Injection.
    - Withdraw a total of 50 mL of Dehydrated Alcohol Injection with a sterile syringe. Using sterile techniques (the solution does not contain antimicrobial preservatives), inject the 50 mL of Dehydrated Alcohol Injection into either 0.9% Sodium Chloride for Injection or 5% Dextrose for Injection intravenous bag to achieve a final volume of 500 mL. The resultant solution will contain 10% diluted Dehydrated Alcohol Injection (10% ethanol) for infusion.
    - Gently invert the bag to mix the solution.
    - Prepare multiple solutions of 10% ethanol to allow for sufficient treatment of the patient during the loading dose and continuous infusion.
- Dehydrated Alcohol Injection ampules are single use only. Discard unused portions of Dehydrated Alcohol Injection.
- If the admixed 10% ethanol is not used immediately, store at controlled room temperature at 20°C to 25°C (68°F to 77°F) for no more than 24 hours. Discard the unused admixed 10% ethanol after 24 hours.

2.2 Important Administration Instructions

- Administer 10% diluted Dehydrated Alcohol Injection (referred to as "10% ethanol" in this section) via intravenous infusion. Do not administer by bolus injection. Do not administer undiluted Dehydrated Alcohol Injection *[see Dosage and Administration (2.1)]*.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Administer 10% ethanol intravenously. When possible, use a central venous catheter to avoid venous irritation. Administer 10% ethanol in the following order:
    - Loading dose
    - Continuous infusion
        - Initial infusion rate (IIR)
        - Maintenance infusion rate (MIR)

2.3 Recommended Loading Dose

The recommended loading dose of 10% ethanol in adults is 7.6 mL/kg administered over 1 hour.

2.4 Recommended Initial Infusion Rate for Continuous Infusion

Initial Infusion Rate for Continuous Infusion in Adults without Hepatic Disease

The recommended initial infusion rate (IIR) for continuous infusion of 10% ethanol after the loading dose in adults without hepatic disease is based on body weight, chronic drinking status (non-drinker, moderate drinker, or heavy drinker), and whether hemodialysis is active or paused as provided in Table 1.

Table 1: Recommended Initial Infusion Rate (IIR) for Continuous Infusion of 10% Ethanol in Adults without Hepatic Disease

IIR if Hemodialysis is Active	
Chronic Drinking Status[1]	**IIR**[2]
Non-drinker or moderate drinker	2.14 mL/kg/hour
Heavy drinker	3.25 mL/kg/hour
IIR if Hemodialysis is Paused	
Chronic Drinking Status[1]	**IIR**[2]
Non-drinker or moderate drinker	0.84 mL/kg/hour
Heavy drinker	1.95 mL/kg/hour

[1] National Institute on Alcohol Abuse and Alcoholism defines a heavy drinker and moderate drinker as follows:
Heavy drinker: Males - 5 or more drinks on any day or more than 15 drinks per week; Females - 4 or more drinks on any day or 8 or more drinks per week. Moderate drinker: Males - 5 drinks or less in a day; Females - 3 drink or less a day.
[2] Values are based on the density of absolute ethanol (approximately 790 mg/mL at room temperature) and using 10% ethanol.

Initial Infusion Rate for Continuous Infusion in Adults with Hepatic Disease

The recommended IIR for continuous infusion of 10% ethanol after the loading dose in adults with hepatic disease is 2.14 mL/kg/hour if hemodialysis is active or 0.84 mL/kg/hour if hemodialysis is paused, irrespective of chronic drinking status.

2.5 Recommended Maintenance Infusion Rate (After IIR) for Continuous Infusion

Maintenance Infusion Rate (After IIR) for Adults on Continuous Hemodialysis

To ensure ethanol plasma or serum concentration is within the target range of 100 mg/dL to 150 mg/dL during maintenance treatment, obtain ethanol plasma or serum concentrations as recommended *[see Dosage and Administration (2.6)]* and adjust the infusion rate based on the algorithm and example for calculating the maintenance infusion rate (MIR) provided below:

Step 1: Calculate the ethanol clearance (CL) to be used in Step 2.

$$CL = IIR - \frac{LD \times (C_1 - C_0)}{C_0 \times \Delta T_1}$$

CL (mL/hour): Ethanol clearance
IIR (mL/hour): 10% Ethanol initial infusion rate *[see Dosage and Administration (2.4)]*
LD (mL): 10% Ethanol loading dose
C_0 (mg/dL): Ethanol plasma or serum concentration immediately after the completion of loading dose
C_1 (mg/dL): Ethanol plasma or serum concentration about 1 to 2 hours following the initial infusion
ΔT_1 (hour): Time interval between collection of C_1 and C_0

Step 2: Calculate the maintenance infusion rate (MIR) until the next planned monitoring time point T_2.

$$MIR = CL + \frac{LD \times (125 - C_1)}{C_0 \times \Delta T_2}$$

MIR (mL/hour): 10% Ethanol maintenance infusion rate until the next monitoring time point
CL (mL/hour): Ethanol clearance calculated from Step 1
LD (mL): 10% Ethanol loading dose
125 (mg/dL): Median target ethanol plasma or serum concentrations (target ethanol value 100 mg/dL -150 mg/dL)
C_0 (mg/dL): Ethanol plasma or serum concentration immediately after the completion of loading dose
C_1 (mg/dL): First ethanol plasma or serum concentration measured following the initial infusion
ΔT_2 (hour): Time interval between C_1 collection and the next planned concentration collection time point at T_2

- Further adjustment of the MIR may be warranted based on additional ethanol plasma or serum concentrations obtained during ethanol concentration monitoring, especially when the MIR differs substantially from the IIR.

- Calculate subsequent MIR utilizing the Step 2 equation by replacing the value of C_1 with the newly obtained ethanol plasma or serum concentration. The time interval will be the value between the most recent ethanol concentration collection time point and the next planned concentration collection time point.

Example: The MIR for a **70** kg person who is a non-drinker, on active hemodialysis, has serum ethanol concentrations of **100** mg/dL following the completion of loading dose and **115** mg/dL after **1** hour into the initial infusion rate recommended by Table 1, and has a planned ethanol monitoring timepoint **2** hours after the preceding measurement is calculated as follows:

$$\text{LD} = 7.6\ \text{mL/kg} \times 70\ \text{kg} = 532\ \text{mL}$$

$$\text{IIR} = 2.14\ \text{mL/kg/hr} \times 70\ \text{kg} = 150\ \text{mL/hr}$$

$$\text{Step 1: CL} = 150\ \text{mL/hr} - \frac{532\ \text{mL} \times (115\ \text{mg/dL} - 100\ \text{mg/dL})}{100\ \text{mg/dL} \times 1\ \text{hr}} = 70\ \text{mL/hr}$$

$$\text{Step 2: MIR} = 70\ \text{mL/hr} + \frac{532\ \text{mL} \times (125\ \text{mg/dL} - 115\ \text{mg/dL})}{100\ \text{mg/dL} \times 2\ \text{hr}} = 97\ \text{mL/hr}$$

Maintenance Infusion Rate (After IIR) for Adults on Intermittent Hemodialysis

To ensure ethanol plasma or serum concentration is within the target range of 100 mg/dL to 150 mg/dL during maintenance treatment, the infusion rate can be initially adjusted upon the change in hemodialysis status (active versus paused) *[see Dosage and Administration (2.4)]*. Ethanol plasma or serum concentrations should be obtained immediately before and about 1 hour after the change in hemodialysis status to inform the further adjustment of MIR based on the algorithm provided below:

Step 1: Calculate the ethanol clearance (CL) upon change in hemodialysis status to be used in Step 2.

$$\text{CL} = \text{IR} - \frac{\text{LD} \times (C_n - C_{n-1})}{C_0 \times \Delta T_n}$$

IR (mL/hour): 10% Ethanol infusion rate upon first change in hemodialysis status *[see Dosage and Administration (2.4)]*

C_{n-1} (mg/dL): Ethanol plasma or serum concentration immediately before the change in hemodialysis status

C_n (mg/dL): Ethanol plasma or serum concentration about 1 hour after the change in hemodialysis status

ΔT_n (hour): Time interval between collection of C_{n-1} and C_n

Step 2: Calculate the MIR until the next planned monitoring time point T_2.

$$\text{MIR} = \text{CL} + \frac{\text{LD} \times (125 - C_n)}{C_0 \times \Delta T_2}$$

MIR (mL/hour): 10% Ethanol maintenance infusion rate until the next monitoring time point
CL (mL/hour): Ethanol clearance calculated from Step 1
LD (mL): 10% Ethanol loading dose
125 (mg/dL): Median target ethanol plasma or serum concentrations (target ethanol value 100 mg/dL-150 mg/dL)
C_0 (mg/dL): Ethanol plasma or serum concentration immediately after the completion of loading dose
C_n (mg/dL): Ethanol plasma or serum concentration about 1 hour after the change of the hemodialysis status
ΔT_2 (hour): Time interval between C_n collection and the next planned concentration collection time point at T_2

- Further adjustment of the MIR may be warranted based on additional ethanol plasma or serum concentrations obtained during ethanol concentration monitoring.

- Calculate subsequent MIR utilizing the Step 2 equation by replacing the value of C_n with the newly obtained ethanol plasma or serum concentration. The time interval will be the value between the most recent ethanol concentration collection time point and the next planned concentration collection time point.

2.6 Recommended Ethanol Concentration Monitoring

- The target ethanol plasma or serum concentration is 100 mg/dL to 150 mg/dL. If ethanol concentration is measured using whole blood, multiply the whole blood concentration by 1.11 to obtain the ethanol plasma or serum concentration.
- Measure ethanol blood, plasma, or serum concentration (using an FDA-cleared alcohol dehydrogenase enzyme-based assay without interference in the presence of methanol) immediately after the completion of the loading dose, and then every 1 to 2 hours until the target ethanol plasma or serum concentration is achieved. Thereafter, measure ethanol plasma or serum concentrations every 2 to 4 hours to ensure the ethanol plasma or serum concentrations are maintained within the target range.
- More frequent monitoring is needed in patients on intermittent hemodialysis compared to patients on continuous hemodialysis. For example, obtain ethanol plasma or serum concentrations immediately before and about 1 hour after a change in hemodialysis status to determine the change of ethanol clearance (CL) *[see Dosage and Administration (2.5)]*.
- The MIR is expected to approach the value of CL of the individual patient after adjustment.

2.7 10% Ethanol Treatment Discontinuation

- Discontinue 10% ethanol treatment when the patient is asymptomatic, has a normal arterial pH, and methanol serum or plasma concentration <20 mg/dL.
- Monitor methanol plasma or serum concentrations using a validated bioanalytical assay (e.g., gas chromatography).

2.8 Pregnancy Testing in Females of Reproductive Potential

Pregnancy testing is recommended for females of reproductive potential prior to treatment with Dehydrated Alcohol Injection. If alternative treatments with less potential for embryo-fetal toxicity are available, avoid use of Dehydrated Alcohol Injection in pregnant females *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: ≥ 98% ethanol by volume as a clear, colorless liquid in single-dose glass ampules.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Dehydrated Alcohol Injection can cause fetal harm when administered during pregnancy. However, treatment of methanol poisoning should not be delayed. Consider the risks and benefits of treating methanol poisoning with Dehydrated Alcohol Injection. If alternative treatments with less potential for embryo-fetal toxicity are available, avoid use of Dehydrated Alcohol Injection in pregnant females *[see Use in Specific Populations (8.1)]*.

5.2 Ethanol Toxicity

Ethanol toxicity may occur from treatment with Dehydrated Alcohol Injection. Symptoms of ethanol toxicity may overlap with methanol poisoning. Monitor plasma or serum ethanol concentrations and plasma or serum methanol concentrations at frequent intervals throughout treatment *[see Dosage and Administration (2.6)]*.

5.3 Central Nervous System and Respiratory Depression

Dehydrated Alcohol Injection can depress the central nervous system (CNS) and cause respiratory depression at high concentrations. Monitor for signs and symptoms of CNS and respiratory depression and medically manage as needed.

5.4 Fluid Status Monitoring During Treatment

Treatment with Dehydrated Alcohol Injection may cause fluid overload. Monitor intravascular and fluid volume status during treatment with Dehydrated Alcohol Injection.

5.5 Acetaldehyde Accumulation and Toxicity

Ethanol is metabolized to acetaldehyde in the human body. Treatment with Dehydrated Alcohol Injection may cause acetaldehyde accumulation and toxicity. Patients with a history of ethanol intolerance, including patients with the *ALDH2*2* variant (decrease in function allele resulting in decreased acetaldehyde metabolism), are at increased risk for acetaldehyde accumulation and toxicity. The *ALDH2*2* variant is primarily prevalent in East Asian populations (e.g., Chinese, Japanese, and Korean) *[see Clinical Pharmacology (12.5)]* in which approximately 20% to 50% of patients may have ethanol intolerance.

Avoid use of Dehydrated Alcohol Injection in patients with a history of ethanol intolerance if alternative treatment options are available. Monitor for clinical signs of acetaldehyde toxicity which include flushing, throbbing headache, nausea, vomiting, tachycardia, diaphoresis, dyspnea, hypotension, marked uneasiness, weakness, thirst, blurred vision, and confusion during treatment with Dehydrated Alcohol Injection. Occurrence of one or more of these symptoms, especially flushing, throbbing headache, and nausea or vomiting, may indicate acetaldehyde accumulation *[see Clinical Pharmacology (12.3, 12.5)]*. If signs and symptoms of acetaldehyde toxicity occur, continuation of hemodialysis and consideration of an alternative treatment may be required.

5.6 Risk of QT Interval Prolongation

Dehydrated Alcohol Injection may prolong the QT interval *[see Clinical Pharmacology (12.2)]*. Monitor electrocardiograms during treatment. Consider alternative treatments if QT prolongation is present and/or arrhythmias develop.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Ethanol Toxicity *[see Warnings and Precautions (5.2)]*
- Central Nervous System and Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Acetaldehyde Accumulation and Toxicity *[see Warnings and Precautions (5.5)]*
- Risk of QT Interval Prolongation *[see Warnings and Precautions (5.6)]*

The following adverse reactions associated with the use of dehydrated alcohol injection products were identified in published literature. It is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Central nervous system: central nervous system depression
Disulfiram-like reactions: flushing, throbbing headache and nausea and vomiting, tachycardia, diaphoresis, dyspnea, hypotension, marked uneasiness and weakness, thirst, blurred vision, and confusion
Gastrointestinal disorders: dry mouth
General disorders: hypothermia
Nervous system disorders: headache, tremors
Respiratory, thoracic and mediastinal disorders: respiratory depression

7 DRUG INTERACTIONS

7.1 Disulfiram and Disulfiram-Like Drugs

If available, consider alternative treatments in patients who concomitantly use disulfiram or disulfiram-like drugs.

Concomitant use of ethanol with disulfiram or disulfiram-like drugs, including aldehyde dehydrogenase (ALDH) inhibitors, may cause acetaldehyde accumulation *[see Warnings and Precautions (5.5)]*.

7.2 Central Nervous System Depressants

If available, consider alternative treatments in patients who concomitantly use central nervous system (CNS) depressants.

Ethanol may enhance the acute effects of drugs that depress the central nervous system, including hypnotics, tranquilizers, antihistamines, muscle relaxants, opioid analgesics, antiepileptics, and antidepressants. Monitor for signs of central nervous system depression, including respiratory depression, in patients who concomitantly use CNS depressants during treatment with Dehydrated Alcohol Injection.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Treatment of methanol poisoning should not be delayed *(see Clinical Considerations)*. Consider the risks and benefits of treating methanol poisoning with Dehydrated Alcohol Injection. If alternative treatments with less potential for embryo-fetal toxicity are available, avoid use of Dehydrated Alcohol Injection in pregnant females. Based on data from published observational studies over decades, ethanol use during pregnancy is known to cause miscarriage, stillbirth and a pattern of anomalies known as fetal alcohol syndrome. There is no available information to support a safe dose of ethanol during pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Treatment in pregnant women with methanol poisoning should not be delayed because potentially toxic formic acid levels may increase the risk of maternal and fetal morbidity and mortality.

8.2 Lactation

Ethanol is present in human milk and inhibits the milk-ejection reflex resulting in decreased milk production. Because of the potential for serious adverse reactions in the breastfed infant, including drowsiness, weakness and decreased linear growth, breastfeeding is not recommended during treatment with Dehydrated Alcohol Injection.

8.3 Females and Males of Reproductive Potential

Based on data from published observational studies over decades, ethanol can cause fetal harm.

To prevent unplanned exposure during pregnancy, pregnancy testing is recommended for females of reproductive potential before initiation of treatment with Dehydrated Alcohol Injection *[see Dosage and Administration (2.8)].*

8.4 Pediatric Use

The safety and effectiveness of Dehydrated Alcohol Injection have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies have not been conducted with Dehydrated Alcohol Injection. There is insufficient data from published literature reports to determine whether patients 65 years of age and older respond differently from younger adult patients. The recommended loading dose, IIR for continuous infusion, and MIR calculation for continuous infusion in patients 65 years and older is the same as younger adult patients *[see Dosage and Administration (2.3, 2.4, 2.5)].*

8.6 Hepatic Impairment

The recommended loading dose is the same in patients with hepatic disease as in patients without hepatic disease. The recommended IIR for continuous infusion in patients with hepatic disease is 2.14 mL/kg/hour during active hemodialysis and 0.84 mL/kg/hour during pause of intermittent hemodialysis, irrespective of chronic drinking status *[see Dosage and Administration (2.4)]*.

10 OVERDOSAGE

An overdosage of Dehydrated Alcohol Injection may lead to signs and symptoms of central nervous system depression. To prevent overdosage, frequently assess blood ethanol levels to maintain levels between 100 mg/dL to 150 mg/dL *[see Dosage and Administration (2.6)]*.

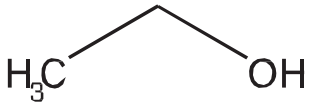
If overdosage with Dehydrated Alcohol Injection occurs, provide supportive treatment and keep the patient warm. Maintain fluid balance with use of suitable electrolyte solution. If respiratory depression or hypoglycemia occurs, assisted ventilation and glucose may be needed, respectively.

Ethanol is dialyzable, and hemodialysis may be required in treating cases of overdosage. Consider contacting the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

Dehydrated Alcohol Injection, USP is a sterile, preservative free solution of ≥ 98% ethanol by volume and no excipients. Dehydrated Alcohol Injection is a competitive alcohol dehydrogenase inhibitor and is for intravenous administration after dilution to 10% ethanol by volume with 5% dextrose or 0.9% normal saline.

Ethanol is a clear, colorless, volatile, and flammable liquid miscible with water, methanol, ether, and acetone. It has the following structural formula:



molecular formula: C_2H_6O molecular weight: 46.07 g/mol

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ethanol is a competitive alcohol dehydrogenase inhibitor. Ethanol has higher binding affinity for human alcohol dehydrogenases (ADHs) than methanol. At high concentrations, ethanol functions as a competitive substrate of ADHs which inhibits metabolism of methanol. Methanol poisoning is primarily due to its toxic metabolite formic acid. Inhibition of methanol metabolism by ethanol reduces the production of formic acid in human body.

12.2 Pharmacodynamics

Literature indicates an ethanol plasma or serum concentration of approximately 100 mg/dL can sufficiently inhibit metabolism of methanol up to approximately 200 mg/dL in vivo. The literature suggests the target therapeutic plasma or serum concentration ethanol ranges between 100 mg/dL to 150 mg/dL to avoid the toxicity of ethanol at high plasma or serum concentrations during the treatment of methanol poisoning.

Cardiac Electrophysiology

Literature reports that prolongation of QTc intervals occurred in some subjects with serum or plasma ethanol concentrations within the target range (i.e., 100 mg/dL to 150 mg/dL) *[see Warnings and Precautions (5.6)].*

12.3 Pharmacokinetics

Distribution

Once in the systemic circulation, ethanol is rapidly distributed throughout the body. Literature reports the volume of distribution of ethanol is approximately 0.70 L/kg and 0.60 L/kg for males and females, respectively.

Elimination

Within the target therapeutic plasma or serum concentration range of ethanol (i.e., 100 mg/dL to 150 mg/dL), ethanol generally follows a zero-order elimination, in which a constant amount of ethanol is eliminated from the human body per unit of time. Literature reports typical ethanol zero-order clearance

is about 15 to 20 mg/dL/h or approximately 7 to 9 g/h. However, there is considerable variability reported for ethanol zero-order clearance between individuals.

Metabolism
Ethanol is primarily metabolized in the liver by alcohol dehydrogenase (ADH) to acetaldehyde, which is then oxidized by aldehyde dehydrogenase (ALDH) to acetate. An alternative ethanol metabolism pathway is through CYP2E1.

Excretion
Other than hepatic metabolism, literature reports approximately 10% of unchanged ethanol is excreted by a combination of respiratory and renal clearance.

Specific Populations
Based on literature reports, the effect of age (adults) and sex on ethanol clearance is generally modest. Due to the small fraction of unchanged ethanol excreted in the urine, renal impairment is not expected to have a clinically relevant effect on ethanol clearance within the target therapeutic plasma or serum concentration range (i.e., 100 mg/dL to 150 mg/dL).

Race
Acetaldehyde metabolism may be slower in patients of East Asian descent, resulting in a higher risk for ethanol intolerance, because of the higher frequency of the *ALDH2*2* variant (decrease in function allele) in this population *[see Warning and Precautions (5.4) and Clinical Pharmacology (12.5)]*.

Chronic Drinker
Chronic drinking can induce CYP2E1 levels in the liver which increases the hepatic clearance of ethanol. Literature reports that ethanol mean zero-order clearance can be about 2 to 3 times higher in chronic drinkers compared to non-drinkers *[see Dosage and Administration (2.4)]*.

Patients with Hepatic Impairment
Literature reports that the ethanol clearance in subjects with hepatic disease, including alcoholic cirrhosis, is similar to that of non-alcoholic healthy subjects *[see Dosage and Administration (2.4)]*.

Therapeutic Interactions
Hemodialysis eliminates ethanol from the human body via a first-order pattern. Ethanol hemodialysis clearance increases with increase of plasma or serum ethanol concentrations and increase of hemodialysis blood flow rate.

Drug Interactions
ALDH inhibitors such as disulfiram and some disulfiram-like drugs can cause substantial accumulation of acetaldehyde in the human body during treatment with ethanol for methanol poisoning [*see Drug Interactions (7.1)*].

12.5 Pharmacogenomics
Ethanol is metabolized by ADH and ALDH enzymes *[see Clinical Pharmacology (12.3)]*. According to the literature, acetaldehyde plasma concentrations are elevated in individuals with the *ALDH2*2* variant (decrease in function allele). Carriers of the *ALDH2*2* variant may experience adverse reactions associated with acetaldehyde toxicity *[see Warnings and Precautions (5.5)]*. The *ALDH2*2* variant is primarily prevalent in East Asian populations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Ethanol and its primary in vivo metabolite, acetaldehyde, both gave negative results in bacterial mutagenicity tests, even in the presence of exogenous metabolic activation systems. In mammalian cells in vitro, ethanol was not usually able to produce gene mutations or chromosomal aberrations. In animals in vivo, ethanol induced DNA adducts, DNA strand breaks, and sister chromatid exchanges and dominant lethal mutations. No effect of ethanol was seen in the micronucleus or chromosome aberration assays in vivo. Acetaldehyde caused DNA protein crosslinks, DNA strand breaks, DNA adducts, sister chromatid exchanges, chromosomal aberrations, and micronuclei in eukaryotic cells in vitro. Acetaldehyde induced DNA protein crosslinks, sister chromatid exchanges, and chromosomal aberrations in rodents in vivo. Ethanol and acetaldehyde are both carcinogenic in experimental animals.

Impairment of Fertility

In male rats treated with ethanol intraperitoneally at a single dose of 5 g/kg (human equivalent dose (HED) of 0.8 g/kg, 0.12x the maximum recommended human dose (MRHD) based on body surface area (BSA)) 24 hours before mating, there were findings of reduced pregnancy rates (50% reduction), smaller litter sizes (30% reduction), and increased fetal mortality (2x increase). In male rats treated with ethanol at 6 g/kg/day (0.14x the MRHD based on BSA) by gastric intubation for 30 days, there were findings of reduced pregnancy rates (60% reduction) and smaller litter sizes (50% reduction). Regarding embryonic fetal development, in pregnant cynomolgus monkeys treated with gradually increased doses of ethanol (from 2 g/kg/day to 5 g/kg/day (0.24x the MRHD based on BSA)) by intragastric intubation from day 20 to 150 of gestation, there were findings of increased abortions and stillbirths (increased from 29% in the control group to 67% in the 5 g/kg/day group) and decreased birth weight (16% reduction).

14 CLINICAL STUDIES

Evidence of the effectiveness of Dehydrated Alcohol Injection for the treatment of methanol poisoning in combination with hemodialysis in adults is obtained from published literature involving over 1,500 patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dehydrated Alcohol Injection, USP is a clear, colorless liquid supplied as 5 mL in a clear, glass, single-dose ampules. Each 5 mL contains ≥ 98% ethanol by volume.

Dehydrated Alcohol Injection, USP is supplied as follows:

Package Configuration	NDC
10 ampules per carton (5 mL per ampule)	68791-505-10

Store at 20°C to 25°C (68°F to 77°F); Excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Highly flammable, store away from any heat source.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise patients that Dehydrated Alcohol Injection can cause fetal harm due to adverse fetal effects of ethanol. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].*

Lactation

Advise females not to breastfeed during treatment with Dehydrated Alcohol Injection *[see Use in Specific Populations (8.2)]*.

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