Disodium Edetate 3% Concentrate for Infusion  
30mg in 1mL

This product is an unapproved therapeutic good in Australia. It is manufactured in a TGA approved pharmaceutical manufacturing facility in Australia and is provided under Schedule 5A – subregulation 12(1A) of the Therapeutic Goods Act and Regulations. The product is supplied under contract between a public or private hospital or public institution and the licensed manufacturer in Australia in accordance with a specified formulation.

Approval for use is required from the hospital pharmacist and / or drug committee as appropriate. Informed consent should be obtained in accordance with good medical practice where applicable and practicable. Records of the use of the product should be fully detailed and include dose, route of administration, duration of treatment, clinical, biochemical, haematological and immunological monitoring as appropriate. Adverse events and reactions must be reported to Phebra Pty Ltd and the TGA.

The responsibility for the use of this product remains with the prescriber and the institution. The following product information has not been evaluated or approved by the Therapeutic Goods Administration. Physicians should consult the medical literature for the most recent advice concerning the appropriate dose, route of administration, warnings and adverse effects.

Warning: The name EDTA is often used to refer to two separate drugs: Disodium EDTA (disodium edetate); and Calcium disodium EDTA (also known as Calcium Disodium Versenate).

In the US there have been cases where children and adults have died when they were mistakenly given Disodium Edetate instead of Calcium Disodium Edetate (Calcium Disodium Versenate) or when Disodium Edetate was used for “chelation therapies” and other uses that are not approved by the Food and Drug Administration.

NAME OF THE MEDICINE

Disodium Edetate

Chemical Name: Disodium dihydrogen (ethylenedinitrilo) tetraacetate dehydrate.

The molecular weight of the compound is 372.2 and the CAS registry number is 139-33-3. The molecular formula is C_{10}H_{14}N_{2}Na_{2}O_{8},2H_{2}O.

Structural Formula:
PRODUCT INFORMATION
Disodium Edetate 3% Concentrate for Infusion
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DESCRIPTION
Disodium Edetate 3% Concentrate for Infusion is a clear and colourless sterile solution containing 30 mg disodium edetate in 1 mL of water for injections. Sodium hydroxide and hydrochloric acid are also added, when required, for pH adjustment. It is presented in amber glass vials. The solution has a pH of 6.8-7.0 and does not contain any preservative.

PHARMAKOLOGY
Pharmacodynamics
Disodium edetate is a synthetic chelating agent.

In hypercalcaemia, disodium edetate forms soluble complexes with calcium in the blood, which are filtered by the glomeruli and not reabsorbed by the renal tubules. Chelation with calcium produces a lowering of serum calcium concentrations and a mobilization of extracellular calcium stores, especially from bone, during slow intravenous infusion. Theoretically, 1 gram of disodium edetate will chelate 120 mg of calcium.

Hypocalcaemic tetany, seizures, severe cardiac arrhythmias, and respiratory arrest may occur with the rapid decrease in serum calcium concentrations. However, the mobilization of calcium from bone may lessen the risk of hypocalcaemia. Calcium ion concentrations in cerebrospinal fluid are not affected by disodium edetate.

In digitalis toxicity disodium edetate exerts a negative inotropic effect on the heart. The chronotropic and inotropic effects of digitalis glycosides on the ventricles of the heart are transiently antagonized by the hypocalcaemia induced by disodium edetate.

Disodium edetate also forms chelates with and increases urinary excretion of other polyvalent metals, such as magnesium, zinc, and other trace elements.

Although disodium edetate does not form a chelate with potassium, the serum concentration of potassium may be decreased and the urinary excretion of potassium increased.

Disodium edetate is rapidly excreted by the kidneys, principally as the calcium chelate; 50% of the chelate appears in the urine in 1 hour and over 95% in 24 hours; changes in urine flow and pH do not affect the rate of excretion of the chelate.

INDICATIONS

Treatment of Hypercalcaemia: Disodium Edetate 3% Concentrate for Infusion is indicated in selected patients for the emergency treatment of acute hypercalcaemia, but is recommended only when the severity of the clinical condition (as when there has been a judgment of imminent death from hypercalcaemic crisis) justifies the aggressive measures associated with this therapy. Other therapies should be started simultaneously so that treatment with Disodium Edetate 3% Concentrate for Infusion will not exceed 48 hours.

Some physicians recommend not using Disodium Edetate 3% Concentrate for Infusion for hypercalcaemia, especially when it is associated with metastatic bone disease, because of minimal and temporary beneficial effects and the great risk of renal damage.

Treatment of digitalis glycoside toxicity: Disodium Edetate 3% Concentrate for Infusion is indicated for the control of ventricular arrhythmias associated with digitalis toxicity. Although its onset of action is rapid, the short-term effects require that alternative therapy be undertaken quickly.

Disodium Edetate 3% Concentrate for Infusion is rarely used to treat digitalis-induced ventricular arrhythmias since other more effective agents are available. Although disodium edetate may have been useful when other medications, such as potassium or phenytoin, were contraindicated or ineffective, or when controlling arrhythmias caused by digitalis poisoning in children who had ingested massive doses, it has now been replaced by digoxin immune Fab as the first-line agent for treatment of life-threatening digitalis glycoside toxicity.
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CONTRAINDICATIONS
Disodium Edetate 3% Concentrate for Infusion is not indicated for the treatment of lead poisoning because unlike calcium disodium edetate, it causes hypocalcaemia.

Disodium Edetate 3% Concentrate for Infusion is not indicated for the treatment of renal calculi by retrograde irrigation.

Disodium Edetate 3% Concentrate for Infusion is not indicated for the treatment of arteriosclerosis or atherosclerotic vascular disease involving coronary or peripheral vessels associated with advancing age, since it has not been proven effective and severe nephrotoxicity may occur.

PRECAUTIONS
Due to the possible irritant effect on the tissues and the danger of hypocalcaemia, Disodium Edetate Concentrate for Infusion must be diluted before infusion.

The dilute solution must be infused slowly over three hours or more, preferably four to six hours, and the cardiac reserve of the patient not exceeded.

Rapid intravenous infusion or high serum concentrations of disodium edetate may cause a sudden drop in serum calcium concentration, resulting in hypocalcaemic tetany, convulsions, severe cardiac arrhythmias, and death from respiratory arrest. 

Patients with the following conditions should be treated with caution or only when the clinical benefit outweighs the risk:

- **Anuria or renal function impairment** (excretion of disodium edetate may be delayed by reduced glomerular filtration, increasing the risk of nephrotoxicity)
- **Hypocalcaemia** (this may be exacerbated)
- **Diabetes**, since treatment with disodium edetate may reduce blood sugar concentrations and require adjustment of insulin dosage in diabetic patients
- **Heart disease** (myocardial contractility may be affected)
- **Hypokalaemia** (disodium edetate may exacerbate hypokalaemia and produce ECG changes)
- **History of intracranial lesions or seizure disorders**. (disodium edetate may induce seizures because of hypocalcaemia)
- **Active tuberculosis**, or with healed calcified lesions may be exacerbated
- **Sensitivity to disodium edetate**

Use in Pregnancy
Disodium edetate crosses the placenta. Since adequate and well-controlled studies in humans have not been done it is recommended that this product not be used in pregnant women.

Use in Lactation
It is not known whether disodium edetate is distributed in breast milk. However, although no problems in humans have been documented, it is not recommended that Disodium Edetate 3% Concentrate for Infusion be used with lactating women unless the clinical benefits outweigh the risks.

Paediatric Use
No information is available on the effects of disodium edetate in paediatric patients. Thus it is not recommended that Disodium Edetate 3% Concentrate for Infusion be used with children unless the clinical benefits outweigh the risks.

Effect on Laboratory Tests
The following have been selected on the basis of their potential clinical significance:
Electrocardiograms (ECGs): may cause changes such as sagging of the S-T segment, depression of the T wave, and elevation of the U wave as a result of reduced serum potassium concentrations.

**Calcium determinations:** The serum calcium determination using the oxalate method tends to give low readings in the presence of disodium edetate. Sampling just before a subsequent dose will produce the least interference, alternatively, acidifying the sample or using an alternate method may be necessary.

**Alkaline phosphatase:** its serum concentration may be lowered because of hypomagnesaemia induced by disodium edetate.

**Glucose:** treatment with disodium edetate may cause a lowering of blood sugar concentrations. In the urine the glucose concentration may be increased.

**Other:** serum potassium and magnesium concentrations may be decreased.

**INTERACTIONS WITH OTHER MEDICINES**

The following drug interactions should be considered:

**Digitalis glycosides:** the sudden drop in serum calcium concentrations induced by disodium edetate may reverse effects of digitalis.

**Insulin:** the concurrent use of insulin with disodium edetate may require adjustments in the dosage of insulin due to decreased serum glucose and possible chelation of zinc in the insulin.

**ADVERSE EFFECTS**

Thrombophlebitis (pain, burning or swelling at site of injection) is a more frequent adverse effect and may require medical attention.

Less frequent events include: anaemia (unusual tiredness or weakness), exfoliative dermatitis (skin rash or other skin and mucous membrane lesions) febrile reaction, (chills or sudden fever; fatigue; headache; malaise; muscle cramps; excessive thirst; weakness), secondary gout (severe pain or inflammation in feet, knees, hands, or elbows), hyperuricaemia which may result from renal tubular toxicity, hypocalcaemia (convulsions; difficulty in breathing; irregular heartbeats; mood or mental changes; muscle spasms (tetany) in hands, arms, feet, legs, or face; numbness and tingling around the mouth, fingertips, or feet) due to the sudden decrease in serum calcium concentration caused by rapid intravenous infusion or high dose of disodium edetate, hypokalaemia or hypomagnesaemia (drowsiness; loss of appetite; muscle twitching or trembling; nausea or vomiting; unusual tiredness or weakness). These may be accompanied by hypocalcaemia.

Nephrotoxicity, (cloudy urine; frequent or sudden urge to urinate, large or small volume of urine, painful or difficult urination). Nephrotoxicity may be due to damage to the reticuloendothelial system with haemorrhagic tendencies, or may indicate possible renal tubular necrosis, microscopic haematuria, proteinuria, and/or large renal epithelial cells in urine may be observed. Nephrotoxicity is usually associated with high doses of disodium edetate. Signs are often reversible within a few days after discontinuation of medication.

**Note:** Prolonged use of Disodium Edetate 3% Concentrate for Infusion may cause lesions similar to those seen with pyridoxine deficiency, such as cracking and dry scaly skin and sores in mouth and on lips, possibly due to zinc depletion.

Some adverse reactions may indicate the need for medical attention only if they continue or are bothersome. The more frequent of these include: abdominal or stomach pain or cramps, diarrhoea, and postural hypotension, (dizziness or light-headedness).

Less frequent reactions include: headache, without other symptoms of a febrile reaction, numbness and circumoral paraesthesia, (burning; crawling; itching; numbness; prickling, "pins and needles" or tingling feelings).
TREATMENT OF ADVERSE EFFECTS

The following is recommended:

**Hypocalcaemia:** a parenteral calcium salt, such as calcium gluconate, should be immediately available before administration of Disodium Edetate 3% Concentrate for Infusion for calcium ion replacement. However, intravenous calcium should be administered with caution in the treatment of tetany, especially in patients who are digitalized, since a reversal of digitalis effects may occur.

**Nephrotoxicity:** Disodium Edetate 3% Concentrate for Infusion must be discontinued; maximum hydration compatible with patient's cardiovascular reserve may be necessary.

**Postural hypotension:** patient should remain in bed for a short time after infusion.

**DOSAGE AND ADMINISTRATION**

*Due to the possible irritant effect on the tissues and the danger of hypocalcaemia, Disodium Edetate Concentrate for Infusion must be diluted before use.*

The dilute solution must be infused slowly over three hours or more, preferably four to six hours, and the cardiac reserve of the patient not exceeded.

Rapid intravenous infusion or high serum concentrations of disodium edetate may cause a sudden drop in serum calcium concentration, resulting in hypocalcaemic tetany, convulsions, severe cardiac arrhythmias, and death from respiratory arrest.

**Hypercalcaemia or digitalis toxicity:**

**Adult dose** is intravenous, 50 mg per kg of body weight up to a maximum of 3 g in twenty-four hours. The dosage may be repeated for 4 more consecutive daily doses followed by a two-day drug-free interval, with repeated courses, as necessary, up to fifteen doses.

**Paediatric dose** is intravenous, 40 mg per kg of body weight in twenty-four hours, limited to a maximum of 70 mg per kg in twenty hours.

**Preparation of Dosages for Administration**

**Adults:** The calculated dose is dissolved in 500 mL of 5% glucose injection or 0.9% sodium chloride injection.

**Paediatric:** The calculated dose is dissolved in a sufficient volume of 5% glucose injection or 0.9% sodium chloride injection to make a final concentration of not more than 3% (30 mg per mL).

**The following patient monitoring is recommended to ensure safe use of disodium edetate:**

- Blood pressure determinations prior to and periodically during therapy.
- Blood urea nitrogen concentrations.
- Serum creatinine concentration is recommended prior to and during therapy for evidence of renal function impairment.
- Cardiac function studies, including ECG. Serum and urinary electrolytes, especially potassium and magnesium, are recommended prior to and periodically during administration of disodium edetate especially in patients with ventricular arrhythmias, limited cardiac reserve, congestive heart failure, or a history of seizure disorders or intracranial lesions; since reduced serum potassium concentrations may produce ECG changes.
- Serum magnesium determinations may be required during prolonged therapy.
- Liver function tests are recommended if there is any clinical evidence of liver function impairment during treatment.
- Urinalysis is recommended daily during treatment.
OVERDOSAGE

The acute clinical effects of overdose include hypocalcaemia or hypocalcaemic tetany (abdominal cramps, confusion, convulsions, difficulty in breathing, irregular heartbeats, mood or mental changes, muscle cramps in hands, arms, feet, legs, or face, numbness and tingling around the mouth, fingertips, or feet, shortness of breath and tremor).

Treatment of Overdose

Intravenous calcium replacement, such as calcium gluconate, with monitoring of serum calcium levels. See also patient monitoring in Dosage and Administration above.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Disodium Edetate 3% Concentrate for Infusion contains 30 mg of disodium edetate and water for injections to 1mL. Sodium hydroxide and hydrochloric acid may also be added for pH adjustment. It is a clear, colourless to faint straw coloured solution in an amber glass vial sealed with a rubber stopper and plastic flip off cap.
It is supplied in a carton containing 10 vials.
Store below 30°C

Phebra product code- SOL025

POISONS SCHEDULE

Not Scheduled.

NAME AND ADDRESS OF THE SPONSOR

Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.
Telephone: 1800 720 020

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