1. NAME OF THE MEDICINAL PRODUCT

Lithium Chloride 0.15 mmol/ml. Solution for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 6.36 mg lithium chloride corresponding to 0.15 mmol.
One 10 ml ampoule contains 63.6 mg lithium chloride corresponding to 1.5 mmol.
For a full list of excipients see Section 6.1

3. PHARMACEUTICAL FORM

Solution for Injection.
A clear solution contained in a glass ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
To be used only for the *in-vivo* measurement of cardiac output in conjunction with the LiDCO System.

4.2. Posology and method of administration

Optimising the Dose for Cardiac Output Determination

The optimal dose for the determination of cardiac output is the minimum dose which can achieve a peak arterial blood lithium concentration in the range 0.2 mM to 0.8 mM, using a dose of 0.075 mmol (0.5 ml), 0.15 mmol (1 ml) or 0.3 mmol (2 ml) Lithium Chloride 0.15 mmol/ml Solution for Injection.

In patients where large numbers of determinations of cardiac output are anticipated, it is best to commence with a target dose of 0.15 mmol i.e. 1.0 ml of lithium chloride injection. The LiDCO System monitor will show an 'Alert' if the dose produces a curve with a peak height of less than 0.2 mM. Peaks between 0.1 and 0.2 mM are allowable but the measurement may be less accurate. If the peak is not within the desired range then adjust the dose accordingly, remembering that a single dose may not exceed 0.3 mmol i.e. 2.0 ml or be less than 0.075 mmol i.e. 0.5 ml of the injection.

An interval of at least 5 minutes should be allowed before a subsequent lithium cardiac output determination is attempted.

Dose recommendations for the Lithium Chloride 0.15 mmol/ml Solution for Injection are based on the assumption that the patient weight is in excess of 40 kg.

Please note that a single LiDCO determination within the target dilution curve peak range is sufficient to give a cardiac output reading with the same precision and accuracy as the mean of three thermodilution determinations.

Maximum Dose

Each dose is limited to a maximum of 0.3 mmol (2 ml) lithium chloride.
The cumulative dose of lithium chloride should not exceed 3 mmol.

Method of Administration
THIS PRODUCT SHOULD ONLY BE USED IN ACCORDANCE WITH THE LiDCO SYSTEM USER'S MANUAL SUPPLIED WITH THE MONITORING EQUIPMENT AND SHOULD ONLY BE USED IN MEDICAL AND SURGICAL INTENSIVE CARE UNITS, OPERATIVE SUITES AND ACCIDENT AND EMERGENCY UNITS

Lithium chloride is for single patient use only and should be used immediately upon opening the ampoule. The lithium chloride may be withdrawn from the ampoule into a closed reservoir syringe system supplied by LiDCO and as described in the LiDCO System User's Manual. Any unused solution remaining in the closed reservoir syringe system must be discarded after three (3) hours.

The lithium dose is administered by intravenous injection via a central venous catheter

4.3 Contraindications

The use of Lithium Chloride 0.15 mmol/ml Solution for Injection is contraindicated:

- In patients currently under lithium therapy for control of bipolar disorder.
- In patients less than 40 kg in weight.
- In the first trimester of pregnancy. For more information see section 4.6.

Hypersensitivity to lithium compounds**.**

4.4 Special warning and precautions for use

This medicinal product must only be used in conjunction with the LiDCO System

1. Follow the dose recommendations. Inaccuracies occur with blood levels above 0.3 mM and lithium is toxic at blood concentrations above 1.5 mM.

2. All injections of lithium chloride should be recorded in the patient notes.

3. A minimum of 5 minutes should be left between sequential LiDCO System determinations of cardiac output.

4. Waste blood should not be returned to the patient. The waste blood may clot in the bag and/or pick up contaminant material/particles from contact with the Flow Through Cell assembly wick material.

5. Avoid the use of the LiDCO System during the 30 minutes after bolus injections or infusions of muscle relaxant drugs e.g. vecuronium bromide, atracurium besylate and pancuronium bromide. These agents interfere with the performance of the lithium electrode and concurrent use must be avoided.

6. Lithium sensors are affected by other chemicals notably: detergents/surfactants and solvents. Occasional problems have been noted with contaminants present in saline infusion products such as saline bags.

7. The use of the LiDCO System requires the bolus administration of lithium chloride and saline followed by arterial blood sampling. Only medical staff appropriately qualified for the administration of intravenous fluids and peripheral arterial catheter use should use the system. Usual care should be taken to avoid: patient infection, catheter or line disconnection, arterial or venous blood loss and air embolism.

8. The concurrent use of: electrocautery, electrosurgery, defibrillation and X-ray machinery will cause transient interference with the LiDCO System Monitor trace. Determinations should not be performed during such periods. No such interference is known to occur with infrared irradiation, or equipment generating radiofrequency irradiation.

9 In cases of intracardiac shunt (such as myocardial infarction with interventricular septum rupture), the cardiac output measurement will be distorted when measured by the LiDCO System, as it would by the thermodilution method. An alternative method for cardiac output determination should be considered in such cases.

10. Lithium chloride should not be infused through a line used for the infusion of vasoactive or other potent drugs.

4.5 Interactions with other medicinal products and other forms of interaction

No known interaction with other medicinal products at the doses recommended.

4.6 Pregnancy and lactation

Pregnancy

Data are available on the teratogenic effects of normal therapeutic doses of lithium in the first trimester, notably the increased risk of cardiac anomalies, specifically Ebstein's.

Lactation

Although lithium is distributed into the extracellular fluid (ECF), breast-feeding is allowable following the administration of lithium chloride for cardiac output measurement.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

No undesirable effects related to lithium chloride are expected at the proposed posology.

4.9 Overdose

The dosing recommendations would have to be exceeded 5 fold for lithium toxicity to occur.

Initial manifestations of lithium toxicity often involve the central nervous system and include drowsiness, confusion, giddiness, apathy, hand tremor and dysarthria. Occasionally gastrointestinal symptoms such as decreased appetite, nausea, vomiting or diarrhoea are observed. Muscle rigidity or fasiculations, slight ataxia, tinnitus, increased lethargy, increased tendon reflexes, blurred vision and vertical nystagmus usually follow.

Lithium intoxication can progress to impaired consciousness, increasing fasiculations and ataxia, coarse and irregular limb tremors, choreoathetoid movements, cogwheeel rigidity and other local neurological signs. Coma, twitching, coarse contractions of muscles, generalised tonic-clonic seizures, cardiovascular collapse with oliguria and anuria and death may occur. Dysrhythmias, increasing QRS duration, inverted T waves and myocardial infarction can occur.

The clinical course of lithium intoxication is quite variable so patients may present with any of the above signs and symptoms.

Treatment of lithium intoxication is principally supportive and depends on the patient's clinical condition and blood lithium concentration. Mild lithium toxicity usually responds to temporary discontinuation of therapy and correction of fluid and electrolyte abnormalities. When toxicity is more severe the patient may require intensive care. Discontinuation of lithium and any concurrently administered diuretic is essential.

Intravenous infusion of 0.9% sodium chloride should be started when lithium toxicity is thought to be secondary to total body depletion of sodium. Rapid administration of large volumes of intravenous solutions or administration of potassium or a diuretic apparently provide no additional benefit. Although diuretics may increase lithium clearance, the increased clearance is insufficient to be useful in treating intoxication.

Haemodialysis for 8-12 hours is recommended when the blood lithium concentration exceeds 3 mM, when the blood concentration is 2-3 mM and the patient's condition is deteriorating, when fluid or electrolyte abnormalities are unresponsive to supportive treatment, when creatinine clearance or urine output decrease substantially, or when the blood lithium concentration is not reduced by at least 20% in 6 hours. Blood lithium concentrations usually rebound within 5-6 hours of haemodialysis because of redistribution,

often necessitating repeated courses of haemodialysis. The goal of haemodialysis is to produce a blood lithium concentration of less than 1 mM once 8 hours of haemodialysis is completed. Peritoneal dialysis is less effective at removing lithium and is used only when haemodialysis is not possible.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other diagnostic agents
ATC code: V04CX

The injection is designed to produce a transient lithium peak of between 0.2 and 0.8 mM in arterial blood. The peak is recorded by a lithium ion selective electrode located in a flow cell sampling blood from the arterial line. The dilution of the lithium is used to calculate the blood flow of the patient (l/min). Following its first pass and ECF/tissue fluid distribution the concentration of the lithium ion is below the recommended lower limit of lithium for the treatment of mania. The dose recommendations 0.075-0.3 mmol per determination, at an interval of greater than 5 minutes, with a maximum cumulative dose of 3 mmol, have all been calculated with relation to a worst case scenario. This included severely decreased compartmental volumes, low body weight and total absence of lithium excretion and in such cases administering the maximum dose permitted at the maximum frequency. In clinical trials these recommendations have been exceeded by a factor of three with no untoward events.

5.2 Pharmacokinetic properties

Distribution & excretion of lithium: Lithium chloride 0.15 mmol/ml Solution for Injection is a fully ionised isotonic solution. The marker substance is the lithium ion - administered intravenously as a bolus. Lithium is not metabolised and consequently the pharmacokinetic focus is on distribution and excretion. The pharmacokinetic data fit a model comprised of a central compartment constituted by ECF i.e. plasma and interstitial fluid, and two peripheral compartments. The volumes of distribution in the ECF, shallow and deep compartments in a 71 kg man are 16.4, 19.4 and 3.2 litres respectively.

In the described use of lithium chloride as a marker substance for the determination of cardiac output there is clearly no absorptive phase (in contrast to oral lithium) and the peak arterial plasma value (0.2 to 0.8 mmol/l) is attained during the first pass through the circulation. The blood level continuously declines thereafter as the lithium ion is redistributed and excreted. The peak concentration, which is substantially less than that in the case of patients on oral lithium therapy, is confined to the intravascular compartment from whence it is distributed to the tissues and filtered in the renal glomeruli.

5.3 Preclinical safety data

The general pharmacology of Lithium Chloride 0.15 mmol/ml Solution for Injection was investigated via single and multiple intravenous injections, reproductive/developmental toxicology, mutagenicity and antigenicity studies. Based on the results of these preclinical

safety studies the dose recommendations for Lithium Chloride 0.15 mmol/ml Solution for Injection are considered to be safe.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections.

6.2 Incompatibilities

For Incompatibilities, see section 4.4.

6.3. Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original container.

6.5 Nature and contents of container

Glass ampoule (Type I).
Each ampoule contains 10 ml solution.
Packs of 5 ampoules.

6.6. Special precaution for disposal and other handling

For use only with the LiDCO System in accordance with the LiDCO System Users Manual.

Only clear solutions practically free from particles should be used.

Any unused portion of the Lithium Chloride 0.15 mmol/ml Solution for Injection is to be discarded in accordance with local requirements. Lithium chloride is for single patient use only and should be used immediately upon opening the ampoule. Any lithium chloride solution remaining in the ampoule after use should be discarded immediately after opening. The lithium chloride solution may be withdrawn from the ampoule into a closed reservoir syringe system and should be used immediately. If not used immediately, then any lithium chloride solution remaining in the LiDCO supplied closed reservoir syringe system should be discarded within three (3) hours of filling the closed reservoir syringe system.

7. MARKETING AUTHORISATION HOLDER

LiDCO Ltd.,
Unit D4, Tottenham Commercial Park,
Leeside Road London N17 0QJ,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER

PL 17048/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/06/2006

10 DATE OF REVISION OF THE TEXT

03/02/2026