Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
CIS-CURON Injection

2. Qualitative and quantitative composition
Each ml contains:
Cis-atracurium Besylate USP
Eq. to Cis-atracurium.....2.0mg
For the full list of excipients see section 6.1

3. Pharmaceutical form
Clear Colorless Solution for Injection

4. Clinical particulars
4.1 Therapeutic indications

- As an adjunct to general anesthesia.
- To facilitate non-emergency endotracheal intubation.
- To provide skeletal muscle relaxation during surgery or mechanical ventilation.

4.2 Posology and method of administration

Cis-Curon Injection contains no antimicrobial preservative and is intended for single patient use.

Use by intravenous bolus Injection

Dosage in Adults: Tracheal intubation. The recommended intubation dose of Cis-Curon Injection for adults is 0.15mg/kg bodyweight.

Maintenance: A dose of 0.03mg/kg bodyweight provides approximately 20 minutes of additional clinically effective neuromuscular block during opioid or propofol anesthesia.

Spontaneous recovery: During opioid or propofol anesthesia the median times from 25% to 75% and from 5 to 95% recovery are approximately 13 and 30 minutes respectively.

Reversal: Neuromuscular block following the administration of Cis-Curon injection is readily reversible with standard doses of anti-cholinesterase agents.

Dosage in Pediatric Patients ages 1 month to 12 years:

Tracheal Intubation: As in adults, the recommended intubation dose of Cis-Curon Injection is 0.15 mg/kg bodyweight administered rapidly over 5 to 10 seconds.

Use by intravenous infusion:

Dosage in Adults and Pediatric Patients aged 1 month to 12 years:

An initial infusion rate of 3 µg /kg /min (0.18 mg /kg /hr.) is recommended to restore 89 to 99% T1 suppression following evidence of spontaneous recovery.

Dosage in neonates aged less than 1 month:

Cis-Curon Injection has not been studied in this patient population

Dosage in Intensive Care Unit (ICU) patients:

An initial infusion rate of Cis-Curon Injection of 3 µg/kg/min (0.18mg/kg/hr.) is recommended.

Dosage in elderly patients:

No dosing alterations are required in elderly patients. In these patients Cis-Curon Injection has a similar pharmacodynamic profile to that observed in young adult patients; however, as with other neuromuscular blocking agents, it may have a slightly slower onset.

Dosage in patients with renal impairment:

No dosing alterations are required in patients with renal failure.

Dosage in patients with hepatic impairment:

No dosing alterations are required in patients with end-stage liver disease.

Patients with cardiovascular disease:

Cis-Curon Injection has not been associated with clinically significant cardiovascular effects at any dose studied (up to and including 0.4mg/kg (8 x ED95)).

Dosage in patients undergoing hypothermic cardiac surgery:

There have been no studies of Cis-Curon Injection in patients undergoing surgery with induced hypothermia (25° to 28°C). As with other neuromuscular blocking agents, the rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.

4.3 Contraindications

Cis-Curon Injection is contraindicated in patients known to be hypersensitive to Cis-atracurium Besylate, atracurium besylate or benzene sulphonic acid.

4.4 Special warnings and precautions for use

Product specific topics

Cis-Curon Injection paralyses the respiratory muscles as well as other skeletal muscles but has no known effect on consciousness or pain threshold. Cis-Curon Injection should be only administered by or under the supervision of anesthetists or other clinicians who are familiar with

the use and action of neuromuscular blocking agents. Facilities for tracheal intubation, and maintenance of pulmonary ventilation and adequate arterial oxygenation have to be available.
Caution should be exercised when administering this medicinal product to patients who have shown hypersensitivity to other neuromuscular blocking agents since a high rate of cross-sensitivity (greater than 50%) between neuromuscular blocking agents has been reported (see section 4.3).
Cis-Curon Injection does not have significant vagolytic or ganglion-blocking properties. Consequently, Cis-Curon Injection has no clinically significant effect on heart rate and will not counteract the bradycardia produced by many an aesthetic agent or by vagal stimulation during surgery.
Patients with myasthenia gravis and other forms of neuromuscular disease have shown greatly increased sensitivity to non-depolarizing blocking agents. An initial dose of not more than 0.02 mg/kg Cis-Curon Injection is recommended in these patients.
Severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to neuromuscular blocking agents.
There is no information on the use of this medicinal product in neonates aged less than one month since it has not been studied in this patient population.
Cis-Curon Injection has not been studied in patients with a history of malignant hyperthermia. Studies in malignant hyperthermia- susceptible pigs indicated that Cis-Curon Injection does not trigger this syndrome.
There have been no studies of Cis-Curon Injection in patients undergoing surgery with induced hypothermia (25 to 28°C). As with other neuromuscular blocking agents the rate of infusion required to maintain adequate surgical relaxation under these conditions may be expected to be significantly reduced.

Cis-Curon Injection has not been studied in patients with burns; however, as with other non-depolarizing neuromuscular blocking agents, the possibility of increased dosing requirements and shortened duration of action must be considered if Cis-Curon Injection injection is administered to these patients.

Cis-Curon Injection is hypotonic and must not be applied into the infusion line of a blood transfusion.

Intensive Care Unit (ICU) Patients: -

When administered to laboratory animals in high doses, laudanosine, a metabolite of Cis-Curon Injection and atracurium, has been associated with transient hypotension and in some species, cerebral excitatory effects. In the most sensitive animal species, these effects occurred at laudanosine plasma concentrations similar to those that have been observed in some ICU patients following prolonged infusion of atracurium.

Consistent with the decreased infusion rate requirements of Cis-Curon Injection, plasma laudanosine concentrations are approximately one third

those following atracurium infusion.

There have been rare reports of seizures in ICU patients who have received atracurium and other agents. These patients usually had one or more medical conditions predisposing to seizures (e.g. cranial trauma, hypoxic encephalopathy, cerebral oedema, viral encephalitis, uremia). A causal relationship to laudanosine has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Many drugs have been shown to influence the magnitude and/or duration of action of non-depolarizing neuromuscular blocking agents, including the following:-

Increased Effect:

By anesthetic agents such as enflurane, isoflurane, halothane (see section 4.2) and ketamine, by other non-depolarizing neuromuscular blocking agents or by other drugs such as antibiotics (including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin), anti-arrhythmic drugs (including propranolol, calcium channel blockers, lignocaine, procainamide and quinidine), diuretics, (including frusemide and possibly thiazides, mannitol and acetazolamide), magnesium and lithium salts and ganglion blocking drugs (trimetaphan, hexamethonium).

Administration of suxamethonium to prolong the effects of non-depolarizing neuromuscular blocking agents may result in a prolonged and complex block which can be difficult to reverse with anticholinesterases.

Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to non-depolarizing neuromuscular blocking agents might result. Such drugs include various antibiotics, b-blockers (propranolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

Decreased effect

A decreased effect is seen after prior chronic administration of phenytoin or carbamazepine.

Treatment with anticholinesterases, commonly used in the treatment of Alzheimer's disease e.g. donepezil, may shorten the duration and diminish the magnitude of neuromuscular blockade with Cis-Curon Injection.

No effect

Prior administration of suxamethonium has no effect on the duration of neuromuscular block following bolus doses of Cis-Curon Injection or on infusion rate requirements.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate data from the use of Cis-Curon Injection in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/fetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown.

Cis-Curon Injection should not be used during pregnancy

Breastfeeding

It is not known whether Cis-Curon Injection or its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Due to the short half-life, an influence on the breast-feeding child is not to be expected if the mother restarts breast-feeding after the effects of the substance have worn off. As a precaution breast-feeding should be discontinued during treatment and for at least 24 hours after administration of this medicinal product.

Fertility

Fertility studies have not been performed.

4.7 Effects on ability to drive and use machines

This precaution is not relevant to the use of Cis-Curon Injection. This medicinal product will always be used in combination with a general anesthetic and therefore the usual precautions relating to performance of tasks following general anesthesia apply.

4.8 Undesirable effects

Data from pooled internal clinical trials were used to determine the frequency of very common to uncommon adverse reactions.

Clinical Trial Data

Organ system class	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)
Cardiac disorders		Bradycardia			
Vascular disorders		Hypotension	Cutaneous flushing		
Respiratory, thoracic and mediastinal disorders			Bronchospasm		
Skin and subcutaneous tissue disorders			Rash		

Postmarketing Data

Organ system class	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)
Immune system					Anaphylactic
disorders					reaction
Musculoskeletal and connective tissue disorders					Myopathy, muscle weakness

Anaphylactic reactions of varying degrees of severity have been observed after the administration of neuromuscular blocking agents. Very rarely, severe anaphylactic reactions have been reported in patients receiving Cis-Curon Injection in conjunction with one or more anesthetic agents.

There have been some reports of muscle/weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids. These events have been reported infrequently in association with Cis-Curon Injection and a causal relationship has not been established.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via the relevant national regulatory authority pharmacovigilance.

4.9 Overdose

Symptoms and signs

Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with this medicinal product.

Management

It is essential to maintain pulmonary ventilation and arterial oxygenation until adequate spontaneous respiration returns. Full sedation will be required since consciousness is not impaired by this medicinal product. Recovery may be accelerated by the administration of anti- cholinesterase agents once evidence of spontaneous recovery is present.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

Cis-Curon Injection is a neuromuscular blocking agent, ATC code: M03AC11. Cis-Curon Injection is an intermediate-duration, non-depolarizing benzylisoquinolinium skeletal muscle relaxant.

Pharmacodynamic effects

Clinical studies in man indicated that this medicinal product is not associated with dose dependent histamine release even at doses up to and including 8 x ED95.

Cis-Curon Injection binds to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a competitive block of neuromuscular transmission. This action is readily reversed by anti-cholinesterase agents such as neostigmine or edrophonium.
The ED95 (dose required to produce 95% depression of the twitch response of the adductor pollicis muscle to stimulation of the ulnar nerve) of Cis-Curon Injection is estimated to be 0.05 mg/kg bodyweight during opioid anesthesia (thiopentone/fentanyl/midazolam).
The ED95 of Cis-Curon Injection in children during halothane anesthesia is 0.04 mg/kg.

5.2 Pharmacokinetic properties

Biotransformation/Elimination
Cis-Curon Injection undergoes degradation in the body at physiological pH and temperature by Hofmann elimination (a chemical process) to form laudanosine and the monoquaternary acrylate metabolite. The monoquaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the monoquaternary alcohol metabolite. Elimination of Cis-Curon Injection is largely organ independent but the liver and kidneys are primary pathways for the clearance of its metabolites.
These metabolites do not possess neuromuscular blocking activity.

Pharmacokinetics in adult patients

Non-compartmental pharmacokinetics of Cis-Curon Injection are independent of dose in the range studied (0.1 to 0.2 mg/kg, i.e. 2 to 4 x ED95).
Population pharmacokinetic modelling confirms and extends these findings up to 0.4 mg/kg (8 x ED95). Pharmacokinetic parameters after doses of 0.1 and 0.2 mg/kg Cis-Curon Injection administered to healthy adult surgical patients are summarized in the table below:

Parameter	**Range of Mean Values**
Clearance	4.7 to 5.7 mL/min/kg
Volume of distribution at steady state	121 to 161 mL/kg
Elimination half-life	22 to 29 min

Pharmacokinetics in elderly patients

There are no clinically important differences in the pharmacokinetics of Cis-Curon Injection in elderly and young adult patients. The recovery profile is also unchanged.

Pharmacokinetics in patients with renal/hepatic impairment

There are no clinically important differences in the pharmacokinetics of Cis-Curon Injection in patients with end-stage renal failure or end stage liver disease and in healthy adult patients. Their recovery profiles are also unchanged.

Pharmacokinetics during infusions

The pharmacokinetics of Cis-Curon Injection after infusions of this medicinal product are similar to those after single bolus injection. The recovery profile after infusion of Cis-Curon Injection is independent of duration of infusion and is similar to that after single bolus injection.

Pharmacokinetics in Intensive Care Unit (ICU) patients

The pharmacokinetics of Cis-Curon Injection in ICU patients receiving prolonged infusions are similar to those in healthy surgical adults receiving infusions or single bolus injections. The recovery profile after infusions of this medicinal product in ICU patients is independent of duration of infusion.

Concentrations of metabolites are higher in ICU patients with abnormal renal and/or hepatic function (see section 4.4). These metabolites do not contribute to neuromuscular block.

5.3 Preclinical safety data

Acute toxicity

Meaningful acute studies with Cis-Curon Injection could not be performed. For symptoms of toxicity see section 4.9.

Subacute Toxicity:

Studies with repeated administration for three weeks in dogs and monkeys showed no compound specific toxic signs.

Mutagenicity

Cis-Curon Injection was not mutagenic in an in vitro microbial mutagenicity test at concentrations up to 5000µg/plate.

In an in vivo cytogenetic study in rats, no significant chromosomal abnormalities were seen at s.c doses up to 4mg/kg.

Cis-Curon Injection was mutagenic in an in vitro mouse lymphoma cell mutagenicity assay, at concentrations of 40µg/ml and higher.

A single positive mutagenic response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Carcinogenicity

Carcinogenicity studies have not been performed.

Reproductive toxicology

Fertility studies have not been performed. Reproductive studies in rats have not revealed any adverse effects of Cis-Curon Injection on fetal development.

Local tolerance

The result of an intra-arterial study in rabbits showed that Cis-Curon Injection injection is well tolerated and no drug related changes were seen.

6. Pharmaceutical Particulars

6.1 List of Excipients

Benzene sulfonic acid solution (for pH adjustment), Water for injections.

6.2 Incompatibilities

Degradation of Cis-Curon Injection has been demonstrated to occur more rapidly in lactated Ringer's Injection and 5% Dextrose and lactated Ringer's Injection than in the infusion fluids listed under Section 6.6.
Therefore, it is recommended that lactated Ringer's Injection and 5% Dextrose and lactated Ringer's Injection are not used as the diluent in preparing solutions of Cis-Curon Injection for infusion.
Since Cis-Curon Injection is stable only in acidic solutions it should not be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions, e.g., sodium thiopentone. It is not compatible with ketorolac trometamol or propofol injectable emulsion.

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Store in refrigerator at 2-8˚C. Do not Freeze. Upon removal from refrigeration to room temperature. Storage conditions (25˚C). Use Cis-Curon injection within 21 days even if refrigerated

6.5 Nature and Content of container

5ml clear glass USP type I ampoule. Further packed in bleach board pack containing 05 ampoules with PVC tray and insert.

6.6 Special precautions for disposal and other handling

This product is for single use only. Use only clear and almost colorless up to slightly yellow/greenish yellow-colored solutions. The product should be visually inspected before use, and if the visual appearance has changed or if the container is damaged, the product must be discarded.

Diluted Cis-Curon Injection Injection is physically and chemically stable for at least 24 hours at 5°C and 25°C at concentrations between 0.1 and 2 mg/mL in the following infusion fluids, in either PVC or non-PVC containers.

- Sodium Chloride (0.9% w/v) Intravenous Infusion.
- Glucose (5% w/v) Intravenous Infusion.
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion.
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

However, since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use, or failing this be stored as directed under section 6.3.

Cis-Curon Injection has been shown to be compatible with the following commonly used peri-operative drugs, when mixed in conditions simulating administration into a running intravenous infusion via a Y-site injection port: alfentanil hydrochloride, droperidol, fentanyl citrate, midazolam hydrochloride and sufentanil citrate. Where other drugs are administered through the same indwelling needle or cannula as this medicinal product, it is recommended that each drug be flushed through with an adequate volume of a suitable intravenous fluid, e.g., Sodium Chloride Intravenous Infusion (0.9% w/v).

As with other drugs administered intravenously, when a small vein is selected as the injection site, Cis-Curon Injection should be flushed through the vein with a suitable intravenous fluid, e.g., sodium chloride intravenous infusion (0.9% w/v).

7. Marketing Authorization Holder

Name: **Brookes Pharma (Private) Limited**
Address: 58-59, Sector No. 15, Korangi Industrial Area, Karachi-74900, Pakistan.

8. Marketing Authorization Number

H2022/CTD8414/17887

9. Date of first authorization/renewal of the authorization

12/09/2022

10. Date of revision of the text

12/09/2022