Summary of Product Characteristic

Cissabex (Injection 2 mg/mL)

Cissabex (Injection 5 mg/mL)

1. Name of the Medicinal Product

Cissabex (Injection 2 mg/mL), Cissabex (Injection 5 mg/mL)

2. Quality and Quantitative Composition

Cissabex (Injection 2 mg/mL): Each mL contains: - Cisatracurium besylate eq. to cisatracurium 2 mg

Cissabex (Injection 5 mg/mL): Each mL contains: - Cisatracurium besylate eq. to cisatracurium 5 mg

3. Pharmaceutical Form

Solution for injection/infusion

Clear, colourless to pale yellow or greenish yellow sterile solution for injection

4. Clinical Particulars

4.1 Therapeutic indication

Cissabex is an intermediate-duration, non-depolarizing neuromuscular blocking agent for intravenous administration.

Cissabex is indicated for use during surgical procedures including cardiac surgery, other procedures and in intensive care. It is used as an adjunct to general anesthesia, or sedation in the Intensive Care Unit (ICU), to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation.

Cissabex contains no antimicrobial preservative and is intended for single patient use.

4.2 Posology and method of administration

As with other neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of Cissabex in order to individualize dosage requirements.

• Use by I.V. bolus injection in adults

Tracheal intubation: The recommended intubation dose of Cissabex for adults is 0.15 mg/kg administered rapidly over 5 to 10 seconds. This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection. Higher doses will shorten the time to onset of neuromuscular block. Table 1 summarizes mean pharmacodynamics data when Cissabex injection was administered at doses of 0.1 to 0.4 mg/kg to healthy adult patients during opioid (thiopentone/fentanyl/midazolam) or propofol anesthesia.

Table 1: Mean Pharmacodynamic Data Following a Range of Cissabex Doses

Initial Cissabex injection dose (mg/kg)	Anesthetic background	Time to 90% T_1[a] suppression (minutes)	Time to maximum T_1[a] suppression (minutes)	Time to 25% spontaneous T_1[a] recovery (minutes)
0.1	Opioid	3.4	4.8	45
0.15	Propofol	2.6	3.5	55
0.2	Opioid	2.4	2.9	65
0.4	Opioid	1.5	1.9	91

[a] Single twitch response as well as the first component of the Train-of Four response of the adductor pollicis muscle following supramaximal electrical stimulation of the ulnar nerve.

Enflurane or isoflurane anesthesia may extend the clinically effective duration of an initial dose of Cissabex by as much as 15%

Maintenance: Neuromuscular block can be extended with maintenance doses of Cissabex. A dose of 0.03 mg/kg provides approximately 20 minutes of additional clinically effective neuromuscular block during opioid or propofol anesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect.

Spontaneous recovery: Once spontaneous recovery from neuromuscular block is underway, the rate is independent of the Cissabex dose administered. 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 Cissabex administration is readily reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T_4:T_1 ratio more than 0.7) are approximately 2 and 5 minutes, respectively, following administration of the reversal agent at an average of 13% T_1 recovery.

• Use by I.V. bolus injection in children (1 month to 12 years of age)

Tracheal intubation: As in adults, the recommended initial intubation dose of Cissabex is 0.15 mg/kg administered rapidly over 5 to 10 seconds.

This dose produces good to excellent conditions for tracheal intubation 120 seconds following injection of Cissabex. Pharmacodynamic data for this dose are presented in the Tables 2 and 3. If a shorter clinical duration is required, pharmacodynamics data suggest that a dose of 0.1 mg/kg may produce similar intubation conditions at 120 to 150 seconds.

In pediatric patients aged 1 month to 12 years, Cissabex has a shorter clinically effective duration and a faster spontaneous recovery profile than those observed in adults under similar anesthetic conditions. Small differences in the pharmacodynamics profile were observed between the age ranges 1 to 11 months and 1 to 12 years which are summarized in Tables 2 and 3 below.

Table 2: Pediatric Patients aged 1 to 11 months

Initial Cissabex injection dose (mg/kg)	Anesthetic background	Time to 90% suppression (minutes)	Time to maximum suppression (minutes)	Time to 25% spontaneous T_1 recovery (minutes)
0.15	Halothane	1.4	2.0	52
0.15	Opioid	1.4	1.9	47

Table 3: Pediatric Patients aged 1 to 12 years

Initial Cissabex injection dose (mg/kg)	Anesthetic background	Time to 90% suppression (minutes)	Time to maximum suppression (minutes)	Time to 25% spontaneous T_1 recovery (minutes)
0.08	Halothane	1.7	2.5	31
0.1	Opioid	1.7	2.8	28
0.15	Halothane	2.3	3.0	43
0.15	Opioid	2.6	3.6	38

Halothane may be expected to extend the clinically effective duration of Cissabex by up to 20%. No information is available on the use of Cissabex in children during isoflurane or enflurane anesthesia but these agents may also be expected to extend the clinically effective duration of a dose of Cissabex by up to 20%

Maintenance: Neuromuscular block can be extended with maintenance doses of Cissabex injection. A dose of 0.02 mg/kg provides approximately 9 minutes of additional clinically effective neuromuscular block during halothane anesthesia. Consecutive maintenance doses do not result in progressive prolongation of effect.

Spontaneous recovery: Once recovery from neuromuscular block is underway, the rate is independent of the Cissabex dose administered. During opioid or halothane anesthesia, the median times from 25 to 75% and from 5 to 95% recovery are approximately 11 and 28 minutes, respectively.

Reversal: Neuromuscular block following Cissabex administration is readily reversible with standard doses of anticholinesterase agents. The mean times from 25 to 75% recovery and to full clinical recovery (T_4:T_1 ratio more than or equal to 0.7) are approximately 2 and 5 minutes, respectively, following administration of the reversal agent at an average of 13% T_1 recovery.

• Use by I.V. infusion in adults and children (1 month to 12 years of age)

Maintenance of neuromuscular block may be achieved by infusion of Cissabex. An initial infusion rate of 3 mcg/kg/min (0.18 mg/kg/hr) is recommended to restore 89 to 99% T1 suppression following evidence of spontaneous recovery. After an initial period of stabilization of neuromuscular block, a rate of 1 to 2 mcg/kg/min (0.06 to 0.12 mg/kg/hr) should be adequate to maintain block in this range in most patients.

Reduction of the infusion rate by up to 40% may be required when Cissabex is administered during isoflurane or enflurane anesthesia.

The infusion rate will depend upon the concentration of Cissabex in the infusion solution, the desired degree of neuromuscular block, and the patient's weight. Table 4 provides guidelines for delivery of undiluted Cissabex.

Table 4: Infusion Delivery Rate of Cissabex (injection 2 mg/mL)

Patient weight (kg)	Dose (mcg/kg/min)				Infusion rate
	1.0	**1.5**	**2.0**	**3.0**	
20	0.6	0.9	1.2	1.8	ml/hr
70	2.1	3.2	4.2	6.3	ml/hr
100	3.0	4.5	6.0	9.0	ml/hr

Steady rate continuous infusion of Cissabex is not associated with a progressive increase or decrease in neuromuscular blocking effect.

Following discontinuation of infusion of Cissabex, spontaneous recovery from neuromuscular block proceeds at a rate comparable to that following administration of a single bolus.

Although not specifically studied in pediatric patients under 2 years of age, extrapolation of pharmacodynamics data for bolus doses suggests that Cissabex infusion rates should be similar.

• Neonates aged less than 1 month

No dosage recommendation for neonates can be made as administration of Cissabex has not been studied in this patient population.

• Elderly

No dosing alterations are required in elderly patients. In these patients Cissabex has a similar pharmacodynamics profile to that observed in young adult patients but, as with other neuromuscular blocking agents, it may have a slightly slower onset.

• Patients with renal impairment

No dosing alterations are required in patients with renal failure. In these patients Cissabex has a similar pharmacodynamics profile to that observed in patients with normal renal function but it may have a slightly slower onset.

• Patients with hepatic impairment

No dosing alterations are required in patients with end-stage liver disease. In these patients Cissabex has a similar pharmacodynamics profile to that observed in patients with normal hepatic function but it may have a slightly faster onset.

• Patients with cardiovascular disease

Cissabex has been used effectively to provide neuromuscular block in patients undergoing cardiac surgery. When administered by rapid bolus injection (over 5 to 10 seconds) to patients with serious cardiovascular disease Cissabex has not been associated with clinically significant cardiovascular effects at any dose studied (up to and including 0.4 mg/kg ($8xED_{95}$))

• ICU patients

Cissabex may be administered by bolus dose and/or infusion to adult patients in the ICU.

An initial infusion rate of Cissabex of 3 mcg/kg/min (0.18 mg/kg/hr) is recommended for adult ICU patients. There may be wide inter-patient variation in dosage requirements and these may increase or decrease with time. In clinical studies the average infusion rate was 3 mcg/kg/min [range 0.5 to 10.2 mcg/kg/min (0.03 to 0.6 mg/kg/hr)]. Table 5 provides guidelines for delivery of undiluted Cissabex.

The median time to full spontaneous recovery following long-term (up to 6 days) infusion of Cissabex in ICU patients was approximately 50 minutes.

Table 5: Infusion Delivery Rate of Cissabex injection 5 mg/ml

Patient weight (kg)	Dose (mcg/kg/min)				Infusion rate
	1.0	**1.5**	**2.0**	**3.0**	
70	0.8	1.2	1.7	2.5	ml/hr
100	1.2	1.8	2.4	3.6	ml/hr

The recovery profile after infusions of Cissabex to ICU patients is independent of duration of infusion.

• Patients undergoing hypothermic cardiac surgery

There have been no studies of Cissabex in patients undergoing surgery with induced hypothermia (25°C 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

Cissabex is contraindicated in patients known to be hypersensitive to cisatracurium, atracurium, or benzene sulfonic acid.

4.4 Special warnings and precautions for use

Cissabex paralyses the respiratory muscles as well as other skeletal muscles but has no known effect on consciousness or pain threshold. Cissabex should be only administered by or under the supervision of anesthetists of 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 should be available.

Caution should be exercised when administering cisatracurium 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.

Cissabex does not have significant vagolytic or ganglion-blocking properties. Consequently, Cissabex has no clinically significant effect on heart rate and will not counteract the bradycardia produced by many anesthetic 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 Cissabex 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.

Cissabex has not been studied in patients with a history of malignant hyperthermia. Studies in malignant hyperthermia-susceptible pigs indicated that Cissabex does not trigger this syndrome.

Cissabex 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 Cissabex is administered to these patients.

Cissabex is hypotonic and must not be administered into the infusion line of a blood transfusion.

ICU patients

When administered to laboratory animals in high doses, laudanosine, a metabolite of cisatracurium and atracurium, has been associated with transient hypotension and, in some species, cerebral excitatory effects. Consistent with the decreased infusion rate requirements of Cissabex, plasma laudanosine concentrations are approximately one third those following atracurium infusion.

There have been rare reports of seizure 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, hypoxia encephalopathy, cerebral edema, viral encephalitis, uremia).

A causal relationship to laudanosine has not been established.

4.5Interaction with other medicinal products and other forms of interactions

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

Anesthetics:

- Volatile agents such as enflurane, isoflurane and halothane
- Ketamine
- Other non-depolarizing neuromuscular blocking agents

Other drugs:

- Antibiotics: including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
- Anti-arrhythmic drugs: including propranolol, calcium channel blockers, lidocaine, procainamide and quinidine
- Diuretics: including furosemide and possibly thiazides, mannitol and acetazolamide
- Magnesium salts
- Lithium salts
- Ganglion blocking drugs: trimetaphan, hexamethonium

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, beta-blockers (propranolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

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.

Decreased effect

- 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 cisatracurium.

No effect

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

4.6 Fertility, pregnancy and lactation

Fertility: Fertility studies have not been performed.

Pregnancy: Cissabex should be used during pregnancy only if the expected benefit to the mother out weights any potential risk to the fetus.

Teratogenicity: Animal studies have indicated that cisatracurium has no adverse effects on fetal development.

Lactation: It is not known whether cisatracurium or its metabolites are excreted in human milk.

4.7 Effects on ability to drive and use machine

This precaution is not relevant to the use of Cissabex. Cissabex 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

The following convention has been used for the classification of frequency:- 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).

Clinical trial data

Cardiac disorders

Common Bradycardia

Vascular disorders

Common Hypotension

Uncommon Cutaneous flushing

Respiratory, thoracic and mediastinal disorder

Uncommon Bronchospasm

Skin and subcutaneous tissue disorders

Uncommon Rash

Post marketing data

Immune system disorders

Very rare Anaphylactic reaction

Anaphylactic reaction 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 Cissabex in conjunction with one or more anesthetic agents.

Musculoskeletal and connective tissue disorders

Very rare Myopathy, muscle weakness

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 Cissabex and a causal relationship has not been established.

4.9 Overdose

Symptoms and signs: Prolonged muscle paralysis and its consequences are expected to be the main signs of overdosage with Cissabex.

Treatment: 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 Cissabex. Recovery may be accelerated by the administration of anticholinesterase agents once evidence of spontaneous recovery is present.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Mechanism of action

Cisatracurium is an intermediate-duration, non-depolarizing benzylisoquinolinium skeletal muscle relaxant.

Pharmacodynamic effects

Clinical studies in man indicated that Cissabex is not associated with dose dependent histamine release even at doses up to and including 8 x ED_{95}.

Cisatracurium 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 anticholinesterase agents such as neostigmine or edrophonium.

The ED_{95} (dose required to produce 95% depression of the twitch response of the adductor policies muscle to stimulation of the ulnar nerve) of cistracurium is estimated to be 0.05 mg/kg bodyweight during opioid anesthesia (thiopentone/fentanyl/midazolam).

The ED_{95} of Cissabex in children during halothane anesthesia is 0.04 mg/kg.

5.2 Pharmacokinetics Properties

Non-compartmental pharmacokinetics of Cissabex are independent of dose in the range studied (0.1 to 0.2 mg/kg, i.e., 2 to 4 x ED_{95}).

Population pharmacokinetic modelling confirms and extends these findings up to 0.4 mg/kg (8 x ED_{95})

Distribution

After doses of 0.1 and 0.2 mg/kg Cissabex administered to healthy adult surgical patients volume of distribution at steady-state is 121 to 161 ml/kg.

Metabolism

Cisatracurium 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.

These metabolites do not possess neuromuscular blocking activity.

Elimination

Elimination of cisatracurium is largely organ-independent but liver and kidneys are primary pathways for the clearance of its metabolites.

I.V. bolus injection

Pharmacokinetic parameters after doses of 0.1 and 0.2 mg/kg Cissabex administered to healthy adult surgical patients are summarized in Table 6 below.

Table 6: Mean Pharmacokinetic Data Following a range of Cissabex Doses

Parameter	Range of mean values
Clearance	4.7 to 5.7 ml/min/kg
Elimination half-life	22 to 29 minutes

I.V. infusion

The pharmacokinetics of cisatracurium after infusion are similar to those after single bolus injection. Pharmacokinetics were studied in healthy adult surgical patients who received an initial 0.1 mg/kg bolus dose of cisatracurium followed by a maintenance infusion of Cissabex to maintain 89 to 99% T1 suppression. Mean clearance of cisatracurium was 6.9 mg/kg/min and elimination half-life was 28 minutes. The recovery profile after infusion of Cissabex is independent of duration of infusion and is similar to that after single bolus injections.

Special Patient Populations

• Elderly

There are no clinically important differences in the pharmacokinetics of cisatracurium in elderly and young adult patients. In a comparative study, plasma clearance was not affected by age. Minor differences in volume of distribution (+17%) and half-life (+4 minutes) did not affect the recovery profile.

• Patients with renal impairment

There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage renal failure and in healthy adult patients. In a comparative study, there were no statistically significant or clinically important differences in pharmacokinetic parameters of Cissabex. The recovery profile of Cissabex is unchanged in the presence of renal failure.

• Patients with hepatic impairment

There are no clinically important differences in the pharmacokinetics of cisatracurium in patients with end-stage liver disease and in healthy adult patients. In a comparative study of patients undergoing liver transplantation and healthy adults, there were small differences in volume of distribution (+21%) and clearance (+16%), but no difference in elimination half-life of cisatracurium. The recovery profile was unchanged.

• ICU patients

The pharmacokinetics of cisatracurium in ICU patients receiving prolonged infusions are similar to those in healthy surgical adults receiving infusion of single bolus injections. Mean clearance of cisatracurium was 7.5 ml/kg/min and elimination half-life was 27 minutes. The recovery profile after infusions of Cissabex in ICU patients is independent of duration of infusion.

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

5.3 Preclinical Safety data

Mutagenicity: The mutagenic risk to patients undergoing muscle relaxation with Cissabex is considered negligible.

Carcinogenicity: Carcinogenicity studies have not been performed.

6. Pharmaceutical Particulars

6.1 List of excipients

Benzenesulfonic acid

Water for injection

6.2 Incompatibilities

Cissabex is not chemically stable when diluted with Lactated Ringer's Injection.

Since Cissabex 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

2 years

6.4 Special precautions for storage

Store between 2-8 °C. Protect from light. Do not freeze.

6.5 Nature and contents of container

Cissabex (injection 2mg/mL): 5 mL clear glass vial (Type I) with aluminium flip-off and 5 mL clear glass ampoule (Type I) packed or unpacked in a box of 1, 5, 10, 12 and 20 vials/ampoules

Cissabex (injection 5mg/mL): 30 mL clear glass vial (Type I) with aluminium flip-off packed or unpacked in a box of 1, 5, 10, 12 and 20 vials

6.6 Special precautions for disposal and other handling

Cissabex contains no antimicrobial preservative therefore dilution should be carried out immediately prior to use and administration should commence as soon as possible thereafter. Any unused solution diluted in an infusion fluid, or remaining in a used vial or open ampoule, should be discarded.

Diluted Cissabex is physically and chemically stable for at least 24 hours between 2°C-8°C and store below 30°C at concentrations between 0.1 and 2.0 mg/ml in the following infusion fluids.

- sodium chloride (0.9% w/v) i.v. infusion
- dextrose (5% w/v) i.v. infusion
- sodium chloride (0.18% w/v) and dextrose (4% w/v) i.v. infusion
- sodium chloride (0.45% w/v) and dextrose (2.5% w/v) i.v. infusion
- sodium chloride (0.9% w/v) and dextrose (5% w/v) i.v. infusion

Cissabex has been shown to be compatible with the following commonly used per-operative drugs, when mixed in conditions simulating administration into a running i.v. 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 Cissabex, it is recommended that each drug be flushed through with an adequate volume of a suitable i.v. fluid, e.g., sodium chloride i.v. infusion 0.9% (w/v).

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

7. Marketing Authorization Holder

ABLE MEDICAL COMPANY LIMITED
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Mahasarakham 44160, Thailand

8. Marketing Authorization Numbers

1A 15089/67 (NG)

9. Date of authorization

29 October 2024

10. Date of revision of the text

29 October 2024