SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atracurium Kalceks 10 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 10 mg of atracurium besylate.
Each ampoule (2.5 ml) contains 25 mg of atracurium besylate.

For the full list of excipients, see *List of excipients*.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear colourless or yellowish solution, free from visible particles.
Osmolality is 10 – 30 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atracurium is a highly selective, competitive or non-depolarising neuromuscular blocking agent which is used as an adjunct to general anaesthesia to enable tracheal intubation to be performed and to relax skeletal muscles during surgery or controlled ventilation, and to facilitate mechanical ventilation in Intensive Care Unit (ICU) patients.

4.2 Posology and method of administration

In common with all neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of atracurium in order to individualise dosage requirements.

- **Used by injection in adults**

Atracurium is administered by intravenous injection. The dosage range recommended for adults is 0.3 to 0.6 mg/kg (depending on the duration of full block required) and will provide adequate relaxation for about 15 to 35 minutes.

Endotracheal intubation can usually be accomplished within 90 seconds from the intravenous injection of 0.5 to 0.6 mg/kg.

Full block can be prolonged with supplementary doses of 0.1 to 0.2 mg/kg as required. Successive supplementary dosing does not give rise to accumulation of neuromuscular blocking effect.

Spontaneous recovery from the end of full block occurs in about 35 minutes as measured by the restoration of the tetanic response to 95 % of normal neuromuscular function.

The neuromuscular block produced by atracurium can be rapidly reversed by standard doses of anticholinesterase agents, such as neostigmine and edrophonium, accompanied or preceded by atropine, with no evidence of recurarisation.

- **Use as an infusion in adults**

After an initial bolus dose of 0.3 to 0.6 mg/kg, atracurium can be used to maintain neuromuscular block during long surgical procedures by administration as a continuous infusion at rates of 0.3 to 0.6 mg/kg/hour.

Atracurium can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25° to 26°C reduces the rate of inactivation of atracurium, therefore full neuromuscular block may be maintained by approximately half the original infusion rate at these low temperatures.

Atracurium is compatible with the following infusion solutions for the times stated below:

Infusion solution	*Period of stability*
Sodium chloride intravenous infusion (0.9% w/v)	24 hours
Glucose intravenous infusion (5% w/v)	8 hours
Ringer's intravenous infusion	8 hours
Sodium chloride (0.18% w/v) and glucose (4% w/v) intravenous infusion	8 hours
Ringer lactate intravenous infusion	4 hours

When diluted in these solutions to give atracurium besylate concentrations of 0.5 mg/ml and above, the resultant solutions will be stable in daylight for the stated periods at temperatures of up to 25°C.

Use in children
The dosage in children over the age of one month is similar to that in adults on a bodyweight basis.

Use in the elderly
Atracurium may be used at standard dosage in elderly patients. It is recommended, however, that the initial dose be at the lower end of the range and that it be administered slowly.

Use in patients with reduced renal and/or hepatic function
Atracurium may be used at standard dosage at all levels of renal or hepatic function, including end stage failure.

Use in patients with cardiovascular disease
In patients with clinically significant cardiovascular disease, the initial dose of atracurium should be administered over a period of 60 seconds.

Use in Intensive Care Unit (ICU) patients
After an optional initial bolus dose of atracurium of 0.3 to 0.6 mg/kg, atracurium can be used to maintain neuromuscular block by administering a continuous infusion at rates of between 11 and 13 micrograms/kg/min (0.65 to 0.78 mg/kg/hour). There may be wide inter-patient variability in dosage requirements and these may increase or decrease with time. Infusion rates as low as 4.5 micrograms/kg/min (0.27 mg/kg/hour) or as high as 29.5 micrograms/kg/min (1.77 mg/kg/hour) are required in some patients.

The rate of spontaneous recovery from neuromuscular block after infusion of atracurium in ICU patients is independent of the duration of administration.

Spontaneous recovery to a train-of-four ratio >0.75 (the ratio of the height of the fourth to the first twitch in a train-of-four) can be expected to occur in approximately 60 minutes. A range of 32 to 108 minutes has been observed in clinical trials.

4.3 Contraindications

Atracurium is contraindicated in patients known to be hypersensitive to atracurium, cisatracurium or benzenesulfonic acid.

4.4 Special warnings and precautions for use

As with other neuromuscular blocking agents, atracurium besylate paralyses the respiratory muscles as well as other skeletal muscles but it has no effect on consciousness. This medicine should be administered only in a unit with adequate facilities for endotracheal intubation and artificial ventilation, with adequate general anaesthesia and by or under the close supervision of an experienced anaesthetist.

Release of histamine may occur in susceptible patients during administration of atracurium besylate. Caution should be exercised in administering atracurium besylate to patients with a history suggestive of an increased sensitivity to the effects of histamine. Bronchospasm may occur especially in patients with a history of allergy or asthma.

Caution should also be exercised when administering atracurium 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 *Contraindications*).

Atracurium besylate has no significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, this medicine in the recommended dosage range has no clinically significant influence on heart rate and it does not counteract the bradycardia produced by other anaesthetic agents or by vagal stimulation during surgery.

As with other non-depolarising neuromuscular blocking agents, increased sensitivity to atracurium besylate may be expected in patients with myasthenia gravis or with other forms of neuromuscular diseases, and with severe electrolyte imbalances.

Atracurium besylate should be administered over a period of 60 seconds in patients who can be unusually sensitive to falls in arterial blood pressure, e.g. in patients with hypovolaemia.

Atracurium besylate is inactivated by high pH, and so must not be mixed in the same syringe with solutions of thiopental or other alkaline solutions.

If a small vein is selected as the injection site, atracurium besylate should be flushed through the vein with physiological saline solution after injection. If other medicines are administered through the same in-dwelling needle or cannula as atracurium besylate, it is important that each drug is flushed through with a sufficient volume of physiological saline.

This medicine is a hypotonic solution and must not be administered into the same venous access as a blood transfusion.

Studies of malignant hyperthermia in susceptible animals (swine) and clinical studies in patients susceptible to malignant hyperthermia indicate that atracurium besylate does not cause this syndrome.

In common with other non-depolarising neuromuscular blocking agents, resistance to myorelaxative effect of atracurium besylate may develop in patients suffering from burns. Such patients may require higher doses, dependent on the time elapsed since the burn and on the extent of the burn.

Intensive Care Unit (ICU) patients
Administration of laudanosine, one of metabolites of atracurium besylate, to laboratory animals has been associated with transient hypotension and, in some species, cerebral excitatory effects.

Although seizures have been observed in patients, receiving atracurium besylate in the Intensive Care Unit, a causal relationship to laudanosine has not been established (see section *Undesirable effects*).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of inhalation anaesthetics such as halothane, isoflurane or enflurane may increase the neuromuscular block produced by atracurium besylate.
As with all non-depolarising neuromuscular blocking agents, non-depolarising neuromuscular block may be increased and/or extended by interaction with:

- *antibiotics*, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin;
- *antiarrhythmic agents:* propranolol, calcium channel blockers, lidocaine, procainamide and quinidine;
- *diuretics:* furosemide and possibly mannitol, thiazide diuretics and acetazolamide;
- *magnesium sulfate*;
- *ketamine;*
- *lithium salts*;
- *ganglion blocking agents:* trimetaphan, hexamethonium.

Rarely certain medicines may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; the consequence of such development would be increased sensitivity to this medicine. Such medicines include various antibiotics, beta-blockers (propranolol, oxprenolol), antiarrhythmics (procainamide, quinidine), anti-rheumatic agents (chloroquine, penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

The onset of non-depolarising neuromuscular block is likely to be lengthened and the duration of block shortened in patients receiving long-term anticonvulsant therapy (phenytoin, carbamazepine).

Concomitant administration of other non-depolarising neuromuscular blocking agents with atracurium besylate may produce a degree of neuromuscular block in excess of that which might be expected, were an equipotent total dose of atracurium besylate administered. The degree of synergic effect may be different for various combinations of medicinal products.

A depolarising muscle relaxant such as suxamethonium should not be administered to prolong neuromuscular blocking effect of non-depolarising blocking agents such as atracurium besylate, as this may result in a prolonged and complex block which can be difficult to reverse with cholinesterase inhibitors.

Anticholinesterases, commonly used in the treatment of Alzheimer´s disease (e.g. donepezil), may shorten the duration or diminish the magnitude of neuromuscular blockade with atracurium besylate.

4.6 Fertility, pregnancy and lactation

Fertility
Fertility studies have not been performed.

Pregnancy
Animal studies have indicated that atracurium besylate has no significant effects on foetal development.

As well as all neuromuscular blocking agents, this medicine should only be administered to a pregnant woman if the anticipated benefit to the mother outweighs any potential risk for the foetus.

This medicine is suitable for maintenance of muscle relaxation during caesarean section as it does not cross the placenta in clinically significant amounts following administration of recommended doses.

Breast-feeding
It is not known whether atracurium besylate is excreted into human milk.

4.7 Effects on ability to drive and use machines

This precaution is not relevant to the use of atracurium. Atracurium besylate is always administered under general anaesthesia, therefore the usual precautions relating to ability to perform these activities after general anaesthesia apply.

4.8 Undesirable effects

The most commonly reported adverse reactions during treatment are hypotension (mild, transient) and skin flushing, these events are attributed to histamine release. Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving atracurium in conjunction with one or more anaesthetic agents.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000).

Very common, common and uncommon frequencies were determined from clinical trial data. Rare and very rare frequencies were generally derived from spontaneous data. The frequency classification "Not known" has been applied to those reactions where a frequency could not be estimated from the available data.

Clinical Trial Data

Vascular disorders
Common: hypotension (mild, transient)#, skin flushing#

Respiratory, thoracic and mediastinal disorders
Uncommon: bronchospasm#

Post-Marketing Data

Immune system disorders
Very rare: anaphylactic reaction, anaphylactoid reaction including shock, circulatory failure and cardiac arrest

Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving atracurium in conjunction with one or more anaesthetic agents.

Nervous system disorders
Not known: seizures

There have been reports of seizures in ICU patients who have been receiving atracurium concurrently with several other agents. These patients usually had one or more medical conditions predisposing to seizures (e.g. cranial trauma, cerebral oedema, viral encephalitis, hypoxic encephalopathy, uraemia). A causal relationship to laudanosine has not been established. In clinical trials, there appears to be no correlation between plasma laudanosine concentration and the occurrence of seizures.

Skin and subcutaneous tissue disorders
Rare: urticaria

Musculoskeletal and connective tissue disorders
Not known: 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 seen infrequently in association with atracurium and a causal relationship has not been established.

Events which have been attributed to histamine release are indicated by a hash (#)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Centre for Adverse Drug Reaction Monitoring by visiting the website portal.npra.gov.my

4.9 Overdose

Signs
Prolonged muscle paralysis and its consequences are the main signs of overdosage.

Treatment
It is essential to maintain a patent airway together with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation will be required since consciousness is not impaired. Recovery may be hastened by the administration of anticholinesterase agents accompanied by atropine or glycopyrrolate, once evidence of spontaneous recovery is present.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peripherally acting muscle relaxants: Other quaternary ammonium compounds.
ATC code: M03AC04.

Atracurium is a highly selective competitive (non-depolarising) neuromuscular blocking agent with an intermediate duration of action. Non-depolarising agents antagonise the neurotransmitter action of acetylcholine by binding with receptor sites on the motor-end-plate. Atracurium can be used in a wide range of surgical procedures and to facilitate controlled ventilation.

Paediatric population
The limited data in neonates from literature reports suggest variability in the time to onset and duration of action of atracurium in this population as compared to children (see section *Posology and method of administration*).

5.2 Pharmacokinetic properties

The pharmacokinetics of atracurium in man are essentially linear with the 0.3-0.6 mg/kg dose range. The elimination half-life is approximately 20 minutes, and the volume of distribution is 0.16 L/kg. Atracurium is 82 % bound to plasma proteins.

Atracurium is degraded spontaneously mainly by a non-enzymatic decomposition process (Hofmann elimination) which occurs at plasma pH and at body temperature and produces breakdown products which are inactive. Degradation also occurs by ester hydrolysis catalysed by non-specific esterases. Elimination of atracurium is not dependent on kidney or liver function.

The main breakdown products are laudanosine and a monoquaternary alcohol which have no neuromuscular blocking activity. The monoquaternary alcohol is degraded spontaneously by Hofmann elimination and excreted by the kidney. Laudanosine is excreted by the kidney and metabolised by the liver. The half-life of laudanosine ranges from 3-6 h in patients with normal kidney and liver function. It is about 15 h in renal failure and is about 40 h in renal and hepatic failure. Peak plasma levels of laudanosine are highest in patients without kidney or liver function and average 4 μg/ml with wide variation.

Concentration of metabolites are higher in ICU patients with abnormal renal and/or hepatic function (see section *Special warnings and precautions for use*). These metabolites do not contribute to neuromuscular block.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzenesulfonic acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Atracurium besylate is inactivated by high pH, thus it must not be mixed in the same syringe with alkaline solutions (e.g. solutions of thiopental).
This medicine is a hypotonic solution, thus it must not be administered into the same venous access as a blood transfusion.
This medicinal product must not be mixed with other medicinal products except those mentioned in section *Special precautions for disposal and other handling*.

6.3 Shelf life

Unopened: 2 years.

After opening the ampoule:
Once opened, the product should be used immediately.

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C and 2 °C – 8 °C temperature in sodium chloride intravenous infusion (0.9% w/v), for 8 hours at 25 °C and 2 °C – 8 °C temperature in glucose intravenous infusion (5% w/v), Ringer's intravenous infusion and sodium chloride (0.18% w/v) and glucose (4% w/v) intravenous infusion, and for 4 hours at 25 °C and 2 °C – 8 °C temperature in Ringer lactate intravenous infusion (see section *Special precautions for disposal and other handling*).

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after opening the ampoule, see section *Shelf life*.
For storage conditions after dilution of the medicinal product, see section *Shelf life* and *Special precautions for disposal and other handling*.

6.5 Nature and contents of container

2.5 ml of solution filled in 5.0 ml type I colourless borosilicate glass ampoules with break line or one point cut.

Pack size: 5 ampoules.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.
The solution is to be visually inspected prior to use. Only clear solutions free from particles should be used.

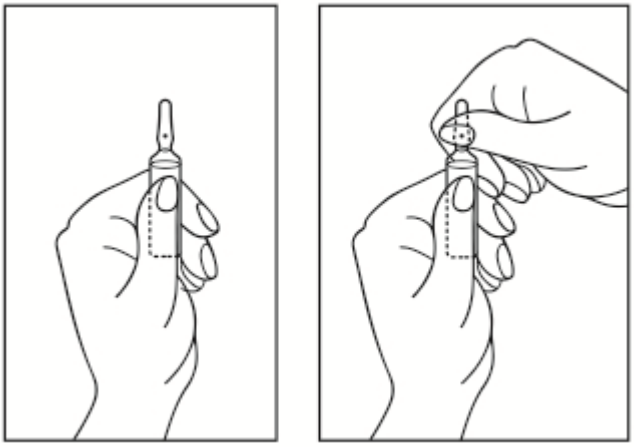
Atracurium besylate is compatible with the following infusion solutions:

Infusion solution	*Period of stability*
Sodium chloride intravenous infusion (0.9% w/v)	24 hours
Glucose intravenous infusion (5% w/v)	8 hours
Ringer's intravenous infusion	8 hours
Sodium chloride (0.18% w/v) and glucose (4% w/v) intravenous infusion	8 hours
Ringer lactate intravenous infusion	4 hours

After dilution with sodium chloride intravenous infusion, glucose intravenous infusion (5% w/v), Ringer's intravenous infusion, sodium chloride (0.18% w/v) and glucose (4% w/v) intravenous infusion, Ringer lactate intravenous infusion, the diluted solutions are clear, colourless and free from particles.

When diluted in these solutions to give atracurium besylate concentrations of 0.5 mg/ml and above, the resultant solutions will be stable in daylight for the stated periods at temperatures of up to 25°C.

Instruction of ampoule opening:
1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



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

7. PRODUCT REGISTRATION HOLDER AND MANUFACTURER

Product Registration Holder:
Eucogen Sdn Bhd
6A, Jalan Sungai Burung U
32/U, Bukit Rimau, 40460 Shah
Alam, Selangor, Malaysia

Brunei Darussalam Product Licence Holder:
Nova Borneo Company Sdn Bhd
Unit 4GF Bangunan Zainuddin & Azizah, Simpang 501
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Manufacturer:
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8. DATE OF REVISION OF THE TEXT

11/2021