1. NAME OF THE MEDICINAL PRODUCT

Atracurium Kalceks 10 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 10 mg of atracurium besilate.
One ampoule (2.5 ml) contains 25 mg of atracurium besilate.
One ampoule (5 ml) contains 50 mg of atracurium besilate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear colourless or yellowish solution, free from visible particles.
pH of solution is 3.30 to 3.65.

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.

4.2 Posology and method of administration

Route of administration: Intravenous injection or continuous infusion.
For instructions on dilution of the medicinal product before administration, see section 6.6.

Used by injection in adults: Atracurium Kalceks 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 Kalceks 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 Kalceks 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 Kalceks can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25^{o} to 26^{o}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.

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 neonates: The use of Atracurium Kalceks is not recommended in neonates since there are insufficient data available (see section 5.1).

Use in the elderly: Atracurium Kalceks 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 Kalceks 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 Kalceks should be administered over a period of 60 seconds.

Use in intensive care unit (ICU) patients: After an optional initial bolus dose of Atracurium Kalceks of 0.3 to 0.6 mg/kg, Atracurium Kalceks 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/hr). 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 microgram/kg/min (0.27 mg/kg/hr) or as high as 29.5

microgram/kg/min (1.77 mg/kg/hr) are required in some patients.

The rate of spontaneous recovery from neuromuscular block after infusion of Atracurium Kalceks 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.

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

4.3 Contraindications

Hypersensitivity to the active substance atracurium, cisatracurium or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Precautions: **In common with all the other neuromuscular blocking agents, Atracurium Kalceks paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. Atracurium Kalceks should be administered only with adequate general anaesthesia and only by or under the close supervision of an experienced anaesthetist with adequate facilities for endotracheal intubation and artificial ventilation.**

The potential for histamine release exists in susceptible patients during Atracurium Kalceks administration. Caution should be exercised in administering Atracurium Kalceks to patients with a history suggestive of an increased sensitivity to the effects of histamine. In particular, bronchospasm may occur in patients with a history of allergy and asthma.

High rates of cross-sensitivity between neuromuscular blocking agents have been reported. Therefore, where possible, before administering atracurium, hypersensitivity to other neuromuscular blocking agents should be excluded. Atracurium should only be used when absolutely essential in susceptible patients. Patients who experience a hypersensitivity reaction under general anaesthesia should be tested subsequently for hypersensitivity to other neuromuscular blockers.

Monitoring of serial creatinine phosphate (cpk) values should be considered in asthmatic patients receiving high dose corticosteroids and neuromuscular blocking agents in ICU.

Atracurium Kalceks does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, Atracurium Kalceks has no clinically

significant effects on heart rate in the recommended dosage range and it will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery.

In common with other non-depolarising neuromuscular blocking agents, increased sensitivity to atracurium may be expected in patients with myasthenia gravis and other forms of neuromuscular disease.

As with other neuromuscular blocking agents severe acid-base and/or serum electrolyte abnormalities may increase or decrease the sensitivity of patients to atracrium.

As with other non-depolarising neuromuscular blockers hypophosphataemia may prolong recovery. Recovery may be hastened by correcting this condition.

Atracurium Kalceks should be administered over a period of 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who are hypovolaemic.

Atracurium Kalceks is inactivated by high pH and so must not be mixed in the same syringe with thiopental or any alkaline agent.

When a small vein is selected as the injection site, Atracurium Kalceks should be flushed through the vein with physiological saline after injection. When other anaesthetic drugs are administered through the same in-dwelling needle or cannula as Atracurium Kalceks it is important that each drug is flushed through with an adequate volume of physiological saline. Atracurium besilate is hypotonic and must not be administered into the infusion line of a blood transfusion.

Studies in malignant hyperthermia in susceptible animals (swine), and clinical studies in patients susceptible to malignant hypothermia indicate that Atracurium Kalceks does not trigger this syndrome.

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

Intensive Care Unit (ICU) patients: When administered to laboratory animals in high doses, Laudanosine, a metabolite of atracrium has been associated with transient hypotension and, in some species, cerebral excitatory effects. Although seizures have been seen in ICU patients receiving atracurium, a causal relationship to laudanosine has not been established (see Undesirable Effects).

4.5 Interaction with other medicinal products and other forms of interaction

The neuromuscular block produced by Atracurium Kalceks may be increased by the

concomitant use of inhalational anaesthetics such as halothane, isoflurane and enflurane.

In common with all non-depolarising neuromuscular blocking agents the magnitude and/or duration of a non-depolarising neuromuscular block may be increased as a result of interaction with:

- antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
- anti-arrhythmic drugs: 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 drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to Atracurium Kalceks would be consequent on such a development. Such drugs include various antibiotics, β-blockers (propranolol, oxprenolol), antiarrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, D-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 chronic anticonvulsant therapy.

The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with Atracurium Kalceks may produce a degree of neuromuscular blockage in excess of that which might be expected were an equipotent total dose of Atracurium Kalceks administered. Any synergistic effect may vary between different drug combinations.

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

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 atracurium.

4.6 Fertility, pregnancy and lactation

Fertility
Fertility studies have not been performed.

Pregnancy

Animal studies have indicated that Atracurium Kalceks has no significant effects on foetal development.

In common with all neuromuscular blocking agents, Atracurium Kalceks should be used during pregnancy only if the potential benefit to the mother outweighs any potential risk to the foetus.

Atracurium Kalceks is suitable for maintenance of muscle relaxation during Caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses.

Breast-feeding
It is not known whether Atracurium Kalceks is excreted in human milk.

4.7 Effects on ability to drive and use machines

This precaution is not relevant to the use of atracurium. Atracurium will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following 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 (>1/10 000 to < 1/1000), very rare (< 1/10 000).

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 disorder

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: /https://sideeffects.health.gov.il

4.9 Overdose

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

Management: It is essential to maintain a patient 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 4.2).

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 3-6h in patients with normal kidney and liver function. It is about 15h in renal failure and is about 40h 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 Special Warnings and Special Precautions for Use). These metabolites do not contribute to neuromuscular block.

5.3 Preclinical safety data

Carcinogenicity: Carcinogenicity studies have not been performed.

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzenesulfonic acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Atracurium besilate 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 6.6.

6.3 Shelf life

Shelf life before first opening:
The expiry date of the product is indicated on the Packaging materials.
For single use only. Once opened, the product should be used immediately.

Shelf life after dilution:
Chemical and physical in-use stability has been demonstrated in 0.9% NaCl Infusion solution for 24 hours at 25°C, in 5% glucose, Ringer and 0.18% NaCl/ 4% glucose infusion solutions for 8 hours at 25°C, and in Ringer lactate infusion solution for 4 hours at 25°C.

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 first opening of the medicinal product, see section 6.3.

For storage conditions after dilution of the medicinal product, see section 6.3 and 6.6.

6.5 Nature and contents of container

2.5 ml or 5.0 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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.
Atracurium besilate is compatible with the following infusion solutions:

Infusion solution	*Period of stability*
Sodium chloride intravenous infusion (9 mg/ml)	24 hours
Glucose intravenous infusion (50 mg/ml)	8 hours
Ringer intravenous infusion	8 hours
Sodium chloride (1.8 mg/ml) and glucose (40 mg/ml) intravenous infusion	8 hours
Ringer lactate intravenous infusion	4 hours

When diluted in these solutions to give atracurium besilate 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.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer

HBM Pharma s.r.o, Sklabinska 30, 036 80 Martin, Slovakia

8. Marketing authorization holder

A.L.Medi-Market Ltd., 3 Hakatif Street, Emek Hefer Industrial Park, 3877701

9. Registration number

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10. DATE OF REVISION OF THE TEXT

Revised in January 2021 according to MoH's Guidelines