Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

Atracurium Hikma 25 mg/2.5 ml solution for injection
Atracurium Hikma 50 mg/5 ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 10 mg Atracuriumbesilate.

Full list of exipients refer to section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intravenous use during surgical and other procedures and in intensive care.
Atracurium besilate is used as an adjunct to general anaesthesia, to facilitate tracheal intubation as well as in the frame of sedation for the muscle relaxation within the intensive-medical range and controlled ventilation.

4.2 Posology and method of administration

Monitoring of neuromuscular function is recommended during the use of atracurium besilate in order to individualise dosage requirements.

The duration of the use of atracurium besilate is defined by the needs of the surgical procedures.

Atracurium besilate 10 mg/ml solution for injection is administered by intravenous injection or infusion and must not be administered intramuscularly.

Muscle relaxation

- *Use as an injection*

Anesthesia
The dosage range recommended for adults is 0.3 to 0.6 mg atracurium besilate/kg (depending on the duration of full block required). This dose will provide adequate relaxation for about 15 to 35 minutes.

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

Repeated dose
Full block can be prolonged in 15 – 20 minute intervals – defined by the individual patient´s needs - with supplementary doses of 0.1 to 0.2 mg atracurium besilate /kg body weight. Successive supplementary dosing does not produce accumulation in neuromuscular blocking effect.

Once evidence of spontaneous recovery is present, the neuromuscular block produced by atracurium besilate can be rapidly reversed by standard doses of anticholinesterase agents, such as neostigmine and edrophonium, accompanied or preceded by atropine or glycopyroniumbromide.

As measured by the restoration of the tetanic response to 95% of normal neuromuscular function, spontaneous recovery occurs about 35 minutes after a full block. A spontaneous recovery of 6 patients after infusion of atracurium besilate up to a “train-of-four-ratio” of > 0.75 after approximately 60 min (with a range of 32 – 108 min) has been reported in the frame of intensive care units.

- *Use as an solution for infusion*

Atracurium besilate is hypotonic and must not be administered via the infusion system of a blood transfusion.

Atracurium besilate, administered as a continuous infusion at rates of 0.3 to 0.6 mg/kg/hour, can be used to maintain neuromuscular block during long surgical procedures.

Atracurium besilate can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates.

Induced hypothermia with body temperature of 25° to 26°C reduces the rate of degradation of atracurium besilate, therefore full neuromuscular block may be maintained with approximately half the original infusion rate.

Atracurium besilate can be diluted with the infusion solutions listed in section 6.6.

Use in risk groups

- *children older than 1 month*

On a bodyweight basis the dosage in children over the age of one month is similar to that in adults.
The use of atracurium besilate is not recommended in neonates (children under the age of one month) as insufficient data are available.

- *Use in the elderyl*

Atracurium besilate 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 besilate may be used at standard dosage at all levels of renal or hepatic function, including endstage failure.

- *Use in patients with cardiovascular disease*

In patients with severe cardiovascular diseases the initial dose should be administered over 1 - 2 minutes.

- *Use in patients suffering from burns*

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.

Long-term use in patients in intensive care units

When there is a need of atracurium besilate for long-term mechanical ventilation in intensive care units, the benefit to risk ratio of neuromuscular block must be considered.

The data available with muscle relaxants in the area of intensive care medicine indicate that the a great variety of dosage requirements between patients and dosage requirements may change over time in dependence of the duration of the administration.

Due to limited experience with atracurium besilate in intensive care units it can be assumed, that for lengthened use may require increased doses.

After an optional initial bolus dose of 0.3 - 0.6 mg/kg, atracurium besilate 10 mg/ml solution for injection can be used to maintain neuromuscular block by administration of a continuous infusion of between 11 and 13 micrograms/kg/min (0.66 - 0.78 mg/kg/h). It has to be taken into consideration that known from experiences in single cases there is a great variety of dosage requirements between patients. Patients may require infusion rates of as low as 4.5 micrograms/kg/min (0.27 mg/kg/h) or as high as 29.5 micrograms/kg/min (1.77 mg/kg/h).

The few findings currently available regarding long-term use of atracurium besilate indicate only minor influence of haemofiltration and haemodialysis on the plasma levels of atracurium besilate and its metabolites.
The effect of the haemoperfusion on the level of atracurium besilate and its metabolites in plasma is not known.

4.3 Contraindications

Atracurium besilate should not be administered to patients known to have an allergic hypersensitivity to the active ingredient atracurium, cisatracurium or to benzenesulfonic acid.

4.4 Special warnings and precautions for use

As with all other neuromuscular blocking agents, atracurium besilate paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. Atracurium besilate has to be administered only with adequate general anaesthesia or with adequate sedation and only by an experienced anaesthetist, with adequate facilities and staff for endotracheal intubation and artificial ventilation, and with an antidote, immediately available.

As with other neuromuscular blocking agents, the potential for histamine release exists in susceptible patients during atracurium besilate administration.

Caution should be exercised in administering Atracurium Hikma to patients with a history of allergy or asthma, as the administration of atracurium besilate may in individual cases trigger a release of histamine (bronchospasm).

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 4.3).

Atracurium besilate does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, atracurium besilate has no clinically relevant effects on heart rate in the recommended dosage range. Bradycardia produced by other anaesthetic agents or by vagal stimulation during surgery will not be counteracted by atracurium besilate and may therefore occur with greater severity.

Caution should be exercised in administering Atracurium Hikma to Patients suffering from myasthenia gravis, other neuromuscular diseases and severe disturbances of the electrolyte metabolism, as increased sensitivity to atracurium besilate is to be expected.

Atracurium besilate should be administered slowly over a period of 60 seconds to patients abnormally susceptible to falls in arterial blood pressure, for example those who are hypovolaemic.

Atracurium Hikma solution for injection must not be administered intramuscularly.

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

After injecting atracurium besilate into a small vein, physiological saline solution (0.9 % NaCl-solution) should be flushed through the vein. If other anaesthetic drugs are administered through the same in-dwelling needle or cannula as atracurium besilate, it is important that after each drug an adequate volume of physiological saline solution (0.9 % NaCl-solution) is flushed through.

Atracurium besilate is hypotonic and must not be administered via the infusion system of a blood transfusion.

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

As 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.

Injection:
Intensive Care unit (ICU) Patients: When administered to laboratory animals in high doses,

laudanosine, a metabolite of atracurium, 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 section 4.8).

Notes:
Atracurium besilate has no direct effect on the intra-ocular pressure, which makes it suitable for use in ophthalmic surgery.

4.5 Interaction with other medicinal products and other forms of interaction

The neuromuscular block produced by atracurium besilate may be increased by the concomitant use of inhalational anaesthetics such as halothane, isoflurane, enflurane, sevoflurane and desflurane.

The neuromuscular block may be intensified and/or prolonged when atracurium besilate is administered concomitantly with the following medicinal products:

- antibiotics including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin, clindamycin;
- antiarrhythmic drugs: propanolol, calcium canal blocker, Lignocain (lidocaine), procainamide and quinidin,
- diuretics: furosemide and possibly mannitol, thiazide diuretics and acetazolamide/magnesium sulphate;
- ketamine;
- lithium salts and quinine
- ganglion blocking agents: trimethaphan, hexamethonium.

Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to atracurium besilate would follow.

Such drugs include:

- beta-blockers: propranolol, oxprenolol;
- antiarrhythmic drugs: procainamide, quinidine;
- antirhymatica: chloroquine, D-penicillamine;
- various antibiotics;
- trimethaphan;
- chlorpromazine;
- steroids;
- phenytoin;
- 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 besilate may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of atracurium besilate 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 besilate, 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 Pregnancy and lactation

Fertility:
Fertility studies have not been performed.

Pregnancy:
There are no or limited amount of data on the use of atracurium besilate during pregnancy. Although animal studies do not indicate any harmful effect on embryo/fetal development, atracurium besilate should only be administered during pregnancy after careful risk-benefit assessment.

Placental transfer is low. Applications within the recommended dose range in caesarean section patients showed no detrimental effects on the new-born (see also toxicological properties).

Atracuruim besilate does not pass the placental barrier in clinically relevant concentrations when administered in the recommended dosage range. Therefore, atracurium besilate is also suitable for maintenance of muscle relaxation during caesarean section.

Lactation:
It is not known whether atracurium besilate passes into breast milk. Due to the short half-life, an influence on the infant is not to be expected if the mother starts breast-feeding (again) after the effects of the substance have worn off. As a precaution restart breast-feeding 24 hours after administration of atracurium besilate.

4.7 Effects on ability to drive and use machines

As the drug is administered under general anaesthesia, the patient must not drive, operate machinery or work in exposed situations after anaesthesia. The time factor should be decided individually by the physician. The patient should be accompanied on his way home and should not ingest alcohol.

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 and < 1/10, uncommon > 1/1000 and < 1/100, rare > 1/10,000 and < 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.

System organ class	**frequency**	**reaction**
Immune system disorders	very rare	severe anaphylactic and 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	very rare	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.
cardiac desease	common	Tachycardy
Vascular disorders	common	mild transient Hypotension[#], Skin flushing[#]
Respiratory, thoracic and mediastinal disorders	common	gasp, bronchospasm[#]
	very rare	Laryngospasm
Skin and subcutaneous	rare	Urticaria

tissue disorders		
Musculoskeletal and connective tissue disorders	very rare	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 reporting system listed in Appendix V*.

4.9 Overdose

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

b) 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. PHARMAKOLOGISCHE EIGENSCHAFTEN

5.1 Pharmakodynamische Eigenschaften

Not translated

5.2 Pharmakokinetische Eigenschaften

Not translated

5.3 Präklinische Daten zur Sicherheit

Not translated

6. PHARMACEUTICAL PARTICULARS

6.1 Exipients

Water for injection
Benzolsulfonic acid

6.2 Incompatibilities

Atracuriumbesilat darf in der Mischspritze nicht mit Thiopental oder anderen alkalischen Lösungen bzw. Substanzen gleichzeitig verabreicht werden, da alkalische pH-Werte zur vorzeitigen Inaktivierung von Atracuriumbesilat führen.
Daher muss zwischen der Infusion von Atracuriumbesilat und Thiopental eine Spülung der Kanüle erfolgen, um die Bildung von Aggregaten zu verhindern, die eine anaphylaktische Reaktion hervorrufen können.

6.3 Shelf-life

Unopened ampoules: 2 years
opened ampoules: after opening the product must be used immediately

Solution for infusion after preparation: for shelf-life of prepared solutions for infusions refer to 6.6

6.4 Special precautions for storage

Store in the refrigerator at 2°C to 8°C protected from light.

Departing from that the storage conditions may be at 25 °C for not longer than 3 days.

Do not freeze.

Discard residual solution if not used.

6.5 Nature and contents of container

Packs with 5 ampoules á 2.5 ml or 5 ml solution for injection
Packs with 10 ampoules á 2.5 ml or 5 ml solution for injection
Packs with 25 (5x5) ampoules á 2.5 ml or 5 ml solution for injection
Packs with 50 (5x10) ampoules á 2.5 ml or 5 ml solution for injection

Not all pack sizes may be marketed.

6.6 Besondere Vorsichtsmaßnahmen für die Beseitigung und sonstige Hinweise zur Handhabung

Keep this medicine out of the sight and reach of children.

Die Atracuriumbesilat-Injektionslösungen sind mit folgenden Infusionslösungen kompatibel (mischbar):

Infusionslösung	Haltbarkeit
1. 0,9%ige NaCl-Lösung (G/V)	24 Stunden
2. 5%ige Glucose-Lösung (G/V)	8 Stunden
3. Ringer-Lösung	8 Stunden
4. 0,18%ige NaCl-Lösung mit 4%iger Glucose-Lösung (G/V)	8 Stunden
5. Hartmann'sche Lösung (Natriumlaktat)	4 Stunden

In Konzentrationen von 0,5 mg Atracuriumbesilat/ml und darüber ist Atracuriumbesilat in den oben genannten Lösungen über die genannten Zeiträume nach Herstellung bei Tageslicht und Temperaturen bis zu 30° C haltbar.

Aus mikrobiologischer Sicht sind diese Lösungen sofort zu verwenden; andernfalls liegt die Aufbewahrung nach Herstellung in der Verantwortung des medizinischen Personals und sollte normalerweise nicht länger als 24 Stunden bei 2°C – 8°C erfolgen, falls die Verdünnung nicht unter kontrollierten und validierten aseptischen Bedingungen vorgenommen wurde.

Nicht verwendetes Arzneimittel oder Abfallmaterial ist entsprechend den nationalen Anforderungen zu entsorgen.

7. MARKETING AUTHORISATION HOLDER

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2705-906 Terrugem SNT
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Co-marketing:

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8. MARKETING AUTHORISATION NUMBER

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10. Date of revision of the text

02/2017

11. LEGAL STATUS

prescription