SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atracurium Besylate Injection USP 10 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Atracurium Besylate USP 10mg

3. PHARMACEUTICAL FORM

Solution for Injection
A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atracurium besylate injection is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

4.2 Posology and method of administration

Use as an adjunct to general anaesthesiaAtracurium Besylate Injection should only be administered by intravenous injection. Do not give Atracurium Besylate Injection intramuscularly since this may result in tissue irritation and there are no clinical data to support this route of administration.

To avoid distress to the patient, Atracurium Besylate Injection should not be administered before unconsciousness has been induced. Atracurium Besylate Injection should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g. barbiturate solutions).

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

Initial bolus doses for intubation an initial atracurium besilate dose of 0.3 to 0.6 mg/kg (depending on the duration of full block required), given as an intravenous bolus injection, is recommended. This will provide adequate relaxation for about 15 to 35 minutes.

Endotracheal intubation can usually be accomplished within 90 to 120 seconds of the intravenous injection of 0.5 to 0.6 mg/kg. Maximum neuromuscular blockade is generally achieved approximately 3 to 5 minutes after administration. 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.

Although atracurium is potentiated by (approximately 35%) isoflurane or enflurane anaesthesia, the same initial atracurium besilate dose (0.3 to 0.6 mg/kg) may be used for intubation if given prior to the administration of these inhalation agents. However if the initial atracurium dose is administered after steady state anaesthesia with isoflurane or enflurane has been achieved, the dose of atracurium should be reduced by approximately one-third. Smaller dosage reductions may be considered with concomitant halothane anaesthesia since it has only a marginal (approximately 20%) potentiating effect on atracurium.

Maintenance doses Intermittent IV injection:

During prolonged surgical procedures neuromuscular blockade may be maintained with atracurium besilate maintenance doses of 0.1 to 0.2 mg/kg. Generally, under balanced anaesthesia, using maintenance doses of 0.1 mg/kg, the first maintenance dose is required within 20 to 45 minutes of the initial bolus dose, then typically at 15 to 25 minute intervals, however, the need for maintenance doses should be determined by the individual patient's requirements and response. Successive supplementary dosing does not give rise to accumulation of neuromuscular blocking effect.

Use as an infusion: After the initial atracurium bolus dose, neuromuscular blockade may be maintained during prolonged surgical procedures by administering atracurium besilate as a

continuous intravenous infusion at a rate of 0.3 to 0.6 mg/kg/hour. The infusion should not be commenced until early spontaneous recovery from the initial atracurium bolus dose is evident. Atracurium besilate infusion solutions may be prepared by admixing Atracurium Besylate Injection with an appropriate diluent (see below) to give an atracurium besilate concentration of 0.5 mg/ml to 5 mg/ml.
Atracurium Besylate Injection 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, and therefore full neuromuscular block may be maintained with approximately half the original infusion rate at these temperatures.
Compatibility with infusion solutions: Atracurium Besylate Injection diluted to 0.5 mg/ml with the following infusion solutions, and stored at 30°C protected from light, was shown to be stable for the times stated below

Infusion Solution	Period of stability
Sodium Chloride 0.9% Intravenous Infusion	24 hours
Glucose 5% Intravenous Infusion	24 hours
Glucose 4% and Sodium Chloride 0.18% Intravenous Infusion	24 hours
Ringer's Injection USP	24 hours
Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution for Injection)	4 hours

Atracurium Besylate Injection diluted to 5 mg/ml with the following infusion solutions, and stored at 30°C protected from light in 50 ml plastic syringes, was shown to be stable for the times stated below.

Infusion Solution	Period of stability
Sodium Chloride 0.9% Intravenous Infusion	24 hours
Glucose 5% Intravenous Infusion	24 hours
Glucose 4% and Sodium Chloride 0.18% Intravenous Infusion	24 hours
Ringer's Injection USP	24 hours
Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution for Injection)	8 hours

Reversal of neuromuscular blockade-
The neuromuscular blockade induced by atracurium can be reversed with an Anticholinesterase agent such as neostigmine or pyridostigmine, usually in conjunction with an anticholinergic agent such as atropine or glycopyrronium to prevent the adverse muscarinic effects of the anticholinesterase. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after the initial atracurium dose, or approximately 10 to 30 minutes after the last atracurium maintenance dose, when recovery of muscle twitch Has started. Complete reversal of neuromuscular blockade is usually achieved within 8 to 10 minutes after administration of the reversing agents.
Rare instances of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacological antagonism of atracurium induced neuromuscular blockade. As with other agents in this class, the tendency for residual neuromuscular block is increased if reversal is attempted at deep levels of blockade or if inadequate doses of reversal agents are employed.

Facilitation of mechanical ventilation in intensive care unit (ICU) patients
After an optional initial bolus dose of 0.3 to 0.6 mg/kg, neuromuscular block may be Maintained by administering a continuous atracurium besilate infusion at rates of between 11 and 13 microgram/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

Besilate 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.
Dosage considerationsUse in children: The dosage in children over the age of 1 month is similar to that in adults on a body weight basis, however, large individual variability in the neuromuscular response in paediatric patients indicates that neuromuscular monitoring is essential.
Use in neonates: The use of atracurium is not recommended in neonates since there are insufficient data available.
Use in the elderly: The standard dose of atracurium may be used in elderly patients, however, it is recommended that it be administered slowly.
Use in patients with reduced renal and/or hepatic function: Standard dosages may be used at All levels of renal or hepatic function, including endstage failure.
Use in patients with cardiovascular disease: In patients with significant cardiovascular disease The initial dose of atracurium should be administered over a period of at least 60 seconds

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed

4.4 Special warnings and precautions for use

Atracurium Besylate Injection should be used only by those skilled in the management of artificial respiration and only when facilities are immediately available for endotracheal intubation and for providing adequate ventilation support, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or control ventilation, and anticholinesterase agents should be immediately available for reversal of neuromuscular blockade.

Atracurium has no known effect on consciousness, pain threshold, or cerebration. In surgery, it should be used only with adequate general anaesthesia.
In common with other neuromuscular blocking agents, the potential for histamine release exists in susceptible patients during administration of atracurium besilate. Caution should be exercised in patients with a history suggestive of an increased sensitivity to the effects of histamine.
Do not give Atracurium Besylate Injection by intramuscular administration.
Atracurium Besylate Injection has an acid pH and therefore should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Atracurium Besylate Injection may be inactivated and a free acid may be precipitated.
When a small vein is selected as the injection site, Atracurium Besylate Injection should be flushed through the vein with physiological saline after injection. When other anaesthetic drugs are administered through the same indwelling needle or cannula as Atracurium Besylate Injection,
it is important that each drug is flushed through with an adequate volume of physiological saline.
Atracurium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of non-depolarising agents has been noted. A reduced dosage of atracurium and the use of a peripheral nerve stimulator for assessing neuromuscular blockade is especially important in these patients. Similar precautions should be taken in patients with severe electrolyte disorders.
Atracurium does not have significant vagal or ganglion blocking properties in the recommended dosage range. Consequently, atracurium will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery. Therefore, bradycardia during anaesthesia may be more common with atracurium than with other muscle relaxants.
As with other non-depolarising neuromuscular blocking agents, resistance to atracurium may develop in patients suffering from burns. Such patients may require increased doses of atracurium

depending on the time elapsed since the burn injury and the extent of the burn.
Atracurium Besylate Injection should be administered over a period of at least 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who
are hypovolaemic. Atracurium Besylate Injection is hypotonic and must not be applied into the infusion line of a blood transfusion.
Monitoring of serial creatine phosphokinase (CPK) values should be considered in asthmatic patients receiving high dose corticosteroids and neuromuscular blocking agents in intensive care units.
Special precautions should be taken in patients with known anaphylactic reactions to curares, as cross-reactivity may be possible with this product.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs which may enhance the neuromuscular blocking action of atracurium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular block induced by atracurium besylate. Atracurium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular block.

4.6 Fertility, pregnancy and lactation

Pregnancy

Atracurium crosses the placenta but there have been no demonstrated adverse effects in the foetus or newborn infant. Animal studies have indicated that atracurium has no adverse effects on foetal development. As with all neuromuscular blocking agents, the use of atracurium in the first three months of pregnancy should be avoided and it should not be used during the second and third trimesters unless clearly necessary.
Atracurium is suitable for maintenance of muscle relaxation during caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses. In an open study, atracurium besilate (0.3 mg/kg) was administered to 26 pregnant women during delivery by caesarean section. No harmful effects were attributable to atracurium in any of the newborn infants, although small amounts of atracurium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following caesarean section during which a neuromuscular blocking agent has been administered.
Anaesthesia during the third trimester of pregnancy exposes the mother to Mendelson syndrome (acid pneumopathy due to gastric acid aspiration). If a muscle relaxant is used at induction of anaesthesia, one should be chosen with a short onset and duration of action and low placental transfer and used in the lowest dose required to induce adequate neuromuscular relaxation. In patients receiving magnesium sulphate, the reversal of neuromuscular blockade may be unsatisfactory and the atracurium dose should be lowered as indicated.
BreastfeedingAtracurium has a relatively high molecular weight and is highly ionized at physiologic pH, both factors that markedly reduce transfer into milk. In addition, even though milk is slightly more acidic than plasma, any atracurium transferred into milk would be rapidly degraded.

Nevertheless, in view of the potential respiratory depressant effect on the neonate, especially if premature, it is recommended that if breastfeeding is started within 24 hours after administration of atracurium, the neonate is closely monitored.

4.7 Effects on ability to drive and use machines

It is not recommended to use potentially dangerous machinery or drive a car within 24 hours after full recovery from the neuromuscular blocking action of atracurium.

4.8 Undesirable effects

The adverse effects are reported in decreasing order of frequency within each system order class (SOC). As with most neuromuscular blocking agents, the potential exists for undesirable effects suggestive of histamine release in susceptible patients. In clinical trials (875 patients) reports of skin flushing ranged from 1% at doses up to 0.3 mg/kg, to 29% at doses of 0.6 mg/kg or greater. The incidence of transient hypotension ranged from 1 to 14% respectively for the corresponding dosages.
After prolonged administration of atracurium besilate in severely ill patients under intensive care, some incidences of muscle weakness and/or myopathy occurred. Most patients were concomitantly treated with corticosteroids. A causal relationship with atracurium therapy has not been established.
There have been rare 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). In clinical trials, there appears to be no correlation between plasma laudanosine concentration and the occurrence of seizures.

4.9 Overdose

Prolonged muscle paralysis and its consequences are the main signs of overdose. There is limited experience with atracurium overdosage following parenteral administration. The possibility of iatrogenic overdosage can be minimised by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of atracurium are likely to produce symptoms consistent with extensions of the usual pharmacological effects. Overdosage may increase the risk of histamine release and adverse cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this should include proper positioning, fluid administration, and the use of vasopressor agents if necessary. It is essential to maintain a patent airway with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation will be required since consciousness is not impaired. The duration of neuromuscular blockade may be prolonged and a peripheral nerve stimulator should be used to monitor recovery. Recovery may be hastened by the administration of an anticholinesterase agent such as neostigmine or pyridostigmine in conjunction with an anticholinergic agent such as atropine, once evidence of spontaneous recovery is present.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Atracurium besilate is a non-depolarising neuromuscular blocking agent (ATC code M03A C04) with an intermediate duration of action, administered intravenously to produce skeletal muscle relaxation.
Non-depolarising neuromuscular blocking agents antagonise the action of the neurotransmitter acetylcholine by competitively binding with cholinergic receptor sites on the motor endplate of the myoneural junction. These effects may be inhibited or reversed by the administration of anticholinesterases such as neostigmine or pyridostigmine.

As with other non-depolarising neuromuscular blocking agents, the time to onset or paralysis is reduced, and the duration of maximum effect prolonged, with increasing atracurium doses. Once recovery from atracurium's neuromuscular blocking effect begins, it proceeds more

rapidly than recovery from tubocurarine, alcuronium, and pancuronium. Regardless of the atracurium dose, the time from start of recovery (from complete block) to complete recovery (as measured by restoration of the tetanic response to 95% of normal) is approximately 30 minutes under balanced anaesthesia, and approximately 40 minutes under halothane, enflurane or isoflurane anaesthesia. Repeated doses have no cumulative effect on recovery rate. With initial atracurium besilate doses up to 0.5 mg/kg, plasma histamine levels were shown to increase by 15% in a dose dependant way, but haemodynamic changes were minor within this dose range. Following the administration of 0.6 mg/kg of atracurium besilate, histamine levels were shown to increase by 92%, and were shown to correlate with a transient (5 minutes) decrease in blood pressure and a brief (2 to 3 minutes) episode of skin flushing. While these effects are of little clinical significance in most patients, the possibility of substantial histamine release at recommended doses must be considered in sensitive individuals, or in patients in whom substantial histamine release would be especially hazardous (e.g. patients with significant respiratory or cardiovascular disease).

5.2 Pharmacokinetic properties

The pharmacokinetics of atracurium besilate in humans are essentially linear within the dose range of 0.3 to 0.6 mg/kg. The elimination half-life is approximately 20 minutes. The protein binding of atracurium is approximately 82%. The volume of distribution of atracurium is 0.16 l/kg and plasma clearance of atracurium is about 6.5 ml/min/kg. Some placental transfer occurs in humans. The umbilical venous to maternal venous drug concentration ratios are between 0.03 and 0.33 (mean 0.12+/- 0.04).

The duration of neuromuscular blockade produced by atracurium does not correlate with plasma pseudocholinesterase levels and is not altered by the absence of renal function. This is consistent with the results of in vitro studies which have shown that atracurium is inactivated in plasma via two non-oxidative pathways: ester hydrolysis, catalysed by non-specific esterases; and Hofmann elimination, a non-enzymatic chemical process which occurs at physiological pH and body temperature. The rate of Hofmann elimination, which is the principal route of elimination for atracurium, is increased at a higher pH or at higher temperatures, and reduced at a lower pH or lower temperatures.

Limited clinical experience on long term administration of atracurium besilate show only minimal effects of haemofiltration or haemodialysis on plasma levels of atracurium and its metabolites. The effects of haemoperfusion on plasma levels of atracurium and its metabolites are not known.

5.3 Preclinical safety data

No relevant information

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol, Benzene Sulphonic acid, Water for Injection

6.2 Incompatibilities

Not known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store between 2°C to 8°C. Do not freeze. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation

10 x 3 ml Amber Ampoule USP Type-I

6.6 Special precautions for disposal and other handling

None.

7. MARKETING AUTHORISATION HOLDER

Ciron Drugs & Pharmaceuticals Pvt. Ltd.
C- 1101 /1102, Lotus Corporate Park, Graham Firth Steel Compound,
Jay Coach Junction, Western Express Highway, Goregaon (East)
Mumbai- 400 063, India.

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21.11.2022

10. DATE OF REVISION OF THE TEXT

14/07/2023

11. Reference

https://www.medicines.org.uk/emc/product/6297/smpc#gref