

## **Product Summary**

### **1. Trade Name of the Medicinal Product**

Atracurium besylate 10 mg/ml injection.

### **2. Qualitative and Quantitative Composition**

Atracurium besylate 10 mg/ml injection is a clear solution for intravenous injection in 2.5 ml, 5 ml, 10 ml and 25 ml ampoules containing 25 mg, 50 mg, 100 mg and 250 mg, respectively, of Atracurium besylate.

### **3. Pharmaceutical Form**

Injection solution.

## **Clinical Particulars**

### **4.1. Therapeutic Indications**

Atracurium is a highly selective, competitive (non-depolarising) neuromuscular blocking agent. It is indicated:

- As an adjunct to general anaesthesia, to relax the skeletal muscles during a wide range of surgical procedures and to facilitate controlled ventilation of the lungs.
- For administration by continuous infusion to maintain neuromuscular blockade during prolonged surgical procedures.
- To facilitate endotracheal intubation where subsequent maintenance of neuromuscular relaxation is required.
- To maintain muscular relaxation during Caesarean section.

### **4.2. Posology and Method of Administration**

Dosage of atracurium besylate should be individualised for each patient and administered by an experienced anaesthetist on the basis of body weight, sensitivity of the patient, other simultaneously used narcotics and duration of surgery. As with all neuromuscular blocking agents, monitoring of neuromuscular function is recommended during use of atracurium in order to determine the individual dosage requirements.

Atracurium besylate 10mg/ml injection should be administered by means of intravenous injection or infusion.

#### **Use by intravenous injection in adults:**

At the induction, the recommended dose range is 0.3 - 0.6mg/kg-body weight, depending on the desired duration of full block. This will provide adequate muscle relaxation for about 15 to 35 minutes.

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

Supplementary doses of 0.1 to 0.2mg/kg may be used every 15 to 25 minutes as required to prolong full block. Successive supplementary doses do not lead to accumulation of

neuromuscular blocking effect and may be administered at the end of a block (beginning of recovery).

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

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

**Use by intravenous infusion in adults:**

Following an initial bolus injection of 0.3 to 0.6mg/kg, atracurium may be administered by continuous intravenous infusion at a rate of 0.3 to 0.6mg/kg/h (5 to 10mcg/kg/min); the usual dose is approximately 6mcg/kg/min to maintain neuromuscular block during long surgical procedures. When necessary the dosage can be adjusted using an appropriate method, for instance the tetany response.

When possible, infusions of atracurium should be administered through a separate infusion line.

During cardiopulmonary bypass surgery, atracurium may be administered by infusion at the recommended infusion rates. If hypothermia is induced to a body temperature of 25<sup>o</sup> to 26<sup>o</sup>C, the rate of inactivation of atracurium is reduced and full neuromuscular block may be maintained by using approximately half the infusion rate during normothermia. The usual dose is approximately 3.4mcg/kg/min.

When atracurium is diluted with the following solutions, giving concentrations of 0.5 to 0.9mg/ml, the drug will be stable in daylight at temperatures of up to 30°C for the following time periods:

| <b>Infusion solution</b>  | <b>Stable during</b> |
|---|----------------------|
| Sodium Chloride Intravenous Infusion (0.9% m/V)                       | 24 h                 |
| Glucose Intravenous Infusion (5% m/V)                                 | 8 h                  |
| Ringer's injection  | 8 h                  |
| Sodium Chloride (0.18% m/V) and Glucose (4% m/V) Intravenous Infusion | 8 h                  |
| Compound sodium Lactate Intravenous Infusion                          | 4 h                  |

**Use in children:**

For children over the age of 1 month, the dosage is similar to that in adults on a mg per kg body weight basis.

**Use in the elderly:**

Atracurium besylate may be used at standard dosage, although the size of the initial dose should be at the lower end of the dose range and the drug should be administered slowly.

**Use in patients with diminished renal and/or hepatic function:**

Atracurium besylate may be used at standard dosage for all degrees of renal or hepatic impairment, including end stage failure of these organs.

**Use in patients with cardiovascular diseases:**

In patients with clinically significant cardiovascular disease, the initial dose of atracurium besylate should be administered over a period of 1 to 2 minutes.

**Use in burn patients:**

Patients who suffer burn injury may develop resistance to non-depolarising neuromuscular blocking drugs, including atracurium, and increased doses may be required, depending on the extent of the burn and the time elapsed since its occurrence.

**Long-term Use in Intensive Care Unit:**

When there is a need for long-term controlled ventilation with use of atracurium in the Intensive Care Unit, the benefit-risk ratio of neuromuscular blockade must be considered.

Experience with muscular relaxants like atracurium in the Intensive Care Unit shows that there is a wide interpatient variability in dosage requirements and these requirements may decrease or increase with time.

On the basis of experience with atracurium in the Intensive Care Unit, it is likely that a dose increase may be required with long-term use.

It is not known whether haemodialysis, haemoperfusion or haemofiltration influence the plasma levels of atracurium or its metabolites.

**4.3. Contra-indications**

**Atracurium is contraindicated in patients known to have or with suspected hypersensitivity to the active and/or the excipients.**

**4.4. Special Warnings and Precautions for Use**

In common with all neuromuscular blocking agents, atracurium paralyses the respiratory as well other skeletal muscles (e.g. muscles of arms, legs, eyelids, and mouth) without having an effect on consciousness. Consequently, the drug should be administered only with adequate anaesthesia and only by an experienced anaesthetist familiar with its pharmacological properties. All facilities for endotracheal intubation and artificial respiration should be available for immediate use.

The neuromuscular block of atracurium is increased during hypothermia and decreases when rewarming the patient.

Atracurium should be administered with care to patients with myasthenia gravis, other neuromuscular diseases, and severe electrolyte imbalance, in view of the increased sensitivity of these patients to the effects of non-depolarising neuromuscular agents. Severe acidosis may result in a slight prolongation of action of atracurium.

In common with other neuromuscular blocking drugs, there is the potential for histamine release in susceptible patients during administration of atracurium. Therefore, caution should be exercised when administering atracurium to patients with a history suggesting an increased sensitivity to the effects of histamine.

It should be considered that, especially in patients with a history of allergy or asthma, bronchospasm may occur sporadically after the administration of atracurium. In such cases, the use of atracurium should be monitored very carefully.

Atracurium besylate should be administered slowly or in divided doses over a period of 1 to 2 minutes in patients who may be especially sensitive to a decrease in arterial blood pressure, e.g. patients with hypovolaemia, and in patients who are more susceptible to the effects of transient hypotonic conditions, such as patients with severe cardiovascular disease.

Patients with carcinomatosis especially when associated with bronchial carcinoma may exhibit a marked sensitivity to neuromuscular blocking agents, and the neuromuscular block produced may respond poorly to anticholinesterase agents.

Special care must be taken to ensure that there is adequate respiratory exchange before the patient is discharged from the care of the anaesthetist.

Atracurium does not show any significant vagal or ganglionic blocking effects in the recommended dose range. Consequently, when used in the recommended dose range, atracurium has no clinically significant effects on the heart rate.

Vagal stimulation during surgical procedures or bradycardia produced by other anaesthetic agents will not be counteracted by atracurium and, therefore, bradycardias may be more common with atracurium than with other muscle relaxants.

Atracurium is not recommended in children under the age of one month since not enough experience has been acquired in this age group so far.

Atracurium besylate (10mg/ml injection) is hypotonic and therefore should not be administered through an infusion line of a blood transfusion. Due to the hypotonic condition of the solution, it is recommended to dilute the intravenous injection 1:1 with the in 6.3 mentioned infusion solutions, as a precaution when used in children.

Atracurium besylate should not be mixed with thiopentone or any alkaline solutions in the same syringe since the high pH would cause inactivation of atracurium.

When a small vein is selected as the injection site, atracurium besylate (10mg/ml injection) should be flushed through the vein with physiological saline after injection. Where other (anaesthetic) drugs are administered through the same in-dwelling needle or cannula as atracurium, it is important that each drug is flushed through with physiological saline or water for injections in adequate volume.

Animal studies in malignant hyperthermia in susceptible species (Swine) and clinical studies in susceptible patients indicate that atracurium does not trigger malignant hyperthermia.

Atracurium can be administered during ophthalmic surgery since the drug does not influence the intra-ocular pressure.

Patients with a purulent intrathoracic disease may show a reduction in neuromuscular potency of atracurium.

Patients undergoing surgical procedures of a short duration may be at risk of inappropriately having an early tracheal extubation, as there is a risk of postoperative residual neuromuscular blockade.

#### **4.5. Interactions with other Medicaments and other forms of Interaction**

The neuromuscular blocking action of atracurium may be enhanced by concomitant use of inhalational anaesthetic agents; such as halothane, isoflurane and enflurane. Furthermore, there are a number of drugs, which may enhance and/or prolong the neuromuscular blockade when used simultaneously with atracurium:

- Certain antibiotics including the aminoglycosides (such as neomycin), polypeptide antibiotics (such as polymyxin), spectinomycin, tetracycline, lincomycin and clindamycin
- anti-arrhythmic agents: procainamide, quinidine, lidocaine (lignocaine)
- beta-adrenoceptor blocking agents: propranolol
- Calcium-channel blocking agents
- Diuretics: furosemide (frusemide) and possibly mannitol, thiazide diuretics, acetazolamide

- Magnesium sulphate
- Ketamine
- Lithium salts
- Ganglionic blocking agents, trimetaphan, and hexamethonium

In rare cases, certain agents may aggravate the symptoms of an existing myasthenia gravis, unmask latent myasthenia gravis, or cause this disease itself. In such cases, an increased sensitivity to atracurium should be expected. These agents include:

- various antibiotics
- Anti-arrhythmic agents: procainamide, quinidine
- Beta-adrenoceptor blocking agents: propranolol, oxprenolol
- Anti-rheumatic agents: chloroquine, D-penicillamine
- Trimetaphan
- Steroids
- Chlorpromazine
- Lithium
- Phenytoin

In patients who are receiving long-term treatment with anti-epileptic agents, the onset of non-depolarising neuromuscular block is likely to be lengthened and the duration of the block shortened.

Administration of combinations of other non-depolarising neuromuscular blocking drugs with atracurium may produce a degree of neuromuscular blockade, which is larger than expected after administration of an equipotent total dose of atracurium alone. This synergistic effect can differ from one combination of agents to another.

Depolarising muscle relaxants, such as suxamethonium, should not be administered to prolong the neuromuscular blocking effect of non-depolarising agents, such as atracurium, since the combined action of these drugs may result in a prolonged and complex neuromuscular blockade ("mixed block" or "phase II-block") which is difficult to reverse with anticholinesterase agents.

#### **4.6. Pregnancy and Lactation**

Insufficient information is available about the use of atracurium in pregnant women to be able to evaluate the possible harmfulness. So far, in animal tests no indications have been found showing harmful effects on the foetal development. Therefore, in common with all neuromuscular blocking drugs, atracurium should be used during pregnancy only if the potential benefit to the mother outweighs any potential risk to the foetus.

Atracurium besylate may be administered to maintain muscle relaxation during Caesarean section. Following recommended doses, atracurium does not cross the placental barrier in clinically significant amounts. It is not known to what extent metabolites of atracurium cross the placental barrier.

It is not known whether atracurium is excreted in human milk. No atracurium was found in human milk after its use during Caesarean section. However, from a safety point of view temporary discontinuation of breast-feeding is recommended for at least 24 hours following administration of atracurium.

#### **4.7. Effects on Ability to Drive and Use Machines**

Not relevant, in view of the therapeutic indication for this product.

#### **4.8. Undesirable Effects**

In common with most neuromuscular blocking agents, atracurium may have the potential for histamine release in sensitive patients. Associated with the use of atracurium, there have been reports of skin flushing, transient hypotension and, rarely, bronchospasm, which have been attributed to histamine release. Moreover, tachycardia was observed. In seldom cases skin rash occurs. Anaphylactic reactions and laryngospasm appear very rarely.

#### **4.9. Overdose**

##### Symptoms

Prolonged muscle relaxation and its effects are the main symptoms of an overdosage of atracurium.

##### Treatment

In case of overdosage, controlled ventilation must be maintained until adequate spontaneous respiration has returned. Since atracurium does not influence consciousness, the patient can be fully sedated. When there is evidence of spontaneous recovery, an anticholinesterase agent such as neostigmine or edrophonium in conjunction with atropine or glycopyrronium bromide, may be administered to hasten recovery.

### **Pharmacological Properties**

#### **5.1. Pharmacodynamic Properties**

Atracurium is a selective competitive (non-depolarising) neuromuscular blocking agent. It prevents neurotransmission by competition with acetylcholine for cholinergic receptor sites of the motor end plate, but does not produce any stimulation of the muscle by itself. This results in muscle relaxation.

#### **5.2. Pharmacokinetic Properties**

The onset and duration of action of atracurium besylate are dose dependent. The effect of the recommended dose of atracurium besylate occurs within 2 minutes after administration and maximum neuromuscular blockade is usually reached within 3 to 5 minutes. Good intubation conditions are reached within 1.5 to 2 minutes in most patients. The recommended dose of 0.3 to 0.6mg/kg for adults causes a relaxation of 15 to 35 minutes. Supplementary doses of 0.1 to 0.2mg/kg can prolong the duration of the effect for 15 to 45 minutes. After a dose of 0.3mg atracurium besylate per kg in humans, a plasma concentration of approximately 3mcg/ml was measured after 3 minutes.

Atracurium undergoes degradation via Hofmann elimination, a non-enzymatic breakdown process occurring at physiological pH and temperature, and also by ester hydrolysis by non-specific plasma esterases.

The duration of action of atracurium is not altered to any significant extent by variations in patient's blood pH and body temperature within the physiological range. The metabolites formed have a low activity and are produced in such small amounts that the contribution of the metabolites to the effect of atracurium can be neglected.

Atracurium produces a weak inhibition of acetylcholinesterase and butyrylcholinesterase *in vitro* with no clinical significance. Investigation of plasma from patients with pseudocholinesterase deficiency has shown that the inactivation of atracurium is continued unaffected.

The duration of the neuromuscular blocking effect of atracurium does not depend on metabolism and elimination by liver or kidneys. Consequently, the duration of action of atracurium besylate is not likely to be influenced by impaired renal, hepatic or circulatory function.

Plasma protein binding of atracurium besylate is 82%. Plasma proteins do not influence the rate nor the mode of atracurium besylate degradation.

The elimination half-life of atracurium besylate is between 20 and 30 minutes.

### 5.3. Preclinical Safety Data

*Carcinogenicity:* Carcinogenicity studies have not been performed.

*Teratogenicity:* Animal studies indicate that atracurium has no significant effects on foetal development

*Fertility:* Fertility studies have not been performed.

*Mutagenicity:* Atracurium has been evaluated in short-term mutagenicity tests. It was not mutagenic in either the *in vitro* Ames salmonella assay at concentrations up to 1,000mcg/plate or in an *in vivo* rat bone marrow assay at doses up to those that produced neuromuscular blockade. In a second *in vitro* test, the mouse lymphoma assay, mutagenicity was not observed at doses up to 60mcg/ml, which killed up to 50% of the treated cells. It was moderately mutagenic at concentrations of 80mcg/ml without metabolic activation and was weakly mutagenic at very high concentrations (1,200mcg/ml) when metabolising enzymes were added at both concentrations, over 80% of the cells were killed.

In view of the nature of human exposure to atracurium, the mutagenic risk in surgical patients undergoing muscle relaxation with atracurium must be considered negligible.

## Pharmaceutical Particulars

### 6.1. List of Excipients

Atracurium besylate 10mg/ml injection contains benzenesulfonic acid (to adjust the pH to 3.2-3.7) and water for injections. The injection does not contain any preservatives and is filled in ampoules under nitrogen atmosphere. The solution is strongly hypotonic.

### 6.2. Incompatibilities

Atracurium injection should not be mixed in the same syringe with thiopentone or alkaline solutions since the high pH may inactivate the drug.

### 6.3. Shelf Life

The shelf life of Atracurium besylate 10 mg/ml injection is 1.5 year.

The expiry date (month and year) is printed on the package after the words "do not use after" and on the ampoules after "Exp".

When atracurium is diluted with the following solutions, giving concentrations of 0.5 to 0.9 mg/ml, the drug will be stable in daylight at temperatures of up to 30°C for the following time periods:

|  |               |
|--|---------------|
| Infusion Solution                                | stable during |
| Sodium Chloride Intravenous Infusion (0.9% m/V)  | 24 h          |
| Glucose Intravenous Infusion (5% m/V)            | 8 h           |
| Ringer's Injection                               | 8 h           |
| Sodium Chloride (0.18% m/V) and Glucose (4% m/V) |               |
| Intravenous Infusion                             | 8 h           |
| Compound Sodium Lactate Intravenous Infusion     | 4 h           |

Any unused solution in opened ampoules should be discarded immediately after use.

**6.4. Special Precautions for Storage**

The ampoules should be stored in the original packaging, protected from light, at 2 - 8°C (do not freeze). When Atracurium besylate 10 mg/ml injection is stored for one month at 25°C the loss of potency will be 5%.

Keep all medicines out of the reach of children

**6.5. Nature and Contents of Container**

Ampoules of 2.5, 5 and 10ml (both packaged per 5 or 10 pieces) containing 25, 50 and 100mg of Atracurium besylate, respectively. Ampoules of 25 ml (packaged per 2, 5 or 10 pieces) containing 250 mg of Atracurium besylate.

**6.6. Instruction for Use/Handling**

Finger protection should be used when ampoules are opened.

**Administrative Data**

**7. Marketing Authorisation Holder**

Antigen International Limited  
Roscrea  
Co Tipperary  
Ireland

**8. Marketing Authorization Number**

PL 02848/0205

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

04/07/2006

**10 DATE OF REVISION OF THE TEXT**

04/07/2006