Proposed Core Safety Profile (CSP) for EU PSUR Worksharing Scheme

Active:

Atracurium

Period covered by the submitted PSUR(s):

PSUR (17 December 06 – 16 December 09)

Introduction:

This proposed CSP is based on GlaxoSmithKline’s Company Core Data Sheet (CCDS).

National labels may be subject to on-going variations to align with the CCDS, and/or may contain amendments requested by national regulatory authorities.

This document is formatted as an SmPC but contains only sections 4.3, 4.4, 4.5, 4.6, 4.7, 4.8 and 4.9.
Atracurium
Proposed Core Safety Profile (CSP)

4.3 Contraindications

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

Multi-dose vial:
- Atracurium (Multi-dose vial) is contraindicated in patients known to be hypersensitive to atracurium, cisatracurium, benzenesulfonic acid or benzyl alcohol.

4.4 Special warnings and precautions for use

IN COMMON WITH ALL THE OTHER NEUROMUSCULAR BLOCKING AGENTS ATRACURIUM PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES BUT HAS NO EFFECT ON CONSCIOUSNESS. ATRACURIUM 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 administration. Caution should be exercised in administering atracurium 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.

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 does not have significant vagal or ganglionic blocking properties in the recommended dosage range. Consequently, atracurium 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, other forms of neuromuscular disease and severe electrolyte imbalance.
Atracurium 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 is inactivated by high pH and so must not be mixed in the same syringe with thiopentone or any alkaline agent.

When a small vein is selected as the injection site, atracurium 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 it is important that each drug is flushed through with an adequate volume of physiological saline.

Atracurium 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 hyperthermia indicate that atracurium 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.

**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).

**Multi-dose vial:**

Benzyl alcohol is used as an antimicrobial preservative in many parenteral drug formulations. Because of reports linking the use of parenteral drug formulations containing benzyl alcohol to morbidity and mortality amongst low weight neonates such formulations should be used with caution in neonates and theoretically, in other patient groups suspected of possessing a reduced ability to metabolise benzyl alcohol.

**4.5 Interactions with other medicinal products and other forms of interaction**

The neuromuscular block produced by atracurium 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.
- Antiarrhythmic drugs: propranolol, calcium channel blockers, lignocaine, procainamide and quinidine.
- Diuretics: frusemide and possibly mannitol, thiazide diuretics and acetazolamide.
Magnesium sulphate.
- 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 would be consequent on such a development. Such drugs include various antibiotics, beta-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 may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of atracurium 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 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 has no significant effects on foetal development.

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

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.

Breast-feeding

It is not known whether atracurium is excreted in human milk.
4.7 Ability to perform tasks that require judgement, motor or cognitive skills

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 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.
### Clinical Trial Data

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th>Common</th>
<th>Hypotension (mild, transient)#, Skin flushing#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>Bronchospasm#</td>
</tr>
</tbody>
</table>

### Postmarketing Data

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Very rare</th>
<th>Anaphylactic reaction, anaphylactoid reaction, including shock, circulatory failure and cardiac arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving atracurium in conjunction with one or more anaesthetic agents.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorder</th>
<th>Not known</th>
<th>Seizures</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
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<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Rare</th>
<th>Urticaria</th>
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<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
<th>Not known</th>
<th>Myopathy, muscle weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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.</td>
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</tbody>
</table>

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

Symptoms and 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.