Package Leaflet: Information for the Patient

Mivacron Injection 2 mg/ml
mivacurium

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions about your illness or your medicine, ask your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

What is in this leaflet:

1. What Mivacron is and what it is used for

Mivacron contains a medicine called mivacurium. This belongs to a group of medicines called muscle relaxants.

Mivacron is used:
- to relax muscles during operations on adults and children 2 months of age and over.
- to help insert a tube into the windpipe (tracheal intubation), if a person needs help to breathe

Ask your doctor if you would like more explanation about this medicine.

2. What you need to know before you are given Mivacron

Do not have Mivacron if:
- you are allergic to mivacurium, any other muscle relaxant or any of the other ingredients in Mivacron (listed in Section 6)
- you or your family have reacted badly to an anaesthetic before.

Do not have Mivacron if any of the above apply to you. If you are not sure, talk to your doctor, nurse or pharmacist before you have Mivacron.

Warnings and precautions
Talk to your doctor, nurse or pharmacist before having this medicine if:
- you have muscle weakness, tiredness or difficulty in co-ordinating your movements (myasthenia gravis)
- you have a neuromuscular disease, such as a muscle wasting disease, paralysis, motor neurone disease or cerebral palsy
- you have a burn which requires medical treatment
- you have ever had an allergic reaction to any muscle relaxant that was given as part of an operation.

Talk to your doctor before having this medicine, if you have or have ever had any of the following:

- Tetanus
- A severe or long-standing infection such as tuberculosis (TB)
- Any long-standing illness which has left you weak
- Cancer
- Anaemia
- Malnutrition
- An under-active thyroid gland
- Heart disease
- Stomach ulcers
- Burns
- Liver or kidney disease

Tell your doctor if:

- You are pregnant or have been pregnant recently or you have given birth in the last 6 weeks.
- You have been diagnosed as having a genetically determined abnormal cholinesterase.
- You are particularly sensitive to histamine or if you have asthma.

If you are not sure if any of the above apply to you, talk to your doctor, nurse or pharmacist before you are given Mivacron.

Other medicines and Mivacron

Tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because these medicines can affect how well Mivacron works or can cause side effects.

In particular tell your doctor, nurse or pharmacist if you are taking any of the following:

- anaesthetics (used to reduce sensation and pain during surgical procedures)
- antibiotics (used to treat infections)
- medicines for uneven heart beats (anti-arrhythmics)
- medicines for high blood pressure
- water tablets (diuretics), such as furosemide (previously known as frusemide)
- medicines for inflammation of the joints, such as chloroquine or d-penicillamine
- steroids
- medicines for mental illness, such as lithium, monoamine oxidase inhibitors (MAOIs) or chlorpromazine (which can also be used for sickness)
- medicines containing magnesium.
- medicines used to treat depression and/or anxiety SSRIs (selective serotonin reuptake inhibitors) including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram

Pregnancy and breast-feeding

If you are pregnant, or are breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine.

Driving and using machines

It can be dangerous to drive or operate machinery too soon after having had an operation. Your doctor will tell you how long to wait before you can drive and use machinery.

3. How Mivacron is given

How your injection is given
You will never be expected to give yourself this medicine. It will always be given to you by a person who is qualified to do so.

Mivacron can be given:
- as a single injection into your vein (intravenous bolus injection)
- as a continuous infusion into your vein. This is where the drug is slowly given to you over a long period of time.

Your doctor will decide the way you are given the drug and the dose you will receive. It will depend on:
- your body weight
- the amount and duration of muscle relaxation required
- your expected response to the medicine.

Children under 2 months old should not have this medicine.

If you receive more Mivacron than you should
Mivacron will always be given under carefully controlled conditions. However, if you think that you have been given more than you should tell your doctor or nurse immediately.

4. Possible side effects

Like all medicines, Mivacron can cause side effects, although not everybody gets them.

Allergic reactions (may affect up to 1 in 10,000 people)
If you have an allergic reaction, tell your doctor or nurse straight away. The signs may include:
- sudden wheeziness, chest pain or chest tightness
- swelling of your eyelids, face, lips, mouth or tongue
- a lumpy skin rash or 'hives' anywhere on your body
- a collapse

Very Common (may affect more than 1 in 10 people)
- reddening of the skin

Uncommon (may affect up to 1 in 100 people)
- increase in heart rate
- decrease in blood pressure
- wheezing or coughing
- rash or urticaria (lumpy skin rash) or 'hives' anywhere on your body

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mivacron

- Keep out of the sight and reach of children.
- Do not use Mivacron after the expiry date which is stated on the pack after 'Exp'.
- Store below 25^{o}C. Do not freeze.
- Store in the original package to protect from light.

- When Mivacron is made up it should be used straight away. Do not throw away any medicines via wastewater or household waste. Your doctor, nurse or pharmacist will throw away any medicine that is no longer required. This will help protect the environment.

6. Contents of the pack and other information

What Mivacron contains

- The active substance is mivacurium chloride.
- The other ingredients are hydrochloric acid and Water for Injections.

What Mivacron looks like and contents of the pack

- Mivacron solution for injection comes in ampoules containing 5 ml or 10 ml of the product.

Marketing authorisation holder and manufacturer

Marketing Authorisation holder:
Aspen Pharma Trading Limited, 3016 Lake Drive, City West Business Campus, Dublin 24, Ireland
Service-Tel: 0800 008 7392 (+ 44 1748 828 391)
Manufacturer:
GlaxoSmithKline Manufacturing S.p.A., Strada Provinciale Asolana 90, 43056 San Polo di Torrile, Parma, Italy.

Aspen Pharma Ireland Limited, One George's Quay Plaza, Dublin 2, Ireland.

Aspen Bad Oldesloe GmbH, 32-36 Industriestrasse, 23843 Bad Oldesloe, Germany

Other formats:

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:
0800 198 5000 (UK only).

Please be ready to give the following information:
Product name **Mivacron Injection 2 mg/ml**
Reference number PL 39699/0094

This is a service provided by the Royal National Institute of Blind People.

This leaflet was last revised in October 2020

The following information is intended for medical or healthcare professionals only

Mivacron Injection 2 mg/ml
mivacurium

Product Summary

1. Trade Name of the Medicinal Product

Mivacron Injection 2mg/ml

2. Qualitative and Quantitative Composition

Mivacurium chloride 2.14mg in each 1ml of product

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Liquid for injection

Clinical Particulars

4.1 Therapeutic Indications

Mivacron is a highly selective, short-acting, non-depolarising neuromuscular blocking agent with a fast recovery profile. Mivacron is used as an adjunct to general anaesthesia to relax skeletal muscles and to facilitate tracheal intubation and mechanical ventilation in adults, children and infants 2 months and over.

This formulation contains no antimicrobial preservative and is intended for single patient use.

4.2 Posology and Method of Administration

Use By Injection In Adults
Mivacron is administered by intravenous injection. The mean dose required to produce 95% suppression of the adductor pollicis single twitch response to ulnar nerve stimulations (ED95) is 0.07 mg/kg (range 0.06 to 0.09) in adults receiving narcotic anaesthesia.

The recommended bolus dose range for healthy adults is 0.07-0.25 mg/kg. The duration of neuromuscular blockade is related to the dose. Doses of 0.07, 0.15, 0.20 and 0.25 mg/kg produce clinically effective block for approximately 13, 16, 20 and 23 minutes respectively.

Doses of up to 0.15 mg/kg may be administered over 5 to 15 seconds. Higher doses should be administered over 30 seconds in order to minimise the possibility of occurrence of cardiovascular effects.

The following dose regimens are recommended for tracheal intubation:

I A dose of 0.2 mg/kg, administered over 30 seconds, produces good to excellent conditions for tracheal intubation within 2 to 2.5 minutes.

II A dose of 0.25 mg/kg administered as a divided dose (0.15 mg/kg followed 30 seconds later by 0.1 mg/kg) produces good to excellent conditions for tracheal intubation within 1.5 to 2.0 minutes of completion of administration of the first dose portion.

With Mivacron, significant train-of-four fade is not seen during onset. It is often possible to intubate the trachea before complete abolition of the train-of-four response of the adductor pollicis muscle has occurred.

Full block can be prolonged by maintenance doses of Mivacron. Doses of 0.1 mg/kg administered during narcotic anaesthesia each provide approximately 15 minutes of additional clinically effective block. Successive supplementary doses do not give rise to accumulation of neuromuscular blocking effect.

The neuromuscular blocking action of Mivacron is potentiated by isoflurane or enflurane anaesthesia. If steady-state anaesthesia with isoflurane or enflurane has been established, the recommended initial Mivacron dose should be reduced by up to 25%. Halothane appears to have only a minimal potentiating effect on Mivacron and dose reduction of Mivacron is probably not necessary.

Once spontaneous recovery is underway it is complete in approximately 15 minutes and is independent of the dose of Mivacron administered.

The neuromuscular block produced by Mivacron can be reversed with standard doses of anticholinesterase agents. However, because spontaneous recovery after Mivacron is rapid, a reversal may not be routinely required as it shortens recovery time by only 5-6 minutes.

<u>Use as an Infusion in Adults</u>

Continuous infusion of Mivacron may be used to maintain neuromuscular block. Upon early evidence of spontaneous recovery from an initial Mivacron dose, an infusion rate of 8 to 10 micrograms/kg/min (0.5 to 0.6 mg/kg/hr) is recommended.

The initial infusion rate should be adjusted according to the patient's response to peripheral nerve stimulation and clinical criteria. Adjustments of the infusion rate should be made and should be increments of approximately 1 microgram/kg/min

(0.06 mg/kg/hr). In general, a given rate should be maintained for at least 3 minutes before a rate change is made. On average, an infusion rate of 6 to 7 micrograms/kg/minute will maintain neuromuscular block within the range of 89% to 99% for extended periods in adults receiving narcotic anaesthesia. During steady-state isoflurane or enflurane anaesthesia, reduction in the infusion rate by up to 40% should be considered. A study has shown that the mivacurium infusion rate requirement should be reduced by up to 50% with sevoflurane. With halothane, smaller reductions in infusion rate may be required.

Spontaneous recovery after Mivacron infusion is independent of the duration of infusion and comparable to recovery reported for single doses.

Continuous infusion of Mivacron has not been associated with the development of tachyphylaxis or cumulative neuromuscular blockade.

Mivacron (2 mg/ml) may be used undiluted for infusion.

Mivacron is compatible with the following infusion fluids.

Sodium chloride intravenous infusion (0.9% w/v)
Glucose intravenous infusion (5% w/v)
Sodium chloride (0.18% w/v) and glucose (4% w/v) intravenous infusion
Lactated Ringer's Injection United States Pharmacopoeia (USP)

When diluted with the listed infusion solutions in the proportion of 1 plus 3 (i.e. to give 0.5 mg/ml) Mivacron injection has been shown to be chemically and physically stable for at least 48 hours at 30^{o}C. However, since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use, administration should commence as soon as possible thereafter, and any remaining solution should be discarded.

<u>Doses in Infants and Children Aged 2 Months - 12 Years</u>
Mivacron has a faster onset, shorter clinically effective duration of action and more rapid spontaneous recovery profile in infants and children than in adults.

The ED95 in infants aged 2 to 6 months is approximately 0.07 mg/kg; and in infants and children aged 7 months to 12 years is approximately 0.1 mg/kg.

Pharmacodynamic data for recommended initial doses in infants and children are summarised in the following table:

Age	**Dose for Tracheal Intubation**	**Time to Maximum Neuromuscular Block (min)**	**Duration of Clinically Effective Block (min)**
2 - 6 months[A]	0.15 mg/kg	1.4	9
7 months - 12 years[B]	0.2 mg/kg	1.7	9

[A]Data obtained during halothane anaesthesia.

[B]Data obtained during halothane or narcotic anaesthesia.

Since maximum block is usually achieved within 2 minutes following administration of these doses, tracheal intubation should be possible within this time.

Infants and children generally require more frequent maintenance doses and higher infusion rate than adults. Pharmacodynamic data for maintenance doses are summarised in the table below together with recommended infusion rates:

Age	**Maintenance Dose**	**Duration of Clinically Effective Block (min)**	**Average Infusion Rate Required to Maintain 89-99% Neuromuscular Block**
2 months - 12 years[A]	0.1 mg/kg	6 - 9	11 – 14 mcg/kg/min (0.7 - 0.9 mg/kg/hr)

[A]Data obtained during halothane or narcotic anaesthesia.

The neuromuscular blocking action of mivacurium is potentiated by inhalational agents. A study has shown that the mivacurium infusion rate requirement should be reduced by up to 70% with sevoflurane in children aged 2 – 12 years.

Once spontaneous recovery is underway, it is complete in approximately 10 minutes.

Dose in Neonates and Infants < 2 Months of Age

The safety and efficacy of Mivacron in neonates and infants < 2 months has not yet been established. Currently available data are described in section 5.1, but no recommendation on posology can be made.

Dose in the Elderly

In elderly patients receiving single bolus doses of Mivacron, the onset time, duration of action and recovery rate may be extended relative to younger patients by 20 to 30%. Elderly patients may also require decreased infusion rates or smaller or less frequent maintenance bolus doses.

Dose in Patients with Cardiovascular Disease

In patients with clinically significant cardiovascular disease, the initial dose of Mivacron should be administered over 60 seconds. Mivacron has been administered in this way with minimal haemodynamic effects to patients undergoing cardiac surgery.

Dose in Patients with Reduced Renal Function

In patients with end-stage renal failure the clinically effective duration of block produced by 0.15 mg/kg is approximately 1.5 times longer than in patients with normal renal function. Subsequently, dosage should be adjusted according to individual clinical response.

Prolonged and intensified neuromuscular blockade may also occur in patients with acute or chronic renal failure as a result of reduced levels of plasma cholinesterase (see section 4.4 Special Warnings and Precautions for Use).

Dose in Patients with Reduced Hepatic Function
In patients with end-stage liver failure the clinically effective duration of block produced by 0.15 mg/kg is approximately three times longer than in patients with normal hepatic function. This prolongation is related to the markedly reduced plasma cholinesterase activity seen in these patients. Subsequently, dosage should be adjusted according to individual clinical response.

Dose in Patients with Reduced Plasma Cholinesterase Activity
Mivacurium is metabolised by plasma cholinesterase. Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g. patients heterozygous or homozygous for the atypical plasma cholinesterase gene), in various pathological conditions (see section 4.4 Special Warnings and Precautions for Use) and by the administration of certain drugs (see interactions with other medicaments). The possibility of prolonged neuromuscular block following administration of Mivacron must be considered in patients with reduced plasma cholinesterase activity. Mild reductions (i.e. within 20% of the lower limit of the normal range) are not associated with clinically significant effects on duration (See Contra-indications and Special Warnings and Precautions for information about use in patients who are homozygous or heterozygous for the plasma cholinesterase gene).

Dose in Obese Patients
In obese patients (those weighing 30% or more above their ideal bodyweight for height), the initial dose of Mivacron should be based upon ideal bodyweight and not actual bodyweight.

Instructions to open the ampoule
See Section 6.6 Special precautions for disposal and other handling for further information.

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

4.3 Contraindications

Mivacron should not be administered to patients known to have allergic hypersensitivity to the drug.

Mivacron is contraindicated in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see section 4.4 Special warnings and precautions for use).

4.4 Special Warnings and Precautions for Use

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

Prolonged and intensified neuromuscular blockade following mivacurium may occur secondary to reduced plasma cholinesterase activity in the following states or pathological conditions:

- Physiological variation as in pregnancy and the puerperium (see Pregnancy and Lactation).
- Genetically determined abnormalities of plasma cholinesterase (see below and Contraindications).
- Severe generalised tetanus, tuberculosis and other severe or chronic infections.
- Chronic debilitating disease, malignancy, chronic anaemia and malnutrition.
- Myxoedema and collagen diseases.
- Decompensated heart disease.
- Peptic ulcer.
- Burns (see below).
- End-stage hepatic failure, (see Dosage and Administration).
- Acute, chronic or end-stage renal failure (see Dosage and Administration).
- Iatrogenic: following plasma exchange, plasmapheresis, cardiopulmonary bypass, and as a result of concomitant drug therapy (see Interactions).

In common with suxamethonium/succinylcholine, adult and paediatric patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of Mivacurium. In three such adults patients, a small dose of 0.03 mg/kg (approximately the ED_{10-20} in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes.

In patients heterozygous for the atypical plasma cholinesterase gene, the clinically effective duration of block of mivacurium 0.15 mg/kg is approximately 10 min longer than in control patients.

Once spontaneous recovery had begun, neuromuscular block in these patients was antagonised with conventional doses of neostigmine.

Patients with burns may develop resistance to non-depolarising neuromuscular blocking agents and require increased doses. However such patients may also have reduced plasma cholinesterase activity, requiring dose reduction. Consequently burn patients should be given a test dose of 0.015-0.020 mg/kg Mivacron followed by appropriate dosing guided by monitoring of block with a nerve stimulator.

Caution should be exercised in administering Mivacron to patients with a history suggestive of an increased sensitivity to the effects of histamine e.g. asthma. If Mivacron is used in this group of patients it should be administered over 60 seconds.

High rates of cross-sensitivity (greater than 50%) between neuromuscular blocking agents have been reported. Therefore, where possible, before administering mivacurium, hypersensitivity to other neuromuscular blocking agents should be excluded. Mivacurium 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.

Mivacron 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.

In adults, doses of Mivacron $\geq$ 0.2 mg/kg ($\geq$3 x ED95) have been associated with histamine release when administered by rapid bolus injection. However, the slower administration of the 0.2 mg/kg Mivacron dose and the divided administration of the 0.25 mg/kg Mivacron dose minimised the cardiovascular effects of these doses. Cardiovascular safety did not appear to be compromised in children given a rapid bolus dose of 0.2 mg/kg in clinical studies.

The use in neonates and infants < 2 months is not recommended due to limited data. (see also section 4.2 and 5.1)

Mivacron does not have significant vagal or ganglion blocking properties in the recommended dosage range. Recommended doses of Mivacron consequently have no clinically significant effects on heart rate and 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 mivacurium can be expected in patients with Myasthenia Gravis, other forms of neuromuscular disease and cachectic patients. Severe acid base or electrolyte abnormalities may increase or reduce sensitivity to mivacurium.

Mivacron solution is acidic (approximately pH 4.5) and should not be mixed in the same syringe or administered simultaneously through the same needle as highly alkaline solutions (e.g. barbiturate solutions). It has been shown to be compatible with some commonly used peri-operative drugs supplied as acidic solutions e.g. fentanyl, alfentanil, sufentanil, droperidol and midazolam. Where

other anaesthetic agents are administered through the same indwelling needle or cannula as used for Mivacron, and compatibility has not been demonstrated, it is recommended that each drug is flushed through with physiological saline.

Studies in malignant hyperthermia-susceptible pigs, indicated that Mivacron does not trigger this syndrome. Mivacron has not been studied in malignant hyperthermia-susceptible patients.

No data are available on the long-term use of Mivacron in patients undergoing mechanical ventilation in the intensive care unit.

Reversal of Neuromuscular Block: as with other neuromuscular blocking agents, evidence of spontaneous recovery should be observed prior to administration of reversal agent (e.g. neostigmine). The use of a peripheral nerve stimulator to evaluate recovery prior to and following reversal of neuromuscular block is strongly recommended.

Pharmaceutical Precautions – see section 6.2 Incompatibilities and section 6.4 Special precautions for disposal and other handling.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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

Mivacron has been safely administered following succinylcholine facilitated intubation. Evidence of spontaneous recovery from succinylcholine should be observed prior to administration of Mivacron.

In common with all non-depolarising neuromuscular blocking agents, the magnitude and/or duration of non-depolarising neuromuscular block may be increased and infusion requirements may be reduced 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 thiazides, mannitol and acetazolamide
- magnesium salts
- ketamine
- lithium salts
- ganglion blocking drugs: trimetaphan, hexamethonium

Drugs that may reduce plasma cholinesterase activity may also prolong the neuromuscular blocking action of Mivacron. These include anti-mitotic drugs, monoamine oxidase inhibitors, ecothiophate iodine, pancuronium, organophosphates, anticholinesterases, certain hormones, bambuterol and selective serotonin reuptake inhibitors.

Rarely, certain drugs may aggravate or unmask latent Myasthenia Gravis or actually induce a Myasthenic syndrome: increased sensitivity to Mivacron would be consequent on such a development. Such drugs include various antibiotics, beta-blockers (propranolol, oxprenolol), antiarrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, D-pencillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with Mivacron may produce a degree of neuromuscular blockade in excess of that which might be expected from an equipotent total dose of Mivacron. 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, as this may result in a prolonged and complex block which can be difficult to reverse with anticholinesterase drugs.

4.6. Fertility, Pregnancy and Lactation

Fertility studies have not been performed.

Animal studies have indicated that mivacurium has no adverse effect on foetal development.

Mivacurium should not be used during pregnancy unless the expected clinical benefit to the mother outweighs any potential risk to the foetus.

Plasma cholinesterase levels decrease during pregnancy. Mivacurium has been used to maintain neuromuscular block during Caesarean section, but due to the reduced levels of plasma cholinesterase, dosage adjustments to the infusion rate were necessary. A further reduction in the infusion rate may also be required during Caesarean section in patients pre-treated with magnesium sulfate, due to the potentiating effects of magnesium.

It is not known whether mivacurium is excreted in human milk.

4.7 Effect on Ability to Drive and Use Machines

This precaution is not relevant to the use of mivacurium. Mivacurium 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

Adverse events 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 (≥1/10000 to <1/1000) and very rare (<1/10,000) including isolated reports.

Immune disorders

Very rare: Severe anaphylactic or anaphylactoid reaction. Severe anaphylactic or anaphylactoid reactions have been reported in patients receiving mivacurium chloride in conjunction with one or more anaesthetic agents.

Cardiac disorders

Uncommon: Transient tachycardia*

Vascular disorders

Very common: Flushing*

Uncommon: Hypotension*

Respiratory, thoracic and mediastinal disorders

Uncommon: Bronchospasm*

Skin and subcutaneous tissue disorders

Uncommon: Erythema*, urticaria*

*Associated with the use of Mivacron there have been reports of skin flushing, erythema, urticaria, hypotension, transient tachycardia or bronchospasm which have been attributed to histamine release. These effects are dose related and more common following initial doses of ≥0.2 mg/kg or more when given rapidly and are reduced if Mivacron is injected over 30 to 60 seconds or in divided doses over 30 seconds.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Prolonged muscle paralysis and its consequences are the main signs of overdosage with neuromuscular blocking agents. However, the risk of haemodynamic side-effects especially decreases in blood pressure may be increased.

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. Cardiovascular support may be provided by proper positioning of the patient and administration of fluids or vasopressor agents as required.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Peripherally acting muscle relaxants, other quaternary ammonium compounds, ATC code: M03AC10.

Mivacurium is a short-acting, non-depolarising skeletal muscle relaxant which is hydrolysed by plasma cholinesterase. Mivacurium binds competitively with cholinergic receptors on the motor end-plate to prevent the action of acetylcholine, resulting in a blockade of neuromuscular transmission. This is rapidly reversed by the administration of the cholinesterase inhibitors, neostigmine and edrophonium.

5.2 Pharmacokinetic Properties

Mivacurium chloride is a mixture of three stereoisomers, the trans-trans and cis-trans stereoisomers comprise 92% to 96% of mivacurium chloride and when studied in cats their neuromuscular blocking potencies are not significantly different from each other or from mivacurium chloride. The cis-cis isomer has been estimated from studies in cats to have one-tenth of the neuromuscular blocking potency of the other two stereoisomers. Enzymatic hydrolysis by plasma cholinesterase is the primary mechanism for inactivation of mivacurium and yields a quaternary alcohol and a quaternary monoester metabolite. Pharmacological studies in cats and dogs have shown that metabolites possess insignificant neuromuscular, autonomic or cardiovascular activity at concentrations higher than seen in man.

5.3 Preclinical Safety Data

Mivacurium has been evaluated in four short term mutagenicity tests. Mivacurium was non-mutagenic in the Ames salmonella assay, the mouse lymphoma assay, the human lymphocyte assay and the *in vivo* rat bone marrow cytogenetic assay.

There is no information available on whether Mivacurium has carcinogenic potential.

Fertility studies have not been performed.

Animal studies have indicated that mivacurium has no adverse effect on foetal development.

Pharmaceutical Particulars

6.1 List of Excipients

Hydrochloric Acid EP
Water for Injections EP

6.2 Incompatibilities

Mivacurium is acidic (approximately pH 4.5) and should not be mixed with highly alkaline solutions, e.g. barbiturates.

6.3 Shelf Life

18 months

6.4 Special Precautions for Storage

Store below 25^{o}C. Do not freeze. Protect from light.

6.5 Nature and Contents of Container

Neutral glass ampoules containing 5ml or 10ml of product.

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal and Other Handling

Since no antimicrobial preservative is included, Mivacron must be used under full aseptic conditions and any dilution carried out immediately before use.

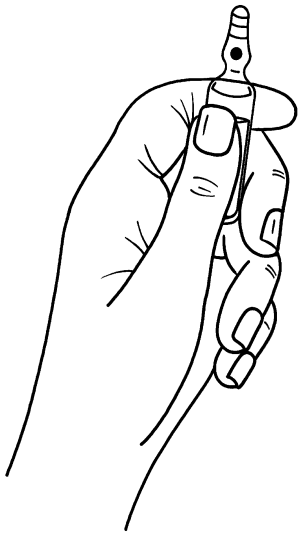
Any unused solution in open ampoules should be disposed of in accordance with local requirements.

Mivacron injection is acidic (approximately pH 4.5) and should not be mixed with highly alkaline solutions (e.g. barbiturates). Mivacron has been shown to be compatible with some commonly used peri-operative drugs supplied as acidic solutions. Where such agents are administered through the same indwelling needle or cannula as used for Mivacron injection, and compatibility has not been demonstrated, it is recommended that each drug is flushed through with physiological saline.

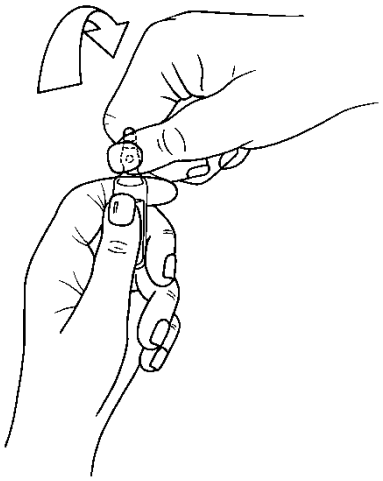
<u>Instructions to open the ampoule</u>
Ampoules are equipped with the OPC (One Point Cut) opening system and must be opened following the below instructions:
1. hold with the hand the bottom part of the ampoule as indicated in picture 1

2. put the other hand on the top of the ampoule positioning the thumb above the coloured point and press as indicated in picture 2

Picture 1



Picture 2



Administrative Data

7. Marketing Authorisation Holder

Aspen Pharma Trading Limited,
3016 Lake Drive,
City West Business Campus,
Dublin 24,

Ireland
Service-Tel: 0800 008 7392 (+ 44 1748 828 391)

8. Marketing Authorisation Number

PL 39699/0094

9. Date of First Authorisation/Renewal of Authorisation

21st January 2009

This leaflet was last revised in October 2020