Package Leaflet: Information for the User

MIVACRON 2 mg/ml Solution for Injection

mivacurium (as mivacurium chloride)

Read all of this leaflet carefully before you start having 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, ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

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, including heart surgery
- 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 have Mivacron

Do not have Mivacron if:

- you are allergic to mivacurium or any of the other ingredients in Mivacron (listed in Section 6)
- you have been diagnosed as having a genetically determined abnormal cholinesterase
- 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) or other form of neuromuscular disease
- 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
- you are sensitive to decreases in arterial blood pressure
- you have had a blood purification procedure called plasmapheresis
- you have received replacement donor plasma (plasma exchange)

- you have undergone cardiopulmonary bypass (a procedure that temporarily takes over the function of the heart and lungs during surgery)
- you have a lower than normal volume of blood (hypovolaemia)
- your body's balance of acids and bases are not normal
- your body's levels of sodium, potassium or calcium are not normal
- you have been pregnant recently or you have given birth in the last 6 weeks

Check with 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
- allergies or asthma
- collagen diseases

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, have recently taken or might take 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 such as ketamine, enflurane, isoflurane, sevoflurane and halothane (used to reduce sensation and pain during surgical procedures)
- muscle relaxants such as suxamethonium chloride and pancuronium
- antibiotics such as aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin (used to treat infections)
- medicines for uneven heart beats such as propranolol (also used to treat high blood pressure), lidocaine, procainamide, quinidine and calcium channel blockers (anti-arrhythmics)
- water tablets (diuretics), such as furosemide, thiazides, mannitol and acetazolamide
- medicines for inflammation of the joints, such as chloroquine or d-penicillamine
- steroids
- medicines for fits (epilepsy), such as phenytoin
- medicines for mental illness, such as lithium, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors or chlorpromazine (which can also be used for sickness)
- medicines containing magnesium, such as those to treat indigestion and heart burn
- ganglion blocking drugs such as trimetaphan and hexamthonium
- medicines for chest pain (angina) such as oxprenolol (also used to treat high blood pressure)
- bambuterol (used to treat asthma)

- drugs that may reduce plasma cholinesterase such as anti-mitotic drugs, ecothiophate iodide, organophosphates, anti-cholinesterases and certain hormones

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking 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 to have Mivacron

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 less than 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 (affects less than 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

Talk to your doctor, nurse or pharmacist if you notice any of the following:

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

Uncommon (affects less than 1 in 100 people)
- increase in heart rate
- decrease in blood pressure
- wheezing or coughing
- rash or urticaria (a lumpy skin rash or ‘hives’ anywhere on your body)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance Website: www.hpra.ie.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mivacron

- Keep this medicine out of the sight and reach of children.
- Do not use Mivacron after the expiry date which is stated on the pack after 'EXP'. The expiry date refers to the last day of the month.
- Store below 25^{o}C. Do not freeze.
- Keep the ampoules in the outer carton in order to protect from light.
- Once opened, Mivacron should be used immediately. Discard any unused contents.

6. Contents of the pack and other information

What Mivacron contains
- The active substance is mivacurium (as mivacurium chloride). Each ml contains 2 mg mivacurium (as mivacurium chloride)
- The other ingredients are hydrochloric acid (for pH-adjustment) and Water for Injections.

What Mivacron looks like and contents of the pack
Mivacron 2 mg/ml solution for injection is supplied as a clear, pale yellow solution and comes in ampoules containing 5 ml or 10 ml of the product. Each 5 ml ampoule contains 10 mg mivacurium (as mivacurium chloride). Each 10 ml ampoule contains 20 mg mivacurium (as mivacurium chloride).

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Aspen Pharma Trading Limited, 3016 Lake Drive, Citywest Business Campus, Dublin 24, Ireland.
Tel: +353 1 6 308 400

Manufacturer:
GlaxoSmithKline Manufacturing S.p.A., Strada Provinciale Asolana 90, 43056 San Polo di Torrile, Parma, Italy.
Or
Aspen Pharma Ireland Limited, One George's Quay Plaza, Dublin 2, Ireland
Or
Aspen Bad Oldesloe GmbH, 32-36 Industriestrasse, 23843 Bad Oldesloe, Germany

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THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY

(Please refer to the Summary of Product Characteristics for further information)

Pharmaceutical form

Mivacron 2 mg/ml Solution for Injection

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 (ED_{95}) is 0.07 mg/kg (range 0.06 to 0.09) in adults receiving narcotic anaesthesia.

The following dose regimens are recommended for tracheal intubation:-

(1) 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.

(2) 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.

The recommended bolus dose range for healthy adults is 0.07 to 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 or as a divided dose in order to minimise the possibility of occurrence of cardiovascular effects.

Full block can be prolonged with 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 mivacurium 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 anti-cholinesterase agents. However, because spontaneous recovery after mivacurium is rapid, reversal may not be routinely required since it shortens recovery time by only 5 to 6 minutes.

Use as an infusion in adults:
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 in 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/min 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°C. However, since the product contains no anti-microbial 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.

Dose in infants and children aged 7 months to 12 years:
Mivacron has a higher ED_{95} (approximately 0.1 mg/kg), faster onset, shorter clinically effective duration of action and more rapid spontaneous recovery in infants and children, aged 7 months to 12 years*,* than in adults.

The recommended bolus dose range for infants and children aged 7 months to 12 years is 0.1 to 0.2 mg/kg administered over 5 to 15 seconds. When administered during stable narcotic or halothane anaesthesia a dose of 0.2 mg/kg produces clinically effective block for an average of 9 minutes.

A Mivacron dose of 0.2 mg/kg is recommended for tracheal intubation in infants and children aged 7 months to 12 years. Maximum block is usually achieved within 2 minutes following administration of this dose and intubation should be possible within this time.

Maintenance doses are generally required more frequently in infants and children than in adults. Available data suggest that a maintenance dose of 0.1 mg/kg will give approximately 6 to 9 minutes of additional clinically effective block during narcotic or halothane anaesthesia*.*

Infants and children generally require higher infusion rates than adults.

During halothane anaesthesia the mean infusion rate required to maintain 89% to 99% neuromuscular block in patients aged 7 to 23 months is approximately 11 micrograms/kg/min (approximately 0.7 mg/kg/hr) [range: 3 to 26 micrograms/kg/min (approximately 0.2 to 1.6 mg/kg/hr)].

For children aged 2 to 12 years the equivalent mean infusion rate is approximately 13 to 14 micrograms/kg/min (approximately 0.8 mg/kg/hr) [range: 5 to 31 micrograms/kg/min (approximately 0.3 to 1.9 mg/kg/hr)] 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 to 12 years.

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

Dose in infants aged 2 to 6 months:
Mivacron has a similar ED_{95} to that in adults (0.07 mg/kg), but a faster onset, shorter clinically effective duration of action and more rapid spontaneous recovery in infants aged 2 to 6 months than in adults.

The recommended bolus dose range for infants aged 2 to 6 months is 0.1 to 0.15 mg/kg administered over 5 to 15 seconds. When administered during stable halothane anaesthesia a dose of 0.15 mg/kg produces clinically effective block for an average of 9 minutes.

A Mivacron dose of 0.15 mg/kg is recommended for tracheal intubation in infants aged 2 to 6 months. Maximum block is achieved approximately 1.4 minutes following administration of this dose and intubation should be possible within this time.

Maintenance doses are generally required more frequently in infants aged 2 to 6 months than in adults. Available data suggest that a maintenance dose of 0.1 mg/kg will give approximately 7 minutes of additional clinically effective block during halothane anaesthesia.

Infants aged 2 to 6 months generally require higher infusion rates than adults. During halothane anaesthesia the mean infusion rate required to maintain 89 to 99% neuromuscular block is approximately 11 micrograms/kg/min (approximately 0.7 mg/kg/hr) [range: 4 to 24 micrograms/kg/min (approximately 0.2 to 1.5 mg/kg/hr)].

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

Dose in neonates and infants under 2 months of age:
The safety and efficacy of Mivacurium chloride in neonates and infants less than 2 months has not yet been established. 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 disease 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.

Dose in patients with reduced hepatic function:
In patients with end-stage liver disease 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. 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.

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

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.

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.

Overdose

Symptoms and Signs:
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.

Management:
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 anti-cholinesterase 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.

Shelf life and special precautions for storage
Unopened: 18 months
Once opened, use immediately and discard any unused contents.

When diluted with the listed infusion solutions in 'instructions for use and handling', 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°C. However, since the product contains no anti-microbial preservative, dilution should be carried out under full aseptic conditions immediately prior to use. Administration should commence as soon as possible thereafter, and any remaining solution should be discarded.

Store below 25°C. Do not freeze. Keep the ampoules in the outer carton in order to protect from light.

Instructions for use and handling

For single use only.

Since no anti-microbial preservative is included, Mivacron Injection must be used under full aseptic conditions and any dilution carried out immediately before use. Any unused solution in open ampoules should be discarded.

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Mivacron Injection 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.

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)

Instructions to open the ampoule:
Ampoules are equipped with the OPC (One Point Cut) opening system and must be opened following the below instructions:

- Hold with the hand the bottom part of the ampoule
- Put the other hand on the top of the ampoule positioning the thumb above the coloured point and press