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Summary of Product Characteristics last updated on the eMC: 20/03/2009

SPC **Hypnomidate**

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Legal Categories

POM – Prescription Only Medicine

Active Ingredients/Generics

etomidate

1. NAME OF THE MEDICINAL PRODUCT

Go to top of the page

Hypnomidate® 2 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Go to top of the page

Each ml of Hypnomidate contains etomidate 2 mg.

3. PHARMACEUTICAL FORM

Go to top of the page

Solution for injection.

4. CLINICAL PARTICULARS

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Hypnomidate is an intravenous induction agent of anaesthesia.

4.2 Posology and method of administration

Go to top of the page

For intravenous administration.

Adults and children:

A dose of 0.3 mg/kg given intravenously at induction of anaesthesia, gives sleep lasting from 6 to 10 minutes.

Elderly:

A dose of 0.15-0.2 mg/kg bodyweight should be given and the dose should be further adjusted according to effects. (see Section 4.4 Special Warnings and Precautions for Use).

Since Hypnomidate has no analgesic action, appropriate analgesics should be used in procedures involving painful

stimuli.

Do not exceed a total dose of 30 ml (3 ampoules).

Hypnomidate should only be given by slow intravenous injection.

Hypnomidate may be diluted with sodium chloride infusion BP or dextrose infusion BP but it is not compatible with compound sodium lactate infusion BP (Hartmann's solution). Combinations with pancuronium bromide may show a very slight opalescence; for this reason the two should not be mixed together.

4.3 Contraindications Go to top of the page

Hypnomidate is contraindicated in patients with known hypersensitivity to etomidate.

4.4 Special warnings and precautions for use Go to top of the page

Warnings: In patients with liver cirrhosis, or in those who have already received neuroleptic, opiate or sedative agents, the dose of etomidate should be reduced.

When Hypnomidate is used, resuscitation equipment should be readily available to manage apnoea. In cases of adrenocortical gland dysfunction and during very long surgical procedures, a prophylactic cortisol supplement may be required (for example 50 to 100 mg hydrocortisone).

Reduced serum cortisol levels, unresponsive to ACTH injections, have been reported in some patients during induction of anaesthesia but particularly during maintenance of anaesthesia with etomidate; for this reason etomidate should not be used for maintenance. However, when etomidate is used for induction, the post-operative rise in serum cortisol which has been observed after thiopentone induction is delayed for approximately 3-6 hours.

Hypnomidate should not be administered to patients with evidence or suggestion of reduced adrenal cortical function.

Hypnomidate should be used with caution in elderly patients, since the potential exists for decreases in cardiac output, which have been reported with doses greater than recommended (see Section 4.2 Posology and Method of Administration for recommended dose in the elderly).

Convulsions may occur in unpremedicated patients.

Precautions: Hypnomidate by injection should be given slowly.

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

Sedative drugs potentiate the hypnotic effect of Hypnomidate.

Hypnomidate is pharmacologically compatible with the muscle relaxants, premedicant drugs and inhalation anaesthetics in current clinical use.

4.6 Pregnancy and lactation Go to top of the page

Hypnomidate has no primary effect on fertility, nor primary embryotoxic or teratogenic effects. At maternally toxic doses in rats, decreased survival was noted. Safety in human pregnancy has not been established. As with other drugs, the possible risks should be weighed against the potential benefits before the drug is administered during pregnancy. Hypnomidate may cross the placental barrier during obstetric anaesthesia.

Lactation: It is not known whether etomidate is excreted in human milk. However, caution should be exercised when Hypnomidate is administered to a nursing mother.

4.7 Effects on ability to drive and use machines Go to top of the page

Not applicable, but no effects likely. After very short surgical procedures (up to 15 minutes) the patient regains normal alertness 30 to 60 minutes after waking. After long operations, normal alertness is regained after 4 to 24 hours, depending on the duration of the operation.

4.8 Undesirable effects Go to top of the page

The use of narcotic analgesics or diazepam as premedication and during surgery will reduce the uncontrolled spontaneous muscle movements shown by some patients after Hypnomidate administration.

Pain can occur after injection into the small veins of the dorsum of the hand. Use of larger veins or an intravenous application of a small dose of fentanyl 1-2 minutes before induction reduces pain on injection. In a small number of patients, thrombophlebitis has been reported.

Nausea and/or vomiting may occur although these are mainly as a result of concurrent use of opiates. Coughing, hiccough and/or shivering may also be experienced. Allergic reactions, including rare cases of bronchospasm and anaphylactoid reactions, have been reported. Rare cases of laryngospasm, cardiac arrhythmias and convulsions have also been reported.

A slight and transient drop in blood pressure may occur due to a reduction of the peripheral vascular resistance. In vulnerable patients, special care should be exercised to minimise this effect.

Respiratory depression and apnoea may occur.

4.9 Overdose Go to top of the page

Overdosing is likely to result in prolonged anaesthesia with the possibility of respiratory depression and even arrest. Hypotension has also been observed. General supportive measures and close observation are recommended. In

addition, administration of 50 -100 mg hydrocortisone (not ACTH) may be required for depression of cortisol secretion.

5. PHARMACOLOGICAL PROPERTIES

Go to top of the page

5.1 Pharmacodynamic properties

Go to top of the page

ATC code N01AX07

Etomidate is a short acting intravenous hypnotic which is rapidly inactivated by enzyme metabolism so that it does not give rise to a hangover effect. It does not release histamine, and has no effect on liver function. *In vitro* studies have shown etomidate to be an inhibitor of microsomal enzymes. Limited *in vivo* studies have demonstrated only minimal inhibition of hepatic metabolism.

5.2 Pharmacokinetic properties

Go to top of the page

Profile in Plasma

After intravenous administration, the time-course of the etomidate plasma levels can be described by a three-compartment model reflecting distribution, metabolism, and elimination processes. Plasma concentrations decrease rapidly for about 30 minutes and then more slowly; traces are still detectable after about 6 hours. Metabolites, chiefly of hydrolysis, are more slowly excreted.

Distribution

Etomidate is approximately 76.5% bound to plasma proteins. Etomidate is rapidly distributed to the brain and other tissues. Its volume of distribution is about 4.5 L/kg.

Metabolism and Elimination

Etomidate is metabolized in the liver. After 24 hours, 75% of the administered dose of etomidate has been eliminated in the urine primarily as metabolites. Only 2% of etomidate is excreted unchanged via the urine. The terminal half-life of about 3 to 5 hours reflects the slow distribution of etomidate from the deep peripheral compartment.

5.3 Preclinical safety data

Go to top of the page

No relevant information other than that contained elsewhere in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

Go to top of the page

6.1 List of excipients

Go to top of the page

Propylene glycol

Water for injections

1N sodium hydroxide*

1N hydrochloric acid*

* for occasional pH adjustment only

6.2 Incompatibilities

Go to top of the page

Combinations with pancuronium bromide may show a very slight opalescence; for this reason the two should not be mixed together.

6.3 Shelf life

Go to top of the page

5 years.

6.4 Special precautions for storage

Go to top of the page

Store at room temperature.

6.5 Nature and contents of container

Go to top of the page

Colourless glass ampoule, PhEur Type I, containing 10 ml Hypnomidate, in packs of 5 and 10 ampoules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Go to top of the page

None stated.

7. MARKETING AUTHORISATION HOLDER

Go to top of the page

Janssen-Cilag Limited

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UK

8. MARKETING AUTHORISATION NUMBER(S)

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PL 0242/0019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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27 October 1978/20 March 2004

10. DATE OF REVISION OF THE TEXT

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17 March 2009

More information about this product

- Patient Information Leaflets (PILs):
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Summary of Product Characteristics last updated on the eMC: 04/04/2006

SPC **Ketalar Injection**

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Legal Categories

POM – Prescription Only Medicine

Active Ingredients/Generics

ketamine hydrochloride

1. NAME OF THE MEDICINAL PRODUCT

Go to top of the page

Ketalar™ 10 mg/ml, 50 mg/ml, 100 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Go to top of the page

Each 1 ml of solution contains:

Ketalar 10mg/ml Injection : ketamine hydrochloride Ph Eur equivalent to 10 mg ketamine base per ml.

Ketalar 50mg/ml Injection : ketamine hydrochloride Ph Eur equivalent to 50 mg ketamine base per ml.

Ketalar 100mg/ml Injection: ketamine hydrochloride Ph Eur equivalent to 100 mg ketamine base per ml.

3. PHARMACEUTICAL FORM

Go to top of the page

Solution for injection or infusion.

A clear solution for injection or infusion.

4. CLINICAL PARTICULARS

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Ketalar is recommended:

As the sole anaesthetic agent for diagnostic and surgical procedures. When used by intravenous or intramuscular injection, Ketalar is best suited for short procedures. With additional doses, or by intravenous infusion, Ketalar can be used for longer procedures. If skeletal muscle relaxation is desired, a muscle relaxant should be used and respiration should be supported.

For the induction of anaesthesia prior to the administration of other general anaesthetic agents.

To supplement other anaesthetic agents.

Specific areas of application or types of procedures:

When the intramuscular route of administration is preferred.

Debridement, painful dressings, and skin grafting in burned patients, as well as other superficial surgical procedures.

Neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms, and lumbar punctures.

Diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions.

Note: Eye movements may persist during ophthalmological procedures.

Anaesthesia in poor-risk patients with depression of vital functions or where depression of vital functions must be avoided, if at all possible.

Orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies.

Sigmoidoscopy and minor surgery of the anus and rectum, circumcision and pilonidal sinus.

Cardiac catheterization procedures.

Caesarian section; as an induction agent in the absence of elevated blood pressure.

Anaesthesia in the asthmatic patient, either to minimise the risks of an attack of bronchospasm developing, or in the presence of bronchospasm where anaesthesia cannot be delayed.

4.2 Posology and method of administration Go to top of the page

For intravenous infusion, intravenous injection or intramuscular injection.

NOTE: All doses are given in terms of ketamine base

Adults, elderly (over 65 years) and children:

For surgery in elderly patients ketamine has been shown to be suitable either alone or supplemented with other anaesthetic agents.

Preoperative preparations

Ketalar has been safely used alone when the stomach was not empty. However, since the need for supplemental agents and muscle relaxants cannot be predicted, when preparing for elective surgery it is advisable that nothing be given by mouth for at least six hours prior to anaesthesia.

Atropine, hyoscine, or another drying agent should be given at an appropriate interval prior to induction.

Midazolam, diazepam, lorazepam, or flunitrazepam used as a premedicant or as an adjunct to ketamine, have been effective in reducing the incidence of emergence reactions.

Onset and duration

As with other general anaesthetic agents, the individual response to Ketalar is somewhat varied depending on the dose, route of administration, age of patient, and concomitant use of other agents, so that dosage recommendation cannot be absolutely fixed. The dose should be titrated against the patient's requirements.

Because of rapid induction following intravenous injection, the patient should be in a supported position during administration. An intravenous dose of 2 mg/kg of bodyweight usually produces surgical anaesthesia within 30 seconds after injection and the anaesthetic effect usually lasts 5 to 10 minutes. An intramuscular dose of 10 mg/kg of bodyweight usually produces surgical anaesthesia within 3 to 4 minutes following injection and the anaesthetic effect usually lasts 12 to 25 minutes. Return to consciousness is gradual.

A. Ketalar as the sole anaesthetic agent

Intravenous Infusion

The use of Ketalar by continuous infusion enables the dose to be titrated more closely, thereby reducing the amount of drug administered compared with intermittent administration. This results in a shorter recovery time and better stability of vital signs.

A solution containing 1 mg/ml of ketamine in dextrose 5% or sodium chloride 0.9% is suitable for administration by infusion.

Induction

An infusion corresponding to 0.5 – 2 mg/kg as total induction dose.

Maintenance of anaesthesia

Anaesthesia may be maintained using a microdrip infusion of 10 - 45 microgram/kg/min (approximately 1 – 3 mg/min).

The rate of infusion will depend on the patient's reaction and response to anaesthesia. The dosage required may be

reduced when a long acting neuromuscular blocking agent is used.

Intermittent Injection

Induction

Intravenous Route

The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5mg/kg (in terms of ketamine base).The average amount required to produce 5 to 10 minutes of surgical anaesthesia has been 2.0 mg/kg. It is recommended that intravenous administration be accomplished slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Note: the 100 mg/ml concentration of ketamine should not be injected intravenously without proper dilution. It is recommended that the drug be diluted with an equal volume of either sterile water for injection, normal saline, or 5% dextrose in water.

Intramuscular Route

The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (in terms of ketamine base). A low initial intramuscular dose of 4 mg/kg has been used in diagnostic manoeuvres and procedures not involving intensely painful stimuli. A dose of 10 mg/kg will usually produce 12 to 25 minutes of surgical anaesthesia.

Maintenance of anaesthesia

Lightening of anaesthesia may be indicated by nystagmus, movements in response to stimulation, and vocalization. Anaesthesia is maintained by the administration of additional doses of Ketalar by either the intravenous or intramuscular route.

Each additional dose is from ½ to the full induction dose recommended above for the route selected for maintenance, regardless of the route used for induction.

The larger the total amount of Ketalar administered, the longer will be the time to complete recovery.

Purposeless and tonic-clonic movements of extremities may occur during the course of anaesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anaesthetic.

B. Ketalar as induction agent prior to the use of other general anaesthetics

Induction is accomplished by a full intravenous or intramuscular dose of Ketalar as defined above. If Ketalar has been administered intravenously and the principal anaesthetic is slow-acting, a second dose of Ketalar may be required 5 to 8 minutes following the initial dose. If Ketalar has been administered intramuscularly and the principal anaesthetic is rapid-acting, administration of the principal anaesthetic may be delayed up to 15 minutes following the injection of Ketalar.

C. Ketalar as supplement to anaesthetic agents

Ketalar is clinically compatible with the commonly used general and local anaesthetic agents when an adequate respiratory exchange is maintained. The dose of Ketalar for use in conjunction with other anaesthetic agents is usually in the same range as the dosage stated above; however, the use of another anaesthetic agent may allow a reduction in the dose of Ketalar.

D. Management of patients in recovery

Following the procedure the patient should be observed but left undisturbed. This does not preclude the monitoring of vital signs. If, during the recovery, the patient shows any indication of emergence delirium, consideration may be given to the use of diazepam (5 to 10 mg I.V. in an adult). A hypnotic dose of a thiobarbiturate (50 to 100 mg I.V.) may be used to terminate severe emergence reactions. If any one of these agents is employed, the patient may experience a longer recovery period.

4.3 Contraindications Go to top of the page

Ketalar is contra-indicated in persons in whom an elevation of blood pressure would constitute a serious hazard (see Undesirable effects) and in those who have shown hypersensitivity to the drug. Ketalar should not be used in patients with eclampsia or pre-eclampsia, severe coronary or myocardial disease, cerebrovascular accident or cerebral trauma.

4.4 Special warnings and precautions for use Go to top of the page

To be used only in hospitals by or under the supervision of experienced medically qualified anaesthetists except under emergency conditions.

As with any general anaesthetic agent, resuscitative equipment should be available and ready for use.

Emergence delirium phenomena may occur during the recovery period. The incidence of these reactions may be reduced if verbal and tactile stimulation of the patient is minimised during the recovery period. This does not preclude the monitoring of vital signs.

Because pharyngeal and laryngeal reflexes usually remain active, mechanical stimulation of the pharynx should be avoided unless muscle relaxants, with proper attention to respiration, are used.

Although aspiration of contrast medium has been reported during Ketalar anaesthesia under experimental conditions (Taylor, P A and Towey, R M, Brit. Med. J. 1971, 2: 688), in clinical practice aspiration is seldom a problem.

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

Since an increase in cerebrospinal fluid pressure has been reported during Ketalar anaesthesia, Ketalar should be used with special caution in patients with preanaesthetic elevated cerebrospinal fluid pressure.

Respiratory depression may occur with overdosage of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to the administration of analeptics.

The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in transient respiratory depression or apnoea and enhanced pressor response.

In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

When Ketalar is used on an outpatient basis, the patient should not be released until recovery from anaesthesia is complete and then should be accompanied by a responsible adult.

Ketalar has been reported as being a drug of abuse. If used on a daily basis for a few weeks, dependence and tolerance may develop, particularly in individuals with a history of drug abuse and dependence. Therefore the use of Ketalar should be closely supervised and it should be prescribed and administered with caution.

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

Ketalar is chemically incompatible with barbiturates and diazepam because of precipitate formation. Therefore, these should not be mixed in the same syringe or infusion fluid.

4.6 Pregnancy and lactation Go to top of the page

Ketalar crosses the placenta. This should be borne in mind during operative obstetric procedures in pregnancy. With the exception of administration during surgery for abdominal delivery or vaginal delivery, no controlled clinical studies in pregnancy have been conducted. The safe use in pregnancy, and in lactation, has not been established and such use is not recommended.

4.7 Effects on ability to drive and use machines Go to top of the page

Patients should be cautioned that driving a car, operating hazardous machinery or engaging in hazardous activities should not be undertaken for 24 hours or more after anaesthesia.

4.8 Undesirable effects Go to top of the page

Cardiovascular

Temporary elevation of blood pressure and pulse rate is frequently observed following administration of ketamine hydrochloride. However, hypotension and bradycardia have been reported. Arrhythmias have also occurred. The median peak rise of blood pressure has ranged from 20 to 25 per cent of preanaesthetic values. Depending on the condition of the patient, this elevation of blood pressure may be considered an adverse reaction or a beneficial effect.

Respiratory

Depression of respiration or apnoea may occur following over rapid intravenous administration or high doses of ketamine hydrochloride. Laryngospasm and other forms of airway obstruction have occurred during ketamine hydrochloride anaesthesia.

Ocular

Diplopia and nystagmus may occur following ketamine hydrochloride administration. A slight elevation in intraocular pressure may also occur.

Psychological

Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia or disorientation. During recovery from anaesthesia the patient may experience emergence delirium, characterised by vivid dreams (pleasant or unpleasant), with or without psychomotor activity, manifested by confusion and irrational behaviour. The fact that these reactions are observed less often in the young (15 years of age or less) makes Ketalar especially useful in paediatric anaesthesia. These reactions are also less frequent in the elderly (over 65 years of age) patient. The incidence of emergence reactions is reduced as experience with the drug is gained. No residual psychological effects are known to have resulted from the use of Ketalar.

Neurological

In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures. These movements do not imply a light plane of anaesthesia and are not indicative of a need for additional doses of the anaesthetic.

Gastro-intestinal

Anorexia, nausea, and vomiting have been observed; however, these are uncommon and are not usually severe. The great majority of patients are able to take liquids by mouth shortly after regaining consciousness.

Hypersensitivity reactions

There have been a number of reported cases of anaphylaxis.

Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported. Increased salivation leading to respiratory difficulties may occur unless an antisialogogue is used.

4.9 Overdose Go to top of the page

Respiratory depression can result from an overdosage of ketamine hydrochloride. Supportive ventilation should be employed. Mechanical support of respiration that will maintain adequate blood oxygen saturation and carbon dioxide elimination is preferred to administration of analeptics.

Ketalar has a wide margin of safety; several instances of unintentional administration of overdoses of Ketalar (up to 10 times that usually required) have been followed by prolonged but complete recovery.

5. PHARMACOLOGICAL PROPERTIES Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Ketamine is a rapidly acting general anaesthetic for intravenous or intramuscular use with a distinct pharmacological action. Ketamine hydrochloride produces dissociative anaesthesia characterised by catalepsy, amnesia, and marked analgesia which may persist into the recovery period. Pharyngeal-laryngeal reflexes remain normal and skeletal muscle tone may be normal or can be enhanced to varying degrees. Mild cardiac and respiratory stimulation and occasionally respiratory depression occur.

5.2 Pharmacokinetic properties Go to top of the page

Ketamine is rapidly distributed into perfused tissues including brain and placenta. Animal studies have shown ketamine to be highly concentrated in body fat, liver and lung. Biotransformation takes place in liver. Termination of anaesthetic is partly by redistribution from brain to other tissues and partly by metabolism. Elimination half-life is approximately 2-3 hours, and excretion renal, mostly as conjugated metabolites.

5.3 Preclinical safety data Go to top of the page

Preclinical safety data does not add anything of further significance to the prescriber.

6. PHARMACEUTICAL PARTICULARS Go to top of the page

6.1 List of excipients Go to top of the page

Ketalar 10mg/ml Injection: sodium chloride, benzethonium chloride, water for injection

Ketalar 50mg/ml Injection: benzethonium chloride, water for injection

Ketalar 100mg/ml Injection: benzethonium chloride, water for injection

6.2 Incompatibilities Go to top of the page

Ketalar is chemically incompatible with barbiturates and diazepam because of precipitate formation. Therefore, these should not be mixed in the same syringe or infusion fluid.

6.3 Shelf life Go to top of the page

3 years

For single use only. Discard any unused product at the end of each operating session.

After dilution the solutions should be used immediately.

6.4 Special precautions for storage Go to top of the page

Do not store above 25°C. Do not freeze. Store in the original container. Discard any unused product at the end of each operating session.

6.5 Nature and contents of container Go to top of the page

Ketalar 10mg/ml Injection:	20 ml white neutral glass vial with rubber closure and aluminium flip-off cap containing 10 mg ketamine base per ml.
Ketalar 50mg/ml Injection:	12 ml vials containing 10 ml of solution as 50 mg ketamine base per ml.
Ketalar 100mg/ml Injection:	12 ml vials containing 10 ml of solution as 100 mg ketamine base per ml.

6.6 Special precautions for disposal and other handling Go to top of the page

For single use only. Discard any unused product at the end of each operating session.

See Section 4.2 Posology and method of administration.

7. MARKETING AUTHORISATION HOLDER Go to top of the page

Pfizer Limited, Sandwich, Kent CT13 9NJ, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S) Go to top of the page

PL 00057/0529, PL 00057/0530, PL 00057/0531

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION Go to top of the page

1st July 2003

10. DATE OF REVISION OF THE TEXT Go to top of the page

January 2006

Company Reference: KE 5_0 UK

More information about this product

- Patient Information Leaflets (PILs):
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- Medicine Guides:
  Ketalar

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Summary of Product Characteristics last updated on the eMC: 04/09/2008

SPC **Diprivan 1%**

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Legal Categories

POM – Prescription Only Medicine

Active Ingredients/Generics

propofol

1. NAME OF THE MEDICINAL PRODUCT

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Diprivan 10 mg/ml (1%) emulsion for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Go to top of the page

Propofol 10 mg/ml

3. PHARMACEUTICAL FORM

Go to top of the page

Emulsion for injection or infusion.

White aqueous isotonic oil-in-water emulsion.

4. CLINICAL PARTICULARS

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

'Diprivan' 1% is a short-acting intravenous anaesthetic agent suitable for induction and maintenance of general anaesthesia.

Diprivan' 1% may also be used for sedation of ventilated patients receiving intensive care.

'Diprivan' 1% may also be used for sedation for surgical and diagnostic procedures.

4.2 Posology and method of administration

Go to top of the page

For specific guidance relating to the administration of 'Diprivan' 1% with a target controlled infusion (TCI) device, which incorporates 'Diprifusor' TCI Software, see Section 4.2.5. Such use is restricted to induction and maintenance of anaesthesia in adults. The 'Diprifusor' TCI system is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures, or in children.

4.2.1 Induction of General Anaesthesia

Adults

In unpremedicated and premedicated patients, it is recommended that 'Diprivan' 1% should be titrated (approximately 4 ml [40 mg] every 10 seconds in an average healthy adult by bolus injection or infusion) against the response of the patient until the clinical signs show the onset of anaesthesia. Most adult patients aged less than 55 years are likely to require 1.5 to 2.5 mg/kg of 'Diprivan' 1%. The total dose required can be reduced by lower rates of administration (2 to 5 ml/min [20 to 50 mg/min]). Over this age, the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 2 ml [20 mg] every 10 seconds).

Elderly Patients

In elderly patients the dose requirement for induction of anaesthesia with 'Diprivan' 1% is reduced. The reduction should take into account of the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response.

Children

'Diprivan' 1% is not recommended for induction of anaesthesia in children aged less than 1 month.

When used to induce anaesthesia in children, it is recommended that 'Diprivan' 1% be given slowly until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or weight. Most patients over 8 years of age are likely to require approximately 2.5 mg/kg of 'Diprivan' 1% for induction of anaesthesia. Under this age the requirement may be more. Lower dosage is recommended for children of ASA grades 3 and 4.

Administration of 'Diprivan' 1% by a 'Diprifusor' TCI system is not recommended for induction of general anaesthesia in children.

4.2.2 Maintenance Of General Anaesthesia

Adults

Anaesthesia can be maintained by administering 'Diprivan' 1% either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia. Recovery from anaesthesia is typically rapid and it is therefore important to maintain 'Diprivan' 1% administration until the end of the procedure.

Continuous Infusion

The required rate of administration varies considerably between patients, but rates in the region of 4 to 12 mg/kg/h usually maintain satisfactory anaesthesia.

Repeat Bolus Injections

If a technique involving repeat bolus injections is used, increments of 25 mg (2.5 ml) to 50 mg (5.0 ml) may be given according to clinical need.

Elderly Patients

When 'Diprivan' 1% is used for maintenance of anaesthesia the rate of infusion or 'target concentration' should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

Children

'Diprivan' 1% is not recommended for maintenance of anaesthesia in children less than 1 month old.

Anaesthesia can be maintained by administering 'Diprivan' 1% by infusion or repeat bolus injection to prevent the clinical signs of light anaesthesia. The required rate of administration varies considerably between patients, but rates in the region of 9 to 15 mg/kg/h usually achieve satisfactory anaesthesia. Younger children, less than 3 years, may have higher dosage requirements within the range of recommended dosages, as compared with older paediatric patients. Dosage should be adjusted individually and particular attention paid to the need for adequate analgesia. A maximum duration of use of approximately 60 minutes should not be exceeded except where there is a specific indication for longer use e.g. malignant hyperthermia where volatile agents must be avoided.

Administration of 'Diprivan' 1% by a 'Diprifusor' TCI system is not recommended for maintenance of general anaesthesia in children.

4.2.3 Sedation During Intensive Care

Adults

For sedation during intensive care it is advised that Diprivan 1% should be administered by continuous infusion. The infusion rate should be determined by the desired depth of sedation. In most patients sufficient sedation can be obtained with a dosage of 0.3 - 4 mg/kg/h of Diprivan 1% (See 4.4 Special warnings and precautions for use). Diprivan 1% is not indicated for sedation in intensive care of patients of 16 years of age or younger (see 4.3 Contraindications). Administration of Diprivan 1% by Diprifusor TCI system is not advised for sedation in the intensive care unit.

Diprivan' 1% may be diluted with 5% Dextrose (see "Dilution and Co-administration" table below).

It is recommended that blood lipid levels be monitored should 'Diprivan' 1% be administered to patients thought to be at particular risk of fat overload. Administration of 'Diprivan' 1% should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid

concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the 'Diprivan' 1% formulation; 1.0 ml of 'Diprivan' 1% contains approximately 0.1g of fat.

If the duration of sedation is in excess of 3 days, lipids should be monitored in all patients.

Elderly Patients

When 'Diprivan' 1% is used for sedation the rate of infusion should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

Children

'Diprivan' 1% is contraindicated for the sedation of ventilated children aged 16 years or younger receiving intensive care.

4.2.4 Sedation For Surgical And Diagnostic Procedures

Adults

To provide sedation for surgical and diagnostic procedures, rates of administration should be individualised and titrated to clinical response.

Most patients will require 0.5 to 1 mg/kg over 1 to 5 minutes for onset of sedation.

Maintenance of sedation may be accomplished by titrating 'Diprivan' 1% infusion to the desired level of sedation - most patients will require 1.5 to 4.5 mg/kg/h. In addition to the infusion, bolus administration of 10 to 20 mg may be used if a rapid increase in the depth of sedation is required. In patients of ASA Grades 3 and 4 the rate of administration and dosage may need to be reduced.

Administration of 'Diprivan' 1% by a 'Diprifusor' TCI system is not recommended for sedation for surgical and diagnostic procedures.

Elderly Patients

When 'Diprivan' 1% is used for sedation the rate of infusion or 'target concentration' should also be reduced. Patients of ASA grades 3 and 4 will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

Children

'Diprivan' 1% is not recommended for sedation in children as safety and efficacy have not been demonstrated.

4.2.5 Administration

'Diprivan' 1% has no analgesic properties and therefore supplementary analgesic agents are generally required in addition to 'Diprivan' 1%.

'Diprivan' 1% can be used for infusion undiluted from glass containers, plastic syringes or 'Diprivan' 1% pre-filled syringes or diluted with 5% Dextrose (Intravenous Infusion BP) only, in PVC infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg propofol per ml) should be prepared aseptically immediately before administration and must be used within 6 hours of preparation.

It is recommended that, when using diluted 'Diprivan' 1%, the volume of 5% Dextrose removed from the infusion bag during the dilution process is totally replaced in volume by 'Diprivan' 1% emulsion. (see "Dilution and Co-administration" table below).

The dilution may be used with a variety of infusion control techniques, but a giving set used alone will not avoid the risk of accidental uncontrolled infusion of large volumes of diluted 'Diprivan' 1%. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be taken into account when deciding the maximum amount of 'Diprivan' 1% in the burette.

When 'Diprivan' 1% is used undiluted to maintain anaesthesia, it is recommended that equipment such as syringe pumps or volumetric infusion pumps should always be used to control infusion rates.

'Diprivan' 1% may be administered via a Y-piece close to the injection site into infusions of the following:

- Dextrose 5% Intravenous Infusion B.P.

- Sodium Chloride 0.9% Intravenous Infusion B.P.

- Dextrose 4% with Sodium Chloride 0.18% Intravenous Infusion B.P.

The glass pre-filled syringe (PFS) has a lower frictional resistance than plastic disposable syringes and operates more easily. Therefore, if 'Diprivan' 1% is administered using a hand held pre-filled syringe, the line between the syringe and the patient must not be left open if unattended.

When the pre-filled syringe presentation is used in a syringe pump appropriate compatibility should be ensured. In particular, the pump should be designed to prevent syphoning and should have an occlusion alarm set no greater than 1000 mm Hg. If using a programmable or equivalent pump that offers options for use of different syringes then choose only the 'B-D' 50/60 ml 'PLASTIPAK' setting when using the 'Diprivan' 1% pre-filled syringe.

'Diprivan' 1% may be premixed with alfentanil injection containing 500 micrograms/ml alfentanil in the ratio of 20:1 to 50:1 v/v. Mixtures should be prepared using sterile technique and used within 6 hours of preparation.

In order to reduce pain on initial injection, 'Diprivan' 1% may be mixed with preservative-free Lidocaine Injection 0.5% or 1%; (see "Dilution and Co-administration" table below).

Target Controlled Infusion - Administration of 'Diprivan' 1% by a 'Diprifusor' TCI System in Adults

Administration of 'Diprivan' 1% by a 'Diprifusor' TCI system is restricted to induction and maintenance of general anaesthesia in adults. It is not recommended for use in ICU sedation or sedation for surgical and diagnostic procedures, or in children.

'Diprivan' 1% may be administered by TCI only with a 'Diprifusor' TCI system incorporating 'Diprifusor' TCI software. Such systems will operate only on recognition of electronically tagged pre-filled syringes containing 'Diprivan' 1% or 2% Injection. The 'Diprifusor' TCI system will automatically adjust the infusion rate for the concentration of 'Diprivan' recognised. Users must be familiar with the infusion pump users' manual, and with the administration of 'Diprivan' 1% by TCI and with the correct use of the syringe identification system.

The system allows the anaesthetist or intensivist to achieve and control a desired speed of induction and depth of anaesthesia by setting and adjusting target (predicted) blood concentrations of propofol.

The 'Diprifusor' TCI system assumes that the initial blood propofol concentration in the patient is zero. Therefore, in patients who have received prior propofol, there may be a need to select a lower initial target concentration when commencing 'Diprifusor' TCI. Similarly, the immediate recommencement of 'Diprifusor' TCI is not recommended if the pump has been switched off.

Guidance on propofol target concentrations is given below. In view of interpatient variability in propofol pharmacokinetics and pharmacodynamics, in both premedicated and unpremedicated patients the target propofol concentration should be titrated against the response of the patient in order to achieve the depth of anaesthesia required.

Induction and Maintenance of General Anaesthesia

In adult patients under 55 years of age anaesthesia can usually be induced with target propofol concentrations in the region of 4 to 8 microgram/ml. An initial target of 4 microgram/ml is recommended in premedicated patients and in unpremedicated patients an initial target of 6 microgram/ml is advised. Induction time with these targets is generally within the range of 60 to 120 seconds. Higher targets will allow more rapid induction of anaesthesia but may be associated with more pronounced haemodynamic and respiratory depression.

A lower initial target concentration should be used in patients over the age of about 55 years and in patients of ASA grades 3 and 4. The target concentration can then be increased in steps of 0.5 to 1.0 microgram/ml at intervals of 1 minute to achieve a gradual induction of anaesthesia.

Supplementary analgesia will generally be required and the extent to which target concentrations for maintenance of anaesthesia can be reduced will be influenced by the amount of concomitant analgesia administered. Target propofol concentrations in the region of 3 to 6 microgram/ml usually maintain satisfactory anaesthesia.

The predicted propofol concentration on waking is generally in the region of 1.0 to 2.0 microgram/ml and will be influenced by the amount of analgesia given during maintenance.

Sedation during intensive care

Target blood propofol concentration settings in the range of 0.2 to 2.0 µg/ml will generally be required. Administration should begin at low target setting which should be titrated against the response of the patient to achieve the depth of sedation desired.

Dilution and CoAdministration of 'Diprivan' 1% with Other Drugs or Infusion Fluids (see also 'Additional Precautions' Section)

Co-administration Technique	Additive or Diluent	Preparation	Precautions
Pre-mixing.	Dextrose 5% Intravenous Infusion	Mix 1 part of 'Diprivan' 1% with up to 4 parts of Dextrose 5% Intravenous Infusion B.P in either PVC infusion bags or glass infusion bottles. When diluted in PVC bags it is recommended that the bag should be full and that the dilution be prepared by withdrawing a volume of infusion fluid and replacing it with an equal volume of 'Diprivan' 1%.	Prepare aseptically immediately before administration. The mixture is stable for up to 6 hours.
	Lidocaine hydrochloride injection (0.5% or 1% without preservatives).	Mix 20 parts of 'Diprivan' 1% with up to 1 part of either 0.5% or 1% lidocaine hydrochloride injection.	Prepare mixture aseptically immediately prior to administration. Use for Induction only.
	Alfentanil injection (500	Mix 'Diprivan' 1% with alfentanil injection in a ratio of 20:1 to	Prepare mixture aseptically; use

	microgram/ml).	50:1 v/v.	within 6 hours of preparation.
Co-administration via a Y-piece connector.	Dextrose 5% intravenous infusion	Co-administer via a Y-piece connector.	Place the Y-piece connector close to the injection site.
	Sodium chloride 0.9% intravenous infusion	As above	As above
	Dextrose 4% with sodium chloride 0.18% intravenous infusion	As above	As above

4.3 Contraindications Go to top of the page

Diprivan is contraindicated in patients with a known hypersensitivity to propofol or any of the excipients.

Diprivan 1% is contraindicated for sedation in intensive care of patients of 16 years of age or younger (See 4.4 Special warnings and precautions for use).

Diprivan 1% contains soya oil and should not be used in patients who are hypersensitive to peanut or soya.

4.4 Special warnings and precautions for use Go to top of the page

'Diprivan' 1% should be given by those trained in anaesthesia or, where appropriate, doctors trained in the care of patients in Intensive Care. Patients should be constantly monitored and facilities for maintenance of a patient airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. 'Diprivan' 1% should not be administered by the person conducting the diagnostic or surgical procedure.

When 'Diprivan' 1% is administered for sedation for surgical and diagnostic procedures patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.

As with other sedative agents, when Diprivan is used for sedation during operative procedures, involuntary patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.

As with other intravenous anaesthetic and sedative agents, patients should be instructed to avoid alcohol before and for at least 8 hours after administration of 'Diprivan' 1%.

'Diprivan' 1% should be used with caution when used to sedate patients undergoing some procedures where spontaneous movements are particularly undesirable, such as ophthalmic surgery.

As with other intravenous sedative agents, when 'Diprivan' 1% is given along with central nervous system depressants, such as potent analgesics, the sedative effect may be intensified and the possibility of severe respiratory or cardiovascular depression should be considered.

During bolus administration for operative procedures, extreme caution should be exercised in patients with acute pulmonary insufficiency or respiratory depression.

Concomitant use of central nervous system depressants e.g., alcohol, general anaesthetics, narcotic analgesics will result in accentuation of their sedative effects. When 'Diprivan' 1% is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. It is recommended that 'Diprivan' 1% is administered following the analgesic and the dose should be carefully titrated to the patient's response (see Section 4.5).

During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedicants and other agents.

Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of 'Diprivan' 1% during the period of anaesthetic maintenance.

An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia. Very rarely the use of 'Diprivan' may be associated with the development of a period of post-operative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.

When 'Diprivan' 1% is administered to an epileptic patient, there may be a risk of convulsion.

As with other intravenous anaesthetic agents, caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic, elderly or debilitated patients.

The risk of relative vagal overactivity may be increased because 'Diprivan' 1% lacks vagolytic activity; it has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic agent before induction, or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate, or when 'Diprivan' 1% is used in conjunction with other agents likely to cause a bradycardia.

Appropriate care should be applied in patients with disorders of fat metabolism and in other conditions where lipid emulsions must be used cautiously.

Use is not recommended with electroconvulsive treatment.

As with other anaesthetics, sexual disinhibition may occur during recovery.

Diprivan 1% is not advised for general anaesthesia in children younger than 1 month of age. The safety and efficacy of Diprivan 1% for (background) sedation in children younger than 16 years of age have not been demonstrated. Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular these effects concerned occurrence of metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

Diprivan is not recommended for use in neonates for induction and maintenance of anaesthesia. Data from 'off-label' use have indicated that if the paediatric (1 month to 16 years of age) dose regimen is applied in neonates, a relative overdose could occur which may result in cardio-respiratory depression.

Similarly very rare reports have been received of occurrence of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/or rapidly progressive cardiac failure (in some cases with fatal outcome) in adults who were treated for more than 58 hours with dosages in excess of 5 mg/kg/h. This exceeds the maximum dosage of 4 mg/kg/h currently advised for sedation in the intensive care unit. The patients affected were mainly (but not only) seriously head-injured patients with raised ICP. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment. Treating physicians are reminded if possible not to exceed the dosage of 4 mg/kg/h. Prescribers should be alert to these possible undesirable effects and consider decreasing the Diprivan 1% dosage or switching to an alternative sedative at the first sign of occurrence of symptoms. Patients with raised ICP should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Diprivan 1% contains 0.0018 mmol sodium per ml.

EDTA is a chelator of metal ions, including zinc. The need for supplemental zinc should be considered during prolonged administration of Diprivan, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

Additional Precautions

'Diprivan' 1% contains no antimicrobial preservatives and supports growth of micro-organisms. When 'Diprivan' 1% is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both 'Diprivan' 1% and infusion equipment throughout the infusion period. Any drugs or fluids added to the 'Diprivan' 1% line must be administered close to the cannula site. 'Diprivan' 1% must not be administered via a microbiological filter.

'Diprivan' 1% and any syringe containing 'Diprivan' 1% are for single use in an individual patient. For use in long term maintenance of anaesthesia or sedation in intensive care it is recommended that the infusion line and reservoir of 'Diprivan' 1% be discarded and replaced at regular intervals.

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

'Diprivan' 1% has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking drugs, inhalational agents and analgesic agents; no pharmacological incompatibility has been encountered. Lower doses of 'Diprivan' 1% may be required where general anaesthesia is used as an adjunct to regional anaesthetic techniques.

The concurrent administration of other CNS depressants such as pre-medication drugs, inhalation agents, analgesic agents may add to the sedative, anaesthetic and cardiorespiratory depressant effects of propofol (see Section 4.4).

4.6 Pregnancy and lactation Go to top of the page

Pregnancy

The safety of Diprivan during pregnancy has not been established. Therefore Diprivan should not be used in pregnancy unless clearly necessary. Diprivan has been used, however, during termination of pregnancy in the first trimester.

Obstetrics

'Diprivan' 1% crosses the placenta and may be associated with neonatal depression. It should not be used for obstetric anaesthesia unless clearly necessary.

Lactation

Safety to the neonate has not been established following the use of 'Diprivan' 1% in mothers who are breast feeding.

4.7 Effects on ability to drive and use machines Go to top of the page

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anaesthesia.

4.8 Undesirable effects Go to top of the page

General

Induction of anaesthesia is generally smooth with minimal evidence of excitation. The most commonly reported ADRs are pharmacologically predictable side effects of an anaesthetic agent, such as hypotension. Given the nature of anaesthesia and those patients receiving intensive care, events reported in association with anaesthesia and

intensive care may also be related to the procedures being undertaken or the recipient's condition.

Very common (>1/10)	*General disorders and administration site conditions:*	Local pain on induction (1)
Common (>1/100, <1/10)	*Vascular disorder:*	Hypotension (2)
	Cardiac disorders:	Bradycardia (3)
	Respiratory, thoracic and mediastinal disorders:	Transient apnoea during induction
	Gastrointestinal disorders:	Nausea and vomiting during recovery phase
	Nervous system disorders:	Headache during recovery phase
	General disorders and administration site conditions:	Withdrawal symptoms in children (4)
	Vascular disorders:	Flushing in children (4)
Uncommon (>1/1000, <1/100)	*Vascular disorders:*	Thrombosis and phlebitis
Rare (>1/10 000, <1/1000)	*Nervous system disorders:*	Epileptiform movements, including convulsions and opisthotonus during induction, maintenance and recovery
Very rare (<1/10 000)	*Musculoskeletal and connective tissue disorders:*	Rhabdomyolysis (5)
	Gastrointestinal disorders:	Pancreatitis
	Injury, poisoning and procedural complications:	Post-operative fever
	Renal and urinary disorders:	Discolouration of urine following prolonged administration
	Immune system disorders:	Anaphylaxis – may include angioedema, bronchospasm, erythema and hypotension
	Reproductive system and breast disorders:	Sexual disinhibition
	Cardiac disorders:	Pulmonary oedema
	Nervous system disorders:	Postoperative unconsciousness

(1) May be minimised by using the larger veins of the forearm and antecubital fossa. With Diprivan 1% local pain can also be minimised by the co-administration of lidocaine.

(2) Occasionally, hypotension may require use of intravenous fluids and reduction of the administration rate of Diprivan.

(3) Serious bradycardias are rare. There have been isolated reports of progression to asystole.

(4) Following abrupt discontinuation of Diprivan during intensive care.

(5) Very rare reports of rhadbomyolysis have been received where Diprivan has been given at doses greater than 4 mg/kg/hr for ICU sedation.

Pulmonary oedema, hypotension, asystole, bradycardia, and convulsions, have been reported. In very rare cases rhabdomyolysis, metabolic acidosis, hyperkalaemia or cardiac failure, sometimes with fatal outcome, have been observed when propofol was administered at dosages in excess of 4 mg/kg/h for sedation in the intensive care unit (see 4.4 Special warnings and precautions for use). Dystonia/dyskinesia have been reported.

Reports from off-label use of Diprivan for induction of anaesthesia in neonates indicates that cardio-respiratory depression may occur if the paediatric dose regimen is applied.

Local

The local pain which may occur during the induction phase of 'Diprivan' 1% anaesthesia can be minimised by the co-administration of lidocaine (see "Dosage and Administration") and by the use of the larger veins of the forearm and antecubital fossa. Thrombosis and phlebitis are rare. Accidental clinical extravasation and animal studies showed minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects.

4.9 Overdose Go to top of the page

Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression would require lowering of the patient's head and, if severe, use of plasma expanders and pressor agents.

5. PHARMACOLOGICAL PROPERTIES Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Propofol (2, 6-diisopropylphenol) is a short-acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. The mechanism of action, like all general anaesthetics, is poorly understood.

In general, falls in mean arterial blood pressure and slight changes in heart rate are observed when 'Diprivan' 1% is administered for induction and maintenance of anaesthesia. However, the haemodynamic parameters normally remain relatively stable during maintenance and the incidence of untoward haemodynamic changes is low.

Although ventilatory depression can occur following administration of 'Diprivan' 1%, any effects are qualitatively similar to those of other intravenous anaesthetic agents and are readily manageable in clinical practice.

'Diprivan' 1% reduces cerebral blood flow, intracranial pressure and cerebral metabolism. The reduction in intracranial pressure is greater in patients with an elevated baseline intracranial pressure.

Recovery from anaesthesia is usually rapid and clear headed with a low incidence of headache and post-operative nausea and vomiting.

In general, there is less post-operative nausea and vomiting following anaesthesia with 'Diprivan' 1% than following anaesthesia with inhalational agents. There is evidence that this may be related to a reduced emetic potential of propofol.

'Diprivan' 1%, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

5.2 Pharmacokinetic properties Go to top of the page

The decline in propofol concentrations following a bolus dose or following the termination of an infusion can be described by a three compartment open model with very rapid distribution (half-life 2 to 4 minutes), rapid elimination (half-life 30 to 60 minutes), and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1.5 to 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in urine.

When 'Diprivan' 1% is used to maintain anaesthesia, blood concentrations asymptotically approach the steady-state value for the given administration rate. The pharmacokinetics are linear over the recommended range of infusion rates of 'Diprivan' 1%.

5.3 Preclinical safety data Go to top of the page

Propofol is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS Go to top of the page

6.1 List of excipients Go to top of the page

Glycerol Ph Eur

Purified Egg Phosphatide

Sodium Hydroxide Ph Eur

Soya-bean Oil, Refined Ph Eur

Water for Injections Ph Eur

Nitrogen Ph Eur

Disodium Edetate Ph Eur

6.2 Incompatibilities Go to top of the page

The neuromuscular blocking agents, atracurium and mivacurium should not be given through the same intravenous line as 'Diprivan' 1% without prior flushing.

6.3 Shelf life Go to top of the page

6.3.1 Shelf life of the product as packaged for sale

Ampoules - 3 years

Vials - 3 years

Pre-filled syringe - 2 years.

6.3.2 Shelf life after dilution

Use of diluted Diprivan must begin immediately following dilution.

6.4 Special precautions for storage Go to top of the page

Store between 2°C and 25°C.

Do not freeze.

6.5 Nature and contents of container Go to top of the page

a) Clear neutral glass ampoules of 20 ml in boxes of 5

b) Clear neutral glass vials of 50 ml and 100 ml

c) Type 1 glass pre-filled syringe of 50 ml

6.6 Special precautions for disposal and other handling Go to top of the page

In-use precautions

Containers should be shaken before use.

Any portion of the contents remaining after use should be discarded.

'Diprivan' 1% should not be mixed prior to administration with injections or infusion fluids other than 5% Dextrose or Lidocaine Injection (see Section 4.2.5).

7. MARKETING AUTHORISATION HOLDER Go to top of the page

AstraZeneca UK Limited,

600 Capability Green,

Luton, LU1 3LU, UK.

8. MARKETING AUTHORISATION NUMBER(S) Go to top of the page

PL 17901/0007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION Go to top of the page

8th July 2000 / 24th September 2004

10. DATE OF REVISION OF THE TEXT Go to top of the page

21st August 2008

More information about this product

- Patient Information Leaflets (PILs):
  Diprivan 1%
- Alternative format Patient Information Leaflets (X-PILs):
  Diprivan 1%
- Medicine Guides:
  Diprivan

Link to this document from your website: http://emc.medicines.org.uk/medicine/2275/SPC/Diprivan 1%/

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Summary of Product Characteristics last updated on the eMC: 22/08/2008

SPC **Esmeron**

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Legal Categories

POM – Prescription Only Medicine

Active Ingredients/Generics

rocuronium bromide

1. NAME OF THE MEDICINAL PRODUCT

Go to top of the page

Esmeron® 10mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Go to top of the page

Each ml Esmeron contains 10 mg rocuronium bromide.

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Go to top of the page

Solution for injection.

pH: 3.8-4.2

4. CLINICAL PARTICULARS

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Esmeron is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

4.2 Posology and method of administration

Go to top of the page

Like other neuromuscular blocking agents, Esmeron should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these drugs.

As with other neuromuscular blocking agents, the dosage of Esmeron should be individualized in each patient. The method of anaesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other drugs that are administered concomitantly, and the condition of the patient should be taken into account when determining the dose.

The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery.

Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Esmeron. This potentiation however, becomes clinically relevant in the course of anaesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with Esmeron should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Esmeron during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (see section 4.5).

In adult patients the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the intensive care unit.

Surgical Procedures

Tracheal intubation

The standard intubating dose during routine anaesthesia is 0.6 mg/kg rocuronium bromide, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0 mg/kg rocuronium bromide is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia, after which adequate intubation conditions are established within 60 seconds in nearly all patients. If a dose of 0.6 mg/kg rocuronium bromide is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

For use of rocuronium bromide during rapid sequence induction of anaesthesia in patients undergoing Caesarean section reference is made to section 4.6.

Higher doses

Should there be reason for selection of larger doses in individual patients, there is no indication from clinical studies that the use of initial doses up to 2 mg/kg rocuronium bromide is associated with an increased frequency or severity of cardiovascular effects. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action (see section 5.1).

Maintenance dosing

The recommended maintenance dose is 0.15 mg/kg rocuronium bromide; in the case of long-term inhalational anaesthesia this should be reduced to 0.075-0.1 mg/kg rocuronium bromide. The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to train of four stimulation are present.

Continuous infusion

If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg/kg rocuronium bromide and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 to 2 responses to train of four stimulation. In adults under intravenous anaesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h (300-600 micrograms/kg/h) and under inhalational anaesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Paediatric patients

For infants (28 days–23 months), children (2-11 years) and adolescents (12–18 years) the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those in adults.

For continuous infusion in paediatrics, the infusion rates, with the exception of children, are the same as for adults. For children higher infusion rates might be necessary. For children the same initial infusion rates as for adults are recommended and this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to train of four stimulation during the procedure.

There are insufficient data to support dose recommendations for the use of rocuronium bromide in neonates (0-1 month).

The experience with rocuronium bromide in rapid sequence induction in paediatric patients is limited. Rocuronium bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure

The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0.6 mg/kg rocuronium bromide. A dose of 0.6 mg/kg should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg/kg rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg/kg/h (see also Continuous infusion).

Overweight and obese patients

When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account ideal body weight.

Intensive Care Procedures

Tracheal intubation

For tracheal intubation, the same doses should be used as described above under surgical procedures.

Maintenance dosing

The use of an initial loading dose of 0.6 mg/kg rocuronium bromide is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80-90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3-0.6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6-12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant.

A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5 mg/kg/h depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration up to 7 days has been investigated.

Special Populations

Esmeron is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and geriatric patients due to a lack of data on safety and efficacy.

Administration

Esmeron is administered intravenously either as a bolus injection or as a continuous infusion (see section 6.6).

4.3 Contraindications

Go to top of the page

Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients.

4.4 Special warnings and precautions for use

Go to top of the page

Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

As with other neuromuscular blocking agents, residual neuromuscular blockade has been reported for Esmeron. In order to prevent complications resulting from residual neuromuscular blockade, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual neuromuscular blockade after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal agent should be considered, especially in those cases where residual neuromuscular blockade is more likely to occur.

Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported.

Rocuronium may increase the heart rate.

In general, following long term use of neuromuscular blocking agents in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of neuromuscular blocking agents. In addition, patients should receive adequate analgesia and sedation. Furthermore, neuromuscular blocking agents should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques.

Myopathy after long term administration of other non-depolarising neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported regularly. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible.

If suxamethonium is used for intubation, the administration of Esmeron should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Esmeron:

Hepatic and/or biliary tract disease and renal failure

Because rocuronium is excreted in urine and bile, it should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg/kg rocuronium bromide.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular disease, old age and oedematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. The duration of action may also be prolonged due to a reduced plasma clearance.

Neuromuscular disease

Like other neuromuscular blocking agents, Esmeron should be used with extreme caution in patients with a

neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Esmeron may have profound effects and Esmeron should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking effect of Esmeron is increased and the duration prolonged.

Obesity

Like other neuromuscular blocking agents, Esmeron may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients when the administered doses are calculated on actual body weight.

Burns

Patients with burns are known to develop resistance to non-depolarising neuromuscular blocking agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of Esmeron

Hypokalaemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia, cachexia.

Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

4.5 Interaction with other medicinal products and other forms of interaction

Go to top of the page

The following drugs have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents.

Effect of other drugs on Esmeron

Increased effect:

• Halogenated volatile anaesthetics potentiate the neuromuscular block of Esmeron. The effect only becomes apparent with maintenance dosing (see section 4.2). Reversal of the block with anticholinesterase inhibitors could also be inhibited.

• After intubation with suxamethonium (see section 4.4).

• Long-term concomitant use of corticosteroids and Esmeron in the ICU may result in prolonged duration of neuromuscular block or myopathy (see section 4.4 and 4.8).

Other drugs:

• antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.

• diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lidocaine i.v, bupivacaine epidural) and acute administration of phenytoin or β-blocking agents.

Recurarisation has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see section 4.4).

Decreased effect:

• Prior chronic administration of phenytoin or carbamazepine.

• Calcium chloride, potassium chloride.

• Protease inhibitors (gabexate, ulinastatin).

Variable effect:

• Administration of other non-depolarising neuromuscular blocking agents in combination with Esmeron may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.

• Suxamethonium given after the administration of Esmeron may produce potentiation or attenuation of the neuromuscular blocking effect of Esmeron.

Effect of Esmeron on other drugs

Esmeron combined with lidocaine may result in a quicker onset of action of lidocaine.

4.6 Pregnancy and lactation

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Pregnancy

For rocuronium bromide, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal

development. Caution should be exercised when prescribing Esmeron to pregnant women.

Caesarean section

In patients undergoing Caesarean section, Esmeron can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. However, Esmeron, administered in doses of 0.6 mg/kg may not produce adequate conditions for intubation until 90 seconds after administration. This dose has been shown to be safe in parturients undergoing Caesarean section. Esmeron does not affect Apgar score, foetal muscle tone or cardiorespiratory adaptation.

From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs which does not lead to the observation of clinical adverse effects in the newborn.

Note 1: doses of 1.0 mg/kg have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients. Therefore, only a dose of 0.6 mg/kg is recommended in this patient group.

Note 2: Reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of Esmeron should be reduced and be titrated to twitch response.

Lactation

It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown insignificant levels of rocuronium bromide in breast milk.

Insignificant levels of rocuronium bromide were found in the milk of lactating rats. There are no human data on the use of Esmeron during lactation. Esmeron should be given to lactating women only when the attending physician decided that the benefits outweigh the risks

4.7 Effects on ability to drive and use machines Go to top of the page

Since Esmeron is used as an adjunct to general anaesthesia, the usual precautionary measures after a general anaesthesia should be taken for ambulatory patients.

4.8 Undesirable effects Go to top of the page

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms. See also the explanations below the table.

MedDRA SOC	Preferred term[1]	
	Uncommon/rare[2] (<1/100,>1/10 000)	Very rare (<1/10 000)
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock
Nervous system disorders		Flaccid paralysis
Cardiac disorders	Tachycardia	
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing
Skin and subcutaneous tissue disorders		Angioneurotic edema Urticaria Rash Erythematous rash
Musculoskeletal and connective tissue disorders		Muscular weakness[3] Steroid myopathy[3]
General disorders and administration site conditions	Drug ineffective Drug effect/ therapeutic response decreased	Face oedema

	Drug effect/ therapeutic response increased Injection site pain Injection site reaction	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia

[1] Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.
[2] Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over two rather than five categories.
[3] after long-term use in the ICU

MedDRA version 8.1

Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. Anaphylactic/anaphylactoid reactions are: bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse - shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions.

Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous reaction at the site of injection and/or generalised histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these drugs.

In clinical studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0.3-0.9 mg/kg rocuronium bromide.

Prolonged neuromuscular block

The most frequent adverse reaction to nondepolarising blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Myopathy

Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU in combination with corticosteroids (see section 4.4).

Local injection site reactions

During rapid sequence induction of anaesthesia, pain on injection has been reported, especially when the patient has not yet completely lost consciousness and particularly when propofol is used as the induction agent. In clinical studies, pain on injection has been noted in 16% of the patients who underwent rapid sequence induction of anaesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

4.9 Overdose Go to top of the page

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. Upon start of spontaneous recovery an acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of Esmeron, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

In animal studies, severe depression of cardiovascular function, ultimately leading to cardiac collapse did not occur until a cumulative dose of 750 x ED_{90} (135 mg/kg rocuronium bromide) was administered.

5. PHARMACOLOGICAL PROPERTIES Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Pharmacotherapeutic group (ATC code)

Muscle relaxants, peripherally acting agents. ATC code: M03AC09.

Mechanism of Action

Esmeron (rocuronium bromide) is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic effects

The ED_{90} (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anaesthesia is approximately 0.3 mg/kg rocuronium bromide. The ED_{95} in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg respectively).

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6 mg/kg rocuronium bromide is 30–40 minutes. The total duration (time until spontaneous recovery to 90% of control twitch height) is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75% (recovery index) after a bolus dose of 0.6 mg/kg rocuronium bromide is 14 minutes. With lower dosages of 0.3-0.45 mg/kg rocuronium bromide (1 -1½ x ED_{90}), onset of action is slower and duration of action is shorter. With high doses of 2 mg/kg, clinical duration is 110 minutes.

Intubation during routine anaesthesia

Within 60 seconds following intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x ED_{90} under intravenous anaesthesia), adequate intubation conditions can be achieved in nearly all patients of which in 80% intubation conditions are rated excellent. General muscle paralysis adequate for any type of procedure is established within 2 minutes. After administration of 0.45 mg/kg rocuronium bromide, acceptable intubation conditions are present after 90 seconds.

Rapid Sequence Induction

During rapid sequence induction of anaesthesia under propofol or fentanyl/thiopental anaesthesia, adequate intubation conditions are achieved within 60 seconds in 93% and 96% of the patients respectively, following a dose of 1.0 mg/kg rocuronium bromide. Of these, 70% are rated excellent. The clinical duration with this dose approaches 1 hour, at which time the neuromuscular block can be safely reversed. Following a dose of 0.6 mg/kg rocuronium bromide, adequate intubation conditions are achieved within 60 seconds in 81% and 75% of the patients during a rapid sequence induction technique with propofol or fentanyl/thiopental, respectively.

Special populations

Mean onset time in infants and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults.

The duration of action of maintenance doses of 0.15 mg/kg rocuronium bromide might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic and/or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes). No accumulation of effect (progressive increase in duration of action) with repetitive maintenance dosing at the recommended level has been observed.

Intensive Care Unit

Following continuous infusion in the Intensive Care Unit, the time to recovery of the train of four ratio to 0.7 depends on the level of block at the end of the infusion. After a continuous infusion for 20 hours or more the median (range) time between return of T_2 to train of four stimulation and recovery of the train of four ratio to 0.7 approximates 1.5 (1-5) hours in patients without multiple organ failure and 4 (1-25) hours in patients with multiple organ failure.

Cardiovascular surgery

In patients scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum block following 0.6-0.9 mg/kg rocuronium bromide are a slight and clinically insignificant increase in heart rate up to 9% and an increase in mean arterial blood pressure up to 16% from the control values.

Reversal of muscle relaxation

Administration of acetylcholinesterase inhibitors, (neostigmine, pyridostigmine or edrophonium) at reappearance of T_2 or at the first signs of clinical recovery, antagonises the action of Esmeron.

5.2 Pharmacokinetic properties Go to top of the page

After intravenous administration of a single bolus dose of rocuronium bromide the plasma concentration time course runs in three exponential phases. In normal adults, the mean (95%CI) elimination half-life is 73 (66-80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193-214) ml/kg and plasma clearance is 3.7 (3.5-3.9) ml/kg/min.

In controlled studies the plasma clearance in geriatric patients and in patients with renal dysfunction was reduced, in most studies however without reaching the level of statistical significance. In patients with hepatic disease, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml/kg/min. (See also Posology and method of administration).

In infants (28 days to 23 months), the apparent volume of distribution at steady state conditions is increased compared to adults and children (2-11 years). In older children (3-8 yr), a trend is seen towards higher clearance and shorter elimination half-life (approximately 20 minutes) compared to adults, younger children and infants.

When administered as a continuous infusion to facilitate mechanical ventilation for 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A large between patient variability is found in controlled clinical studies, related to nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean (± SD) elimination half-life of 21.5 (± 3.3) hours, a (apparent) volume of distribution at steady state of 1.5 (± 0.8) l/kg and a plasma clearance of 2.1 (± 0.8) ml/kg/min were found. (See also Posology and method of administration).

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. After injection of a

radiolabeled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in faeces after 9 days. Approximately 50% is recovered as the parent compound. No metabolites are detected in plasma.

5.3 Preclinical safety data Go to top of the page

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

There is no proper animal model to mimic the usually extremely complex clinical situation of the ICU patient. Therefore the safety of Esmeron when used to facilitate mechanical ventilation in the Intensive Care Unit is mainly based on results obtained in clinical studies.

6. PHARMACEUTICAL PARTICULARS Go to top of the page

6.1 List of excipients Go to top of the page

Esmeron contains the following excipients:

• Sodium acetate (for pH adjustment)

• Sodium chloride

• Acetic acid

• Water

No preservative has been added

6.2 Incompatibilities Go to top of the page

Physical incompatibility has been documented for Esmeron when added to solutions containing the following drugs: amphotericin, amoxicillin**,** azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, intralipid, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin.

Esmeron must not be mixed with other medicinal products except those mentioned in section 6.6.

If Esmeron is administered via the same infusion line that is also used for other drugs, it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl) between administration of Esmeron and drugs for which incompatibility with Esmeron has been demonstrated or for which compatibility with Esmeron has not been established.

6.3 Shelf life Go to top of the page

Esmeron has a shelf life of 3 years, provided it is stored under the prescribed conditions (see Special precautions for storage). The date mentioned on the carton and on the label of the vial is the expiry date; this is the date up to which Esmeron may be used. Since Esmeron does not contain a preservative, the solution should be used immediately after opening the vial.

After dilution with infusion fluids (see section 6.6), chemical and physical in-use stability has been demonstated for 72 hours at 30^{o}c. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user/administrator and would normally not be longer than 24 hours at 2 to 8^{o}C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage Go to top of the page

Storage in the Refrigerator

Esmeron should be stored at 2°-8°C in the dark and used within the expiry date given on the pack.

Storage out of the refrigerator

Esmeron may also be stored outside of the refrigerator at a temperature of up to 30°C for a maximum 12 weeks, after which it should be discarded. The product should not be placed back into the refrigerator, once it has been kept outside. The storage period must not exceed the shelf-life.

6.5 Nature and contents of container Go to top of the page

Esmeron 25 mg in 2.5 ml (10mg/ml)

Packaging of 10 vials each containing 25 mg rocuronium bromide.

Esmeron 50 mg in 5 ml (10mg/ml)

Packaging of 10 vials each containing 50 mg rocuronium bromide.

Esmeron 100 mg in 10 ml (10mg/ml)

Packaging of 10 vials each containing 100 mg rocuronium bromide.

Not all pack sizes may be marketed.

Type 1 Ph.Eur., clear, colourless, glass vial with a rubber closure and flip off cap. The rubber stopper of the vial does not contain latex.

In correspondence please quote batch number.

6.6 Special precautions for disposal and other handling Go to top of the page

Compatibility studies with the following infusion fluids have been performed: In nominal concentrations of 0.5 mg/ml and 2.0 mg/ml Esmeron has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in saline, sterile water for injections, Lactated Ringers and Haemaccel. Administration should be begun immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

7. MARKETING AUTHORISATION HOLDER Go to top of the page

NV Organon, Kloosterstraat 6, PO Box 20, 5340 BH Oss, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S) Go to top of the page

PL 05003/0041

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION Go to top of the page

4 August 2000

10. DATE OF REVISION OF THE TEXT Go to top of the page

March 2008

REF: USEsVial17.0

More information about this product

- Patient Information Leaflets (PILs):
  Esmeron
- Alternative format Patient Information Leaflets (X-PILs):
  Esmeron
- Medicine Guides:
  Esmeron

Link to this document from your website: http://emc.medicines.org.uk/medicine/5166/SPC/Esmeron/

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Summary of Product Characteristics last updated on the eMC: 22/09/2008

SPC **Anectine Injection**

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Legal Categories

POM – Prescription Only Medicine

Active Ingredients/Generics

suxamethonium chloride

1. NAME OF THE MEDICINAL PRODUCT

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Anectine Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Go to top of the page

Suxamethonium Chloride Injection BP 100mg in 2ml.

3. PHARMACEUTICAL FORM

Go to top of the page

Injection.

4. CLINICAL PARTICULARS

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Used in anaesthesia as a muscle relaxant to facilitate endotracheal intubation, mechanical ventilation and a wide range of surgical and obstetric procedures.

It is also used to reduce the intensity of muscular contractions associated with pharmacologically or electrically-induced convulsions.

4.2 Posology and method of administration

Go to top of the page

Usually by bolus intravenous injection.

Adults: The dose is dependent on body weight, the degree of muscular relaxation required, the route of administration, and the response of individual patients.

To achieve endotracheal intubation Anectine is usually administered intravenously in a dose of 1 mg/kg. This dose will usually produce muscular relaxation in about 30 to 60 seconds and has a duration of action of about 2 to 6 minutes. Larger doses will produce more prolonged muscular relaxation, but doubling the dose does not necessarily double the duration of relaxation. Supplementary doses of Anectine of 50% to 100% of the initial dose administered

at 5 to 10 minute intervals will maintain muscle relaxation during short surgical procedures performed under general anaesthesia.

For prolonged surgical procedures Anectine may be given by intravenous infusion as a 0.1% to 0.2% solution, diluted in 5% glucose solution or sterile isotonic saline solution, at a rate of 2.5 to 4 mg per minute. The infusion rate should be adjusted according to the response of individual patients.

The total dose of Anectine given by repeated intravenous injection or continuous infusion should not exceed 500 mg per hour.

Children: Infants and young children are more resistant to Anectine compared with adults.

The recommended intravenous dose of Anectine for neonates and infants is 2 mg/kg. A dose of 1 mg/kg in older children is recommended.

When Anectine is given as intravenous infusion in children, the dosage is as for adults with a proportionately lower initial infusion rate based on body weight.

Anectine may be given intramuscularly to infants at doses up to 4 to 5mg/kg and in older children up to 4 mg/kg. These doses produce muscular relaxation within about 3 minutes. A total dose of 150 mg should not be exceeded.

Use in the elderly: Dosage requirements of Anectine in the elderly are comparable to those for younger adults.

The elderly may be more susceptible to cardiac arrhythmias, especially if digitalis-like drugs are also being taken. See also '*Special warnings and precautions for use*'.

Instructions to open the ampoule

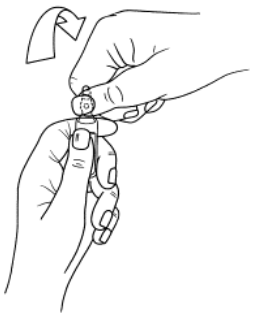
Ampoules are equipped with the OPC (One Point Cut) opening system and must be opened using the following instructions:

hold with the hand the bottom part of the ampoule as indicated in picture 1

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



4.3 Contraindications Go to top of the page

Anectine has no effect on the level of consciousness and should not be administered to a patient who is not fully anaesthetised.

Hypersensitivity to suxamethonium may exist in rare instances, and Anectine should not be administered to patients known to be hypersensitive to the drug.

As suxamethonium can act as a trigger of sustained myofibrillar contraction in susceptible individuals, Anectine is contra-indicated in patients with a personal or family history of malignant hyperthermia. If this condition occurs unexpectedly, all anaesthetic agents known to be associated with its development (including Anectine) must be immediately discontinued, and full supportive measures must be immediately instituted. Intravenous dantrolene sodium is the primary specific therapeutic drug and is recommended as soon as possible after the diagnosis is made.

Anectine is contra-indicated in patients known to have an inherited atypical plasma cholinesterase activity.

An acute transient rise in serum potassium often occurs following the administration of Anectine in normal individuals; the magnitude of this rise is of the order of 0.5 mmol/litre. In certain pathological states or conditions this increase in serum potassium following Anectine administration may be excessive and cause serious cardiac arrhythmias and cardiac arrest. For this reason the use of Anectine is contra-indicated in:

In patients recovering from major trauma or severe burns; the period of greatest risk of hyperkalaemia is from about 5 to 70 days after the injury and may be further prolonged if there is delayed healing due to persistent infection.

Patients with neurological deficits involving acute major muscle wasting (upper and/or lower motor neurone lesions); the potential for potassium release occurs within the first 6 months after the acute onset of the neurological deficit and correlates with the degree and extent of muscle paralysis. Patients who have been immobilised for prolonged periods of time may be at similar risk.

Patients with pre-existing hyperkalaemia. In the absence of hyperkalaemia and neuropathy, renal failure is not a contra-indication to the administration of a normal single dose of Anectine Injection, but multiple or large doses may cause clinically significant rises in serum potassium and should not be used.

Suxamethonium causes a significant transient rise in intra-ocular pressure, and should therefore not be used in the presence of open eye injuries or where an increase in intra-ocular pressure is undesirable unless the potential benefit of its use outweighs the potential risk to the eye.

Anectine should be avoided in patients with a personal or family history of congenital myotonic diseases such as myotonia congenita and dystrophia myotonica since its administration may on occasion be associated with severe myotonic spasms and rigidity.

Anectine should not be used in patients with skeletal muscle myopathies e.g. Duchenne muscular dystrophy since its administration may be associated with malignant hyperthermia, ventricular dysrhythmias and cardiac arrest secondary to acute rhabdomyolysis with hyperkalaemia.

4.4 Special warnings and precautions for use

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Anectine should be administered only by or under close supervision of an anaesthetist familiar with its action, characteristics and hazards, who is skilled in the management of artificial respiration and only where there are adequate facilities for immediate endotracheal intubation with administration of oxygen by intermittent positive pressure ventilation.

High rates of cross-sensitivity between neuromuscular blocking agents have been reported. Therefore, where possible, before administering suxamethonium, hypersensitivity to other neuromuscular blocking agents should be excluded. Suxamethonium, 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.

Anectine should not be mixed in the same syringe with any other agent, especially thiopental.

During prolonged administration of Anectine, it is recommended that the patient is fully monitored with a peripheral nerve stimulator in order to avoid overdosage.

Anectine is rapidly hydrolysed by plasma cholinesterase which thereby limits the intensity and duration of the neuromuscular blockade.

Individuals with decreased plasma cholinesterase activity exhibit a prolonged response to suxamethonium . Approximately 0.05% of the population has an inherited cause of reduced cholinesterase activity. Prolonged and intensified neuromuscular blockade following Anectine Injection may occur secondary to reduced plasma cholinesterase activity in the following states or pathological conditions: physiological variation as in pregnancy and the puerperium; genetically determined abnormal plasma cholinesterase; severe generalised tetanus, tuberculosis, other severe or chronic infections; following severe burns; chronic debilitating disease, malignancy, chronic anaemia and malnutrition; end-stage hepatic failure, acute or chronic renal failure; auto-immune diseases: myxoedema, collagen diseases; iatrogenic: following plasma exchange, plasmapheresis, cardiopulmonary bypass, and as a result of concomitant drug therapy (see *Interactions*).

If Anectine is given over a prolonged period, the characteristic depolarising neuromuscular (or Phase I) block may change to one with characteristics of a non-depolarising (or Phase II) block. Although the characteristics of a developing Phase II block resemble those of a true non-depolarising block, the former cannot always be fully or permanently reversed by anticholinesterase agents. When a Phase II block is fully established, its effects will then usually be fully reversible with standard doses of neostigmine accompanied by an anticholinergic agent.

Tachyphylaxis occurs after repeated administration of Anectine.

Muscle pains are frequently experienced after administration of suxamethonium and most commonly occur in ambulatory patients undergoing short surgical procedures under general anaesthesia. There appears to be no direct connection between the degree of visible muscle fasciculation after Anectine administration and the incidence or severity of pain. The use of small doses of non-depolarising muscle relaxants given minutes before suxamethonium administration has been advocated for the reduction of incidence and severity of suxamethonium-associated muscle pains. This technique may require the use of doses of suxamethonium in excess of 1mg/kg to achieve satisfactory conditions for endotracheal intubation.

Caution should be exercised when using suxamethonium in children, since paediatric patients are more likely to have an undiagnosed myopathy or an unknown predisposition to malignant hyperthermia and rhabdomyolysis, which places them at increased risk of serious adverse events following suxamethonium (see section 4.3 Contraindications and section 4.8 Adverse Reactions).

In patients with severe sepsis, the potential for hyperkalaemia seems to be related to the severity and duration of infection.

It is inadvisable to administer Anectine to patients with advanced myasthenia gravis. Although these patients are resistant to suxamethonium they develop a state of Phase II block which can result in delayed recovery. Patients with myasthenic Eaton-Lambert syndrome are more sensitive than normal to Anectine, necessitating dosage reduction.

In healthy adults, Anectine occasionally causes a mild transient slowing of the heart rate on initial administration. Bradycardias are more commonly observed in children and on repeated administration of suxamethonium in both children and adults. Pre-treatment with intravenous atropine or glycopyrrolate significantly reduces the incidence and severity of suxamethonium-related bradycardia.

In the absence of pre-existing or evoked hyperkalaemia, ventricular arrhythmias are rarely seen following suxamethonium administration. Patients taking digitalis-like drugs are however more susceptible to such arrhythmias. The action of suxamethonium on the heart may cause changes in cardiac rhythm including cardiac arrest.

4.5 Interaction with other medicinal products and other forms of interaction

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Certain drugs or chemicals are known to reduce normal plasma cholinesterase activity and may therefore prolong the neuromuscular blocking effects of Anectine. These include: organophosphorous insecticides and metriphonate; ecothiopate eye drops; trimetaphan; specific anticholinesterase agents: neostigmine, pyridostigmine, physostigmine, edrophonium; tacrine hydrochloride; cytotoxic compounds: cyclophosphamide, mechlorethamine, triethylene-melamine, and thiotepa; psychiatric drugs: phenelzine, promazine and chlorpromazine; anaesthetic agents and drugs: ketamine, morphine and morphine antagonists, pethidine, pancuronium, propanidid.

Other drugs with potentially deleterious effects on plasma cholinesterase activity include aprotinin, diphenhydramine, promethazine, oestrogens, oxytocin, high-dose steroids, and oral contraceptives, terbutaline and metoclopramide.

Certain drugs or substances may enhance or prolong the neuromuscular effects of Anectine by mechanisms unrelated to plasma cholinesterase activity. These include: magnesium salts; lithium carbonate; azathioprine; quinine and chloroquine; antibiotics such as the aminoglycosides, clindamycin and polymyxins; antiarrhythmic drugs: quinidine, procainamide, verapamil, beta-blockers, lidocaine and procaine; volatile inhalational anaesthetic agents: halothane, enflurane, desflurane, isoflurane, diethylether and methoxyflurane have little effect on the Phase I block of Anectine injection but will accelerate the onset and enhance the intensity of a Phase II suxamethonium-induced block.

Patients receiving digitalis-like drugs are more susceptible to the effects of suxamethonium-exacerbated hyperkalaemia.

4.6 Pregnancy and lactation

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No studies of the effect of suxamethonium on female fertility or pregnancy have been performed.

Suxamethonium has no direct action on the uterus or other smooth muscle structures. In normal therapeutic doses it does not cross the placental barrier in sufficient amounts to affect the respiration of the infant.

The benefits of the use of suxamethonium as part of a rapid sequence induction for general anaesthesia normally outweigh the possible risk to the foetus.

Plasma cholinesterase levels fall during the first trimester of pregnancy to about 70 to 80% of their pre-pregnancy values; a further fall to about 60 to 70% of the pre-pregnancy levels occurs within 2 to 4 days after delivery. Plasma cholinesterase levels then increase to reach normal over the next 6 weeks. Consequently, a high proportion of pregnant and puerperal patients may exhibit mildly prolonged neuromuscular blockade following Anectine injection.

It is not known whether suxamethonium or its metabolites are excreted in human milk.

4.7 Effects on ability to drive and use machines

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Not applicable.

4.8 Undesirable effects

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Adverse reactions are listed below by system organ class and frequency. Estimated frequencies were determined from published data. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 and <1/10), uncommon (≥ 1/1,000 and <1/100); rare (≥ 1/10,000 and <1/1,000); very rare (<1/10,000).

Immune system disorders

Very rare Anaphylactic reactions.

Eye disorders

Common Increased intraocular pressure.

Cardiac disorders

Common Bradycardia, tachycardia.

Rare Arrhythmias (including ventricular arrhythmias),

cardiac arrest.

There are case reports of hyperkalaemia-related cardiac arrests following the administration of suxamethonium to patients with congenital cerebral palsy, tetanus, Duchenne muscular dystrophy, and closed head injury. Such events have also been reported rarely in children with hitherto undiagnosed muscular disorders.

Vascular disorders

Common Skin flushing.

Hypertension and hypotension have also been reported.

Respiratory, thoracic and mediastinal disorders

Rare Bronchospasm, prolonged respiratory depression†, apnoea.

Please refer to section 4.4 Special Warnings and Precautions for Use

Gastrointestinal disorders

Very common Increased intragastric pressure.

Excessive salivation has also been reported

Skin and subcutaneous tissue disorders

Common Rash.

Musculoskeletal and connective tissue disorders

Very common Muscle fasciculation, post-operative muscle pains (Please refer to section 4.4 Special Warnings and Precautions for Use).

Common Myoglobinaemia#, myoglobinuria#.

Rare Trismus

Rhabdomyolysis has also been reported (see section 4.3 Contraindications and section 4.4 Special Warnings and Precautions for Use)

General disorders and administration site conditions

Very rare Malignant hyperthermia (Please refer to section 4.4 Special Warnings and Precautions for Use).

Investigations

Common Transient blood potassium increase.

4.9 Overdose

Go to top of the page

Apnoea and prolonged muscle paralysis are the main serious effects of overdosage. It is essential, therefore, to maintain the airway and adequate ventilation until spontaneous respiration occurs.

The decision to use neostigmine to reverse a Phase II suxamethonium-induced block depends on the judgement of the clinician in the individual case. Valuable information in regard to this decision will be gained by monitoring neuromuscular function. If neostigmine is used its administration should be accompanied by appropriate doses of an anticholinergic agent such as atropine.

5. PHARMACOLOGICAL PROPERTIES

Go to top of the page

5.1 Pharmacodynamic properties

Go to top of the page

Short-acting depolarising neuromuscular blocking agent.

5.2 Pharmacokinetic properties

Go to top of the page

None stated.

5.3 Preclinical safety data

Go to top of the page

Genotoxicity:-

No bacterial mutation assays have been conducted.

There are some data to suggest a weak clastogenic effect in mice, but not in patients who had received suxamethonium chloride.

Carcinogenicity:-

Carcinogenicity studies have not been performed.

Embryo-foetal Development:-

Animal reproduction studies have not been conducted with suxamethonium. It is also not known whether suxamethonium can affect reproductive capacity or cause foetal harm when administered to a pregnant woman.

6. PHARMACEUTICAL PARTICULARS

Go to top of the page

6.1 List of excipients

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Water for Injections EP.

6.2 Incompatibilities

Go to top of the page

None known.

6.3 Shelf life

Go to top of the page

18 months.

6.4 Special precautions for storage

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Store between 2 – 8 °C. Do not freeze. Keep in the outer carton.

6.5 Nature and contents of container

Go to top of the page

Neutral glass. 2ml ampoules.

6.6 Special precautions for disposal and other handling

Go to top of the page

For intravenous injection under medical direction.

Administrative Data

Go to top of the page

7. MARKETING AUTHORISATION HOLDER

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Stockley Park West

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8. MARKETING AUTHORISATION NUMBER(S)

Go to top of the page

PL 00003/5203R

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Go to top of the page

25 July 1996

10. DATE OF REVISION OF THE TEXT

Go to top of the page

8 September 2008

11. Legal Status

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POM

More information about this product

- Patient Information Leaflets (PILs):
  Anectine Injection
- Medicine Guides:
  Anectine

Link to this document from your website: http://emc.medicines.org.uk/medicine/704/SPC/Anectine Injection/

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Summary of Product Characteristics last updated on the eMC: 05/05/2004

SPC **Thiopental injection (Link Pharmaceuticals Ltd)**

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Legal Categories

POM – Prescription Only Medicine

Active Ingredients/Generics

thiopental sodium

1. NAME OF THE MEDICINAL PRODUCT

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Thiopental Injection BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Go to top of the page

Thiopental Sodium BP 500mg

3. PHARMACEUTICAL FORM

Go to top of the page

Freeze-dried powder for solution for injection in a vial.

4. CLINICAL PARTICULARS

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

1. Thiopental is used for the induction of general anaesthesia and is also used as an adjunct to provide hypnosis during balanced anaesthesia with other anaesthetic agents, including analgesics and muscle relaxants.

2. Thiopental is also used as an adjunct for control of convulsive disorders of various aetiology, including those caused by local anaesthetics.

3. Thiopental has now been used to reduce the intracranial pressure in patients with increased intracranial pressure, if controlled ventilation is provided.

4.2 Posology and method of administration

Go to top of the page

Intravenous injection.

Thiopental Injection BP is administered intravenously normally as a 2.5% w/v (500mg in 20ml) solution. On occasions it may be administered as a 5% w/v solution (500mg in 10ml).

The intravenous injection preparation should be used after reconstitution of the sterile powder with Water for Injections, usually to produce a 2.5% w/v solution and this should be discarded after seven hours.

Use in anaesthesia

Normal dosage for the induction of anaesthesia is 100mg to 150mg injected over 10 to 15 seconds. If necessary a repeat dose of 100mg to 150mg may be given after one minute. No fixed dosage recommendations for the intravenous injection can be given, since the dosage will need to be carefully adjusted according to the patient's response. Factors such as age, sex, and weight of the patient should be taken into consideration. Thiopental sodium reaches effective concentrations in the brain within 30 seconds and anaesthesia is normally produced within one minute of an intravenous dose.

Adult

100mg to 150mg intravenously over 10 to 15 seconds, normally as a 2.5% w/v solution.

A repeat dose of 100mg to 150mg may be given after one minute.

The intravenous injection should be given slowly and the amounts given titrated against the patient's response to minimise the risk of respiratory depression or the possibility of overdosage. The average dose for an adult of 70kg is roughly 200mg to 300mg (8mls to 12mls of a 2.5% w/v solution) with a maximum of 500mg.

Children

2 to 7mg/kg bodyweight, intravenously over 10 to 15 seconds, normally as a 2.5% w/v solution. A repeat dose of 2 to 7mg/kg may be given after one minute. The dose is 2 to 7mg/kg based on the patient's response. The dose for children should not exceed 7mg/kg.

Elderly

Smaller adult doses are advisable.

Use in convulsive states

75mg to 125mg (3mls to 5mls of a 2.5% w/v solution) should be given as soon as possible after the convulsion begins. Further doses may be required to control convulsions following the use of a local anaesthetic. Other regimens, such as the use of intravenous or rectal diazepam, may be used to control convulsive states.

Use in neurological patients with raised intracranial pressure

Intermittent bolus injections of 1.5 to 3mg/kg of bodyweight may be given to reduce elevations of intracranial pressure if controlled ventilation is provided.

4.3 Contraindications

Go to top of the page

Thiopental is contraindicated in respiratory obstruction, acute asthma, severe shock and dystrophia myotonica. Administration of any barbiturate is contraindicated in porphyria.

Care should also be exercised with severe cardiovascular diseases, severe respiratory diseases and hypertension of various aetiology.

Patients with hypersensitivity reactions to barbiturates.

4.4 Special warnings and precautions for use

Go to top of the page

Special care is needed in administering thiopental to patients with the following conditions:- hypovolaemia, severe haemorrhage, burns, dehydration, severe anaemia, cardiovascular disease, status asthmaticus, severe liver disease, myasthenia gravis and muscular dystrophies, adrenocortical insufficiency (even when controlled by cortisone), cachexia and severe toxaemia, raised intracranial pressure, raised blood urea, raised plasma potassium, metabolic disorders e.g. thyrotoxicosis, myxoedema, diabetes.

Thiopental may precipitate acute circulatory failure in patients with cardiovascular disease, particularly constrictive pericarditis.

Thiopental can cause respiratory depression and a reduction in cardiac output.

Headache is also reported with the use of barbiturate anaesthetics.

Reduced doses are recommended in shock, dehydration, severe anaemia, hyperkalaemia, toxaemia, myxoedema or other metabolic disorders. Thiopental sodium is metabolised primarily by the liver so doses should be reduced in patients with hepatic impairment. Reduced doses are also indicated in the elderly and in patients who have been premedicated with narcotic analgesics.

Thiopental has been shown to interact with sulphafurazole. Reduced initial doses may be required to achieve adequate anaesthesia, but repeat doses may also be necessary to maintain anaesthesia.

Increased doses may be necessary in patients who have either an habituation or addiction to alcohol or drugs of abuse. Under these circumstances it is recommended that supplementary analgesic agents are used.

Accidental intra-arterial injection of thiopental causes severe arterial spasm and an intense burning pain around the injection site. In the case of accidental intra-arterial injection of thiopental the needle should be left in-situ so that an injection of an antispasmodic, such as papaverine or prilocaine hydrochloride may be given. Anticoagulant therapy

may also be started to reduce the risk of thrombosis.

Thiopental injection should be used with caution in patients with adrenocortical insufficiency or with raised intracranial pressure.

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

Thiopental has been shown to interact with sulphafurazole.

It should be noted that thiopental will interact with beta-blockers and calcium antagonists causing a fall in blood pressure.

The sedative properties of antipsychotics and anxiolytics may be potentiated by thiopental.

4.6 Pregnancy and lactation Go to top of the page

Thiopental readily crosses the placental barrier and also appears in breast milk. Therefore, breast-feeding should be temporarily suspended or breast milk expressed before the induction of anaesthesia. It has been shown that thiopental can be used without adverse effects during pregnancy although the total dose should not exceed 250mg. However, when considering use of thiopental the clinician should only use the drug when the expected benefits outweigh any potential risks.

4.7 Effects on ability to drive and use machines Go to top of the page

Post-operative vertigo, disorientation and sedation may be prolonged and out-patients given thiopental should therefore be advised not to drive or use machinery, especially within the first 24 to 36 hours.

4.8 Undesirable effects Go to top of the page

Laryngeal spasm may occur, together with coughing or sneezing, during the induction procedure. For this reason it is not advised to use thiopental alone for peroral endoscopy.

Extravasation causes local tissue necrosis and severe pain. This can be relieved by application of an ice pack and local injection of hydrocortisone. The 5% w/v solution is hypertonic and may cause pain on injection and thrombophlebitis.

Allergic reactions, skin reactions and hypersensitivity have been rarely reported.

Bronchospasm, respiratory depression and myocardial depression or cardiac arrhythmias may occur.

4.9 Overdose Go to top of the page

Overdosage produces acute respiratory depression, hypotension, circulatory failure and apnoea. Treatment must be artificial ventilation, lowering of the patient's head and infusion of plasma volume expanders.

5. PHARMACOLOGICAL PROPERTIES Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Thiopental is a short-acting substituted barbiturate that is more lipid soluble than other groups of barbiturates. The drug reversibly depresses the activity of all excitable tissues. The CNS is particularly sensitive and normally a general anaesthesia can be achieved with thiopental without significant effects on peripheral tissues.

Thiopental acts through the CNS with particular activity in the mesencephalic reticular activating system. The barbiturates exert different effects on synaptic transmission, mostly those dependent on GABA. Autonomic ganglia of the peripheral nervous system are also depressed.

5.2 Pharmacokinetic properties Go to top of the page

Following intravenous administration, unconsciousness occurs within 30 seconds and will be continued for 20 to 30 minutes after a single dose. Rapid uptake occurs to most vascular areas of the brain followed by redistribution into other tissues.

Thiopental is strongly bound to plasma protein, which impairs excretion through the kidney. The metabolites are usually inactive and are then excreted. Thiopental, therefore, whilst having a short duration of action, may have a long elimination phase.

5.3 Preclinical safety data Go to top of the page

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS Go to top of the page

6.1 List of excipients Go to top of the page

None

6.2 Incompatibilities Go to top of the page

Solutions of thiopental injection have a pH of 10 to 11 and are strongly alkaline in order to maintain stability. Solutions are incompatible with acid, acidic salts and solutions such as pethidine, morphine and promethazine.

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6.3 Shelf life

48 months.

6.4 Special precautions for storage Go to top of the page

Do not store above 25ºC. Store reconstituted solution between 2°C to 8ºC in an upright position and use within 7 hours. Use once following reconstitution and discard any residue.

6.5 Nature and contents of container Go to top of the page

20ml Type III clear glass vials with 20mm bromylbutyl caoutchouc siliconised rubber closures.

Pack size: 25 vials per pack.

6.6 Special precautions for disposal and other handling Go to top of the page

Not applicable.

7. MARKETING AUTHORISATION HOLDER Go to top of the page

Link Pharmaceuticals Limited, Bishops Weald House, Albion Way, Horsham, West Sussex RH12 1AH, UK

8. MARKETING AUTHORISATION NUMBER(S) Go to top of the page

PL 12406/0014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION Go to top of the page

5 April 1999

10. DATE OF REVISION OF THE TEXT Go to top of the page

January 2003

11. Legal Category Go to top of the page

POM

More information about this product

- Patient Information Leaflets (PILs):
  Thiopental injection (Link Pharmaceuticals Ltd)
- Alternative format Patient Information Leaflets (X-PILs):
  Thiopental injection (Link Pharmaceuticals Ltd)

Link to this document from your website: http://emc.medicines.org.uk/medicine/14338/SPC/Thiopental injection (Link Pharmaceuticals Ltd)/

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Summary of Product Characteristics last updated on the eMC: 09/08/2006

SPC **NORCURON 10mg**

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Legal Categories

POM – Prescription Only Medicine

Active Ingredients/Generics

vecuronium bromide

1. NAME OF THE MEDICINAL PRODUCT

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NORCURON 10mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Go to top of the page

Norcuron 10 mg, 1 vial contains: Vecuronium bromide 10mg

3. PHARMACEUTICAL FORM

Go to top of the page

Powder for injection.

4. CLINICAL PARTICULARS

Go to top of the page

4.1 Therapeutic indications

Go to top of the page

Norcuron is indicated as an adjunct to general anaesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery.

4.2 Posology and method of administration

Go to top of the page

Dosage: As with all other neuromuscular blocking agents, the dosage of Norcuron should be individualised in each patient. The anaesthetic method used, the expected duration of surgery, the possible interaction with other drugs that are administered before or during anaesthesia and the condition of the patient should be taken into account when determining the dose. The use of a peripheral nerve stimulator is recommended to monitor neuromuscular blockade and recovery.

The following dosages may serve as general guidelines for initial and maintenance intravenous bolus dose requirements of Norcuron to assure appropriate muscle relaxation throughout short, medium and long lasting surgical procedures under balanced anaesthesia, with and without the use of Norcuron for facilitation of endotracheal intubation.

Adults and children (see also use in paediatrics)

Intubating dose: 80 to 100 micrograms vecuronium bromide per kg body weight.

Dosages of Norcuron for surgical procedures after intubation with succinylcholine: 30 to 50 micrograms vecuronium bromide per kg body weight.

If succinylcholine is used for intubation, the administration of Norcuron should be delayed until the patient has clinically recovered from the neuromuscular block induced by succinylcholine.

Maintenance dose: 20 to 30 micrograms vecuronium bromide per kg body weight.

These maintenance doses should best be given when twitch height has recovered to 25% of control twitch height.

Notes:

In obese patients, these doses should be reduced taking into account a lean body mass.

Since inhalational anaesthetics potentiate the action of Norcuron (see interactions), doses of Norcuron in general should be reduced during surgical procedures where these anaesthetics are used.

Should there be reason for selection of larger doses in individual patients, initial doses ranging from 150 micrograms up to 300 micrograms vecuronium bromide per kg body weight have been administered during surgery both under halothane and neurolept anaesthesia without adverse cardiovascular effects being noted as long as ventilation is properly maintained. The use of these high dosages of Norcuron pharmacodynamically decreases the onset time and increases the duration of action.

In caesarean section and neonatal surgery the dose should not exceed 100 micrograms/kg.

Neonates and infants up to one year of age

Because of the possible variations of the sensitivity of the neuromuscular junction, especially in neonates (up to 4 weeks) and probably in infants (up to 4 months of age), it is recommended that an initial test dose of 10 to 20 micrograms vecuronium bromide per kg body weight followed by incremental doses until 90 to 95% depression of twitch response is achieved. Dose requirements in infants of 5 months to 1 year of age are the same as in adults. However, since the onset time of Norcuron in these patients is considerably shorter than in adults and children, the use of high intubating doses in general is not required for early development of good intubating conditions.

Since the duration of action and recovery time with Norcuron is longer in neonates and infants than in children and adults, maintenance doses could be lower and are required less frequently. (see also Use in Paediatrics.)

Dose requirements for administration of Norcuron by continuous infusion

If Norcuron is administered by continuous infusion, it is recommended that a bolus dose of ED_{90} or $2xED_{90}$ (40-100 micrograms per kg) is administered first and, when neuromuscular block starts to recover, administration of Norcuron by infusion is commenced. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height. In adults, the infusion rate required to maintain neuromuscular block at this level, ranges from 0.8 to 1.4 micrograms vecuronium bromide/kg/min. For neonates and infants see above. Repeated monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Administration: Norcuron should be administered intravenously.

4.3 Contraindications

Go to top of the page

Former anaphylactic reactions to vecuronium or the bromide ion.

4.4 Special warnings and precautions for use

Go to top of the page

As with other neuromuscular blocking agents, Norcuron should only be administered by, or under supervision of experienced clinicians who are familiar with the action and use of these drugs.

Since Norcuron causes relaxation of the respiratory muscles, mechanical ventilation until spontaneous respiration is restored, is necessary for patients treated with this drug.

Anaphylactic reactions to neuromuscular blocking agents in general have been reported. Although these are very rarely seen with Norcuron, precautions for treating such reactions if they would occur should always be taken. This is particularly important in the case of previous anaphylactic reactions to neuromuscular blocking agents, since allergic cross-reactivity to neuromuscular blocking agents has been reported.

Since Norcuron has no cardiovascular effects within the clinical dosage range, it does not attenuate bradycardia that may occur due to the use of some types of anaesthetics and opiates or due to vagal reflexes during surgery. Therefore, reassessment of the use and/or dosage of vagolytic drugs such as atropine for premedication or at induction of anaesthesia, may be of value for surgical procedures during which vagal reactions are more likely to occur (e.g. surgical procedures where anaesthetic drugs with known vagal stimulatory effects are used, opthalmic abdominal or anorectal surgery, etc.).

Presently there are insufficient data to give recommendations for the use of Norcuron in the Intensive Care Unit. As with other muscle relaxants prolonged neuromuscular block following long term use of Norcuron in seriously ill patients in the Intensive Care Unit has been reported. It is essential that during continuous neuromuscular block patients receive adequate analgesia and sedation and that neuromuscular transmission is monitored throughout; furthermore, muscle relaxants should be administered in carefully adjusted doses, sufficient for the maintenance of less than complete block by or under the supervision of experienced clinicians who are familiar with its actions with appropriate neuromuscular monitoring techniques.

The following disease states may influence the pharmacokinetics and/or pharmacodynamics of Norcuron:

Hepatic and/or biliary tract disease

Despite the fact that Norcuron is excreted mainly via the bile, in general only moderate changes of the course of neuromuscular block induced by Norcuron are found in patients with hepatic and/or biliary tract diseases. In addition, these changes are dose dependent. With a dose of 100 micrograms vecuronium bromide per kg body weight, a slight, statistically not significant prolongation of the onset time and decrease of the duration of action were found as compared to normal patients. At doses of 150 and 200 micrograms vecuronium bromide per kg body weight, the prolongation of the onset time was even less pronounced (150 micrograms/kg) or absent (200 micrograms/kg), and no alterations of the duration of action were found in the 150 micrograms/kg group, while significant increases in the duration of action and in the recovery time were observed in the 200 micrograms/kg group.

Renal failure

Only limited changes of pharmacodynamic parameters were reported with Norcuron when administered to patients with renal failure.

As with other non-depolarising neuromuscular blocking agents, a limited degree of resistance to the action of Norcuron may occur in patients with renal failure. A slight, clinically not relevant, prolongation of onset time and recovery time may occur when Norcuron is administered to patients with renal failure.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular disease, old age, oedematous state resulting in an increased volume of distribution, may contribute to an increase in the onset time of neuromuscular block.

Neuromuscular disease

As with other neuromuscular blocking agents, Norcuron should be used with extreme caution in cases of neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these patients. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or the myasthenic (Eaton Lambert) syndrome, small doses of Norcuron may have profound effects and Norcuron should be titrated to the response.

Hypothermia

In operations under hypothermia, the neuromuscular blocking effect of Norcuron is prolonged.

Other conditions which may increase the effects of Norcuron are: hypokalaemia (e.g. after severe vomiting, diarrhoea, and diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnoea, cachexia.

Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

Like pancuronium bromide, d-tubocurarine or other non-depolarising neuromuscular blocking agents, Norcuron may cause a reduction in the partial thromboplastin time and the prothrombin time.

4.5 Interaction with other medicinal products and other forms of interaction Go to top of the page

The following drugs have shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents:

Increased effect:

Anaesthetics:

• halothane, ether, enflurane, isoflurane, methoxyflurane, cycloproprane, propofol

• High doses of thiopental, methohexital, ketamine, fentanyl, gammahydroxybutyrate, etomidate

*Other non-depolarising neuromuscular blocking agents.

*Prior administration of succinylcholine (1 mg/kg).

*Other drugs:

• antibiotics:

aminoglycoside and polypeptide antibiotics, acylaminopenicillin antibiotics, high doses of metronidazole

• diuretics, β-adrenergic blocking agents, thiamine, MAO inhibiting agents, quinidine, protamine, α-adrenergic blocking agents, magnesium salts.

Decreased effect:

• neostigmine, edrophonium, pyridostigmine, aminopyridine derivatives.

• prior chronic administration of corticosteroids, phenytoin or carbamazepine

• noradrenaline, azathioprine (only transient and limited effect), theophylline, $CaCl_2$

Variable effect:

• depolarising muscle relaxants, e.g. succinylcholine, given after the administration of Norcuron may produce potentiation or attenuation of the neuromuscular blocking effect of Norcuron.

4.6 Pregnancy and lactation Go to top of the page

There are insufficient data on the use of Norcuron during animal or human pregnancy to assess potential harm to the foetus. Norcuron should be given to a pregnant woman only when the attending physician decides that the benefits outweigh the risks.

Caesarean section:

Studies with Norcuron, administered in doses up to 100 micrograms/kg, have shown its safety for use in Caesarean section. Norcuron does not affect Apgar score, foetal muscle tonus nor cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only very little placental transfer of Norcuron does occur which did not lead to the observation of any clinical adverse effect in the new-born.

Remark:

Reversal of Norcuron-induced neuromuscular block may be unsatisfactory in patients receiving magnesium sulphate for toxaemia of pregnancy because magnesium salts enhance neuromuscular blockade.

Therefore, in patients receiving magnesium sulphate, the dosage of Norcuron should be reduced and be carefully titrated to twitch response.

4.7 Effects on ability to drive and use machines Go to top of the page

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

4.8 Undesirable effects Go to top of the page

The following adverse drug reactions to vecuronium bromide have been reported during post marketing surveillance and are very rare i.e. they occur with a frequency of less than 1 per 10,000:

Prolonged Neuromuscular block

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea

Anaphylactic and histaminoid reactions

Anaphylactic reactions

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Norcuron, have been reported. Examples of anaphylactic/anaphylactoid reactions are: bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse – shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions.

Histamine release and histaminoid reactions

Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalised histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these drugs.

Experimental studies with intradermal injection of Norcuron have demonstrated that this drug has only a weak capacity for inducing local histamine release. Controlled studies in man failed to demonstrate any significant rise in plasma histamine levels after intravenous administration of Norcuron. Nevertheless, such cases have rarely been reported during large scale use of Norcuron.

Myopathy

Although very rare, myopathy following prolonged use of muscle relaxants in conjuction with high doses of steroids has been reported in patients in the Intensive Care Unit.

4.9 Overdose Go to top of the page

In the event of overdosage and prolonged neuromuscular block, the patient should remain under mechanical ventilation and a cholinesterase inhibitor (e.g. neostigmine, pyridostigmine, edrophonium) in adequate doses should be administered as an antidote. When administration of a cholinesterase inhibiting agent fails to reverse the neuromuscular effects of Norcuron, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of a cholinesterase inhibitor can be dangerous.

5. PHARMACOLOGICAL PROPERTIES Go to top of the page

5.1 Pharmacodynamic properties Go to top of the page

Norcuron (vecuronium bromide) is a non-depolarising neuromuscular blocking agent, chemically designated as the aminosteroid 1-(3α, 17β-diacetoxy-2β piperidino-5α -androstan-16β-yl)-1 methylpiperidinium bromide. Norcuron blocks the transmission process between the motor nerve-ending and striated muscle by binding competitively with acetylcholine to the nicotinic receptors located in the motor end-plate region of striated muscle.

Unlike depolarising neuromuscular blocking agents, such as succinylcholine, Norcuron does not cause muscle fasciculations. Within 90 to 120 seconds following intravenous administration of a dose of 80 to 100 micrograms vecuronium bromide per kg body weight (approximately 2xED_{90} under neurolept anaesthesia), good to excellent conditions for endotracheal intubation occur and within 3 to 4 minutes following administration of these dosages, general muscle paralysis adequate for any type of surgery is established.

The duration of action to 25% recovery of control twitch height (clinical duration) with this dose is 20 to 30 minutes. The time to 95% recovery of control twitch height following this dose is approximately 40 to 50 minutes.

With higher dosages of Norcuron, onset time to maximal block is shortened and duration of action is prolonged. At dosages of 150, 200, 250 and 300 micrograms vecuronium bromide per kg body weight, the mean onset time under neurolept anaesthesia amounts to 146, 110, 92 and 77 seconds respectively. The mean clinical duration of action with these is 41, 55, 70 and 86 minutes respectively. With these high dosages, also a gradual, but relatively slight increase of the recovery rate from neuromuscular block occurs.

When Norcuron is administered by continuous intravenous infusion, a steady state neuromuscular blockade of 90% can be maintained at a constant rate of drug delivery and without clinically significant prolongation of the recovery time from neuromuscular block at termination of the infusion. Norcuron has no cumulative effects if maintenance doses are administered at 25% recovery of control twitch height. Several maintenance doses can therefore be give in succession.

These properties allow the use of Norcuron in short, medium and long lasting surgical procedures.

Within the clinical dosage range, Norcuron exerts no vagolytic or ganglion blocking activity.

Administration of acetylcholinesterase inhibitors, such as neostigmine, pyridostigmine or edrophonium, antagonises the action of Norcuron.

5.2 Pharmacokinetic properties Go to top of the page

After intravenous administration of Norcuron, the distribution half-life of vecuronium amounts to approx. 2.2 (± 1.4) minutes. Vecuronium is mainly distributed in the extracellular fluid compartment. At steady state, the volume of distribution averages 0.27 $l.kg^{-1}$ and its plasma elimination half-life averages 71 (± 20) minutes.

The extent of metabolism of vecuronium is relatively low. In humans, a 3-hydroxy derivative having approximately 50% less neuromuscular blocking potency than vecuronium could be demonstrated in the urine and bile as metabolite of Norcuron. In patients not suffering from renal or hepatic failure, the plasma concentration of this derivative is below detection limit, and does not contribute to the neuromuscular block occurring after administration of Norcuron.

Biliary excretion is the main elimination route. It is estimated that within 24 hours after intravenous administration of Norcuron, 40 to 80% of the dose administered is excreted into the bile as monoquaternary compounds. Approximately 95% of these monoquaternary compounds is unchanged vecuronium and 5% is 3-hydroxy vecuronium.

Renal elimination is relatively low. The amount of monoquaternary compounds excreted in the urine collected by intravesical catheter for 24 hours following Norcuron administration averages 30% of the dose administered.

Use in paediatrics: Neonates and infants:

In neonates and infants the ED_{90} dose of vecuronium bromide under halothane anaesthesia was found to be approximately the same (approx. 28 micrograms/kg body weight) as in adults.

The onset time of Norcuron in neonates and infants is considerably shorter as compared to children and adults, probably due to the shorter circulation time and larger cardiac output. Also, a greater sensitivity of the neuromuscular junction to the action of neuromuscular blocking agents in these patients may account for a more rapid onset of action. The duration of action and recovery time with Norcuron is longer in neonates and infants than in adults. Maintenance doses of Norcuron should therefore be less frequently administered.

Children: In children the ED_{90} dose of vecuronium bromide under halothane anaesthesia was found to be somewhat higher (approx. 32 micrograms/kg body weight), although statistically not significant, than in adults. In comparison to adults, the duration of action and recovery time with Norcuron in children are in general approximately 30% and 20-30% shorter respectively.

Similar to adults, cumulative effects with repeat maintenance doses of approximately one quarter of the initial dose and administered at 25% recovery of control twitch height are not observed in paediatric patients. The longer recovery time of Norcuron in neonates and infants is not of a magnitude which would require routine use of reversal agents. If used, these reversal agents are as efficacious for antagonising the neuromuscular block in neonates and infants as they are in children and adults.

5.3 Preclinical safety data Go to top of the page

In animal studies, at high doses, a toxicity related to the pharmacological activity of vecuronium bromide was seen.

6. PHARMACEUTICAL PARTICULARS Go to top of the page

6.1 List of excipients Go to top of the page

Norcuron is supplied as a freeze dried powder containing citric acid monohydrate, disodium hydrogen phosphate dihydrate, mannitol, sodium hydroxide (for pH correction) and phosphoric acid (for pH correction). No preservative has been added.

6.2 Incompatibilities Go to top of the page

As is the case for many other drugs, incompatibility has been documented for Norcuron when added to thiopental.

Except for those solutions with which Norcuron has been shown to be compatible, it is not recommended that Norcuron should be mixed with other solutions or drugs in the same syringe or bag (see Section 6.6).

If Norcuron is administered via the same infusion line that is also used for other drugs, it is important that this infusion line is adequately flushed (e.g. with 0.9% sodium chloride) between administration of Norcuron and drugs for which incompatibility has been demonstrated or for which compatibility with Norcuron has not been established.

6.3 Shelf life Go to top of the page

Norcuron can be kept until the expiry date indicated on the packaging, provided it is stored under the prescribed conditions.

The shelf life is as follows: Norcuron 10mg - 2 years

When reconstituted as indicated under 'Reconstitution' or diluted as described under 'Compatibility', the solution obtained can be kept for 24 hours at room temperature and in daylight. However, in order to avoid microbiological contamination it is recommended to discard any unused solution.

6.4 Special precautions for storage Go to top of the page

Norcuron should be stored at a temperature below 25°C, protected from light.

6.5 Nature and contents of container Go to top of the page

Packaging of 20 vials each containing 10 mg vecuronium bromide, and 20 ampoules each containing 5ml water for injections (solvent).

6.6 Special precautions for disposal and other handling Go to top of the page

Reconstitution: Norcuron 10 mg

Addition of 5ml water for injections results in an isotonic solution of pH 4 containing 2 mg vecuronium bromide per ml. (2 mg/ml).

Alternatively, in order to obtain a solution with a lower concentration Norcuron 10 mg may be reconstituted with a volume up to 10 ml respectively of the following infusion fluids:

• 5% glucose injection fluid

• 0.9% sodium chloride injection fluid

• Lactated Ringer's solution

• Lactated Ringer's injection and 5% glucose

• Glucose 5% and 0.9% sodium chloride injection

• Water for injections

• Compatibilities

Norcuron can be injected into the line of a running infusion containing the following drugs: fentanyl, droperidol, nicomorphinehydrochloride and pancuronium bromide.

Compatibility studies with other drugs have not been performed.

When Norcuron is reconstituted with water for injections, the resultant solution can be mixed with the following infusion fluids, packed in PVC or glass, to a dilution up to 40 mg/litre:

• 0.9% NaCl solution

• 5% glucose solution

• Ringer's solution

• Ringer's glucose

The above-mentioned reconstituted solution can also be injected in to the line of a running infusion of the following fluids:

• Lactated Ringer's solution

• Lactated Ringer's solution and 5% glucose

• Glucose 5% and 0.9% NaCl solution

• Haemaccel

• Dextran-40 5% in 0.9% NaCl solution

• Water for injections

Compatibility studies with other infusion fluids have not been performed.

7. MARKETING AUTHORISATION HOLDER Go to top of the page

N V Organon, Kloosterstraat 6,

PO Box 20, 5340 BH, Oss,

The Netherlands

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  NORCURON 10mg
- Alternative format Patient Information Leaflets (X-PILs):
  NORCURON 10mg
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