Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Anectine 50mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml ampoule contains 100 mg Suxamethonium Chloride Injection.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion
A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Anectine Injection is an ultra-short acting, depolarising, neuromuscular blocking agent. It is used in anaesthesia as a skeletal muscle relaxant to facilitate tracheal intubation and mechanical ventilation in surgical procedures.

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

4.2 Posology and method of administration

Instructions for use
The dose of Anectine Injection is dependent on age, body weight, the degree of muscle relaxation required and the route of administration.

The usual method of Anectine Injection administration is by bolus intravenous injection.

Use by intravenous bolus injection
Dosage in adults: A single intravenous dose of suxamethonium chloride dihydrate of approximately 1mg/kg bodyweight will usually provide profound neuromuscular blockade and good conditions for tracheal intubation within 30-60 seconds of its administration. The duration of clinically useful neuromuscular relaxation produced by this dose is on average 2-6 minutes, although wide inter-patient variability exists.

Larger single doses of Anectine Injection may slightly accelerate the speed at which neuromuscular paralysis develops, and will produce longer durations of clinically useful muscle relaxation but not in a direct dose-dependent manner; doubling the dose of Anectine Injection does not necessarily double the duration of relaxation.

Supplementary intravenous doses of Anectine Injection of 50-100% of the initial dose may be administered for the maintenance of muscle relaxation during short surgical or other procedures performed under general anaesthesia, at intervals of 5-10 minutes as required.

During administration of Anectine Injection by repeated intravenous bolus injection, the total dose should not exceed 500mg per hour.

Dosage in children: Compared with adults, infants and young children are more resistant to the neuromuscular blocking effects of suxamethonium on a mg per kg bodyweight basis.

In neonates and infants, the recommended intravenous bolus dose of Anectine Injection is 2mg/kg bodyweight. A dose of 1mg/kg bodyweight in an older child is recommended (see section 4.4 Special warnings and precautions for use).

Dosage in the elderly: Dosage requirements of Anectine Injection in the elderly are comparable to those of younger adults (see *Dosage in adults*).

Administration of Anectine Injection may be associated with transient cardiac arrhythmias (see section 4.4 Special warnings and precautions for use); the elderly may be more susceptible to such arrhythmias especially if digitalis-like drugs are also being taken.

Use by intramuscular bolus dosing
Dosage in children: Anectine Injection may be administered intramuscularly at doses up to 4-5mg/kg bodyweight in infants and up to 4mg/kg bodyweight in older children. The onset of clinically useful neuromuscular relaxation following intramuscular administration of Anectine Injection is apparent within about 3 minutes.

Not more than 150mg total dose should be given.

Use by intravenous infusion
Dosage in adults and children: For prolonged surgical procedures in adults and older children, Anectine Injection may be administered by intravenous infusion as a 0.1% (1mg/ml) or 0.2% (2mg/ml) solution of suxamethonium chloride dihydrate in sterile 5% glucose solution or sterile 0.9% w/v saline solution.

In adults, the initial rate of infusion of Anectine Injection should be 36 micrograms/kg/min to 57 micrograms/kg/min (2.15mg/kg/hr to 3.42mg/kg/hr). A proportionately lower initial infusion rate based on bodyweight should be used in children. The infusion rate should thereafter be adjusted in accordance with the response of each individual patient.

Dosage requirements of Anectine Injection may increase with time during intravenous infusion.

During administration of Anectine Injection by intravenous infusion, the total dose should not exceed 500mg per hour.

Dosage in the elderly: In the absence of specific dosage studies for the elderly, refer to *Dosage in adults and children* and section 4.4 Special warnings and precautions for use.

Dosage in renal impairment: A normal single dose of Anectine Injection may be administered to patients with renal insufficiency in the absence of hyperkalaemia. Multiples or larger doses may cause clinically significant rises in serum potassium and should not be used (see section 4.3 Contraindications, and section 4.4 Special warnings and precautions for use).

Dosage in hepatic impairment: Termination of the action of suxamethonium is dependent on plasma cholinesterase, which is synthesised in the liver. Although plasma cholinesterase levels often fall in patients with liver disease, levels are seldom low enough to significantly prolong suxamethonium-induced apnoea (see section 4.4 Special warnings and precautions for use). 3

Dosage in patients with reduced plasma cholinesterase: Patients with reduced plasma cholinesterase activity may experience prolonged and intensified neuromuscular blockade following administration of suxamethonium. In these patients it may be advisable to administer reduced dosages of Anectine Injection (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

Monitoring advice: Monitoring of neuromuscular function is recommended during infusion of Anectine Injection or if Anectine Injection is to be administered in relatively large cumulative doses over a relatively short period of time in order to individualise dosage requirements (see section 4.4 Special warnings and precautions for use).

4.3 Contraindications

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

Hypersensitivity to suxamethonium, or to any of the excipients listed in section 6.1.

Suxamethonium is recognised as a potential triggering agent in individuals susceptible to malignant hyperthermia and therefore the use of Anectine Injection is contra-indicated in patients with a personal or family history of this condition. If this condition occurs unexpectedly, all anaesthetic agents known to be associated with its development (including Anectine Injection) 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.

Suxamethonium should not be used in patients with a history of previous prolonged apnoea after suxamethonium or in those with atypical plasma cholinesterase.

Prolonged and intensified neuromuscular blockade following Anectine Injection may occur secondary to reduced plasma cholinesterase in the following states or pathological conditions; end stage hepatic failure, acute or chronic renal failure.

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

• 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.

• In patients with neurological deficits involving spinal cord injury, peripheral nerve injury, 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.

• In any patient with pre-existing hyperkalaemia. In the absence of hyperkalaemia and neuropathy, renal failure is not a contraindication 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 intraocular 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 expected benefit of its use outweighs the potential risk to the eye.

Suxamethonium 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.

Suxamethonium 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.

Since the action of suxamethonium may be prolonged in patients known to have inherited atypical plasma cholinesterase, Anectine Injection should not be used in this group unless the expected benefit of its use outweighs the risk (see section 4.4 Special warnings and precautions for use and section 4.2 Posology and method of administration).

4.4 Special warnings and precautions for use

Suxamethonium paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. Anectine Injection should be administered only with adequate general anaesthesia and only by or under the close supervision of an experienced anaesthetist with adequate facilities available for immediate tracheal intubation and artificial ventilation.

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 administration (see section 4.3 Contraindications and section 4.8 Undesirable effects).

In patients with severe sepsis; the potential for hyperkalaemia appears to be related to the severity of the infection and to its duration.

Caution should be exercised when administering suxamethonium to patients who have shown hypersensitivity to other neuromuscular blocking agents since a high rate of cross-sensitivity (greater than 50%) between neuromuscular blocking agents has been reported.

Caution should be exercised when this drug is used in neonates, since they are relatively resistant to its action and may develop a phase 2 (non-depolarising) block rapidly.

Suxamethonium is rapidly hydrolysed in the body by plasma cholinesterase; this is the single most important mechanism of drug elimination and is responsible for the rapid spontaneous recovery of neuromuscular function following suxamethonium administration in normal individuals.

Muscle pains are frequently experienced 1 to 2 days after administration of suxamethonium and most commonly occur in ambulatory patients undergoing short surgical procedures under general anaesthesia (see Adverse Reactions). There appears to be no direct connection between the degree of visible muscle fasciculation after suxamethonium 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 1 mg/kg to achieve satisfactory conditions for tracheal intubation.

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 (See section 4.6 Fertility, pregnancy and lactation).
• Genetically determined abnormalities of plasma cholinesterase (See section 4.3 Contraindications).
• Severe generalised tetanus, tuberculosis, other severe or chronic infections.
• Following severe burns (see section 4.3 Contraindications).
• Chronic debilitating disease, malignancy, chronic anaemia and malnutrition.
• Auto-immune diseases, myxoedema, collagen diseases.
• End-stage hepatic failure, acute or chronic renal failure (see section 4.2 Posology and method of administration).
• *Iatrogenic:* Following plasma exchange, plasmapheresis, cardiopulmonary bypass, and as a result of concomitant drug therapy (see section 4.5 Interaction with other medicinal products and other forms of interaction).

If Anectine Injection is repeatedly or continually administered over a relatively short period of time (minutes to hours), the characteristic depolarising block produced by its initial administration (Phase I block) may gradually change to a neuromuscular block with characteristics resembling those of a block produced by non-depolarising muscle relaxants; the latter suxamethonium-induced block is termed Phase II block.

The development of Phase II block may be associated with prolonged suxamethonium-induced neuromuscular blockade.

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.

As Phase II block develops, the suxamethonium dose requirement to maintain a constant level of neuromuscular blockade increases, i.e. tachyphylaxis develops.

If Anectine Injection is to be administered in relatively large cumulative doses over a relatively short period of time (particularly by infusion), monitoring of neuromuscular function is recommended in order to tailor dosage to the individual patient's needs

and to provide information on the feasibility or need for pharmacological reversal of a Phase II block with anticholinesterase agents.

It is inadvisable to administer suxamethonium to patients with advanced myasthenia gravis. Although these patients are resistant to suxamethonium, they may easily develop a state of Phase II block which can result in delayed recovery. Patients with the myasthenic Eaton-Lambert syndrome are more sensitive than normal to suxamethonium and the dose should be reduced in these patients. Patients in remission from myasthenic Eaton-Lambert syndrome may however demonstrate a normal response to suxamethonium.

In healthy adults, suxamethonium 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.

This agent may cause a bradycardia and may potentiate the bradycardia due to halothane or other agents. This should be borne in mind when both agents are used during anaesthetic procedures and use should be preceded by atropine. Continuous infusion may give rise to tachycardia and rise in blood pressure.

Approximately one person in three thousand is unable to hydrolyse suxamethonium, due to presence of abnormal plasma cholinesterase.

This agent should be used with caution in ill and cachectic patients, in patients with acid-base disturbances or electrolyte imbalance, parenchymatous liver disease, obstructive jaundice, carcinomatosis, in those in contact with certain insecticides, e.g. organophosphorous compounds and in those receiving therapeutic radiation.

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.

Suxamethonium should be used with caution in patients with fractures or muscle spasms because the initial muscle fasciculations may cause additional trauma.

Muscarinic effects of this compound e.g. increased bronchial and salivary secretions may be prevented by atropine.

When this agent is given as an infusion, this should be monitored with care to avoid overdose.
Suxamethonium has no direct effect on the myocardium, but by stimulation of both autonomic ganglia and muscarinic receptors suxamethonium may cause changes in cardiac rhythm, including cardiac arrest.

Anectine Injection should not be mixed with any other drug prior to its administration.

Anectine Injection is acidic and should not be mixed with highly alkaline solutions, e.g. barbiturates.

4.5 Interaction with other medicinal products and other forms of interactions

Certain drugs or chemicals are known to reduce normal plasma cholinesterase activity and may therefore prolong the neuromuscular blocking effects of Anectine Injection. These include:

• Organophosphorous insecticides and metriphonate
• Ecothiopate eye drops
• Specific anticholinesterase agents: including neostigmine, pyridostigmine, physostigmine, edrophonium, tacrine hydrochloride
• Cytotoxic compounds: including cyclophosphamide, mechlorethamine, triethylene-melamine and thio-tepa
• Trimetaphan
• Psychiatric drugs: including phenelzine, promazine and chlorpromazine
• Anaesthetic agents and drugs: including ketamine, morphine and morphine antagonists, pethidine, pancuronium
• Selective serotonin reuptake inhibitors
• Other drugs with potentially deleterious effects on plasma cholinesterase activity include aprotinin, diphenhydramine, promethazine, oestrogens, high-dose steroids, oral contraceptives, terbutaline and metoclopramide.

Certain drugs or substances may enhance or prolong the neuromuscular effects of Anectine Injection by mechanisms unrelated to plasma cholinesterase activity. These include:

• Volatile inhalational anaesthetic agents: including 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.
• Antibiotics such as the aminoglycosides, clindamycin and polymyxins
• Antiarrhythmic drugs: including quinidine, procainamide, verapamil, beta-blockers, lidocaine and procaine
• Magnesium salts
• Lithium carbonate
• Azathioprine

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy: 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. Anectine Injection should nevertheless not be administered to pregnant women unless the expected benefit of its use outweighs possible risks to the foetus.

Plasma cholinesterase levels may fall during the first trimester of pregnancy to about 70-80% of their pre-pregnancy values; a further fall to about 60-70% of the pre-pregnancy levels occurs within 2-4 days after delivery. Plasma cholinesterase levels then increase to reach normal over the next 6 weeks. Consequently, a high proportion of pregnancy and puerperal patients may exhibit mildly prolonged neuromuscular blockade following Anectine Injection (see section 4.4 Special warnings and precautions for use).

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

4.7 Effects on ability to drive and use machines

This precaution is not relevant to the use of Anectine. Suxamethonium will always be used in combination with a general anaesthetic and therefore, the usual precautions relating to performance of tasks following general anaesthesia apply.

4.8 Undesirable effects

There is limited clinical documentation that can be used as support for determining the frequency of adverse reactions. The frequency categories assigned to the adverse reactions are estimates. For most reactions, the frequency was determined from published data and the background incidence was not considered when determining the frequency groups.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) very rare (<1/10,000), including isolated reports.

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†.

†Individuals with decreased plasma cholinesterase activity exhibit a prolonged response to suxamethonium (see Warnings and Precautions).
Approximately 0.05% of the population has an inherited cause of reduced cholinesterase activity.

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 (see Warnings and Precautions).
Common Myoglobinaemia**#**, myoglobinuria**#**.

#Rhabdomyolysis has also been reported (see Contra-indications and Special Warnings & Precautions for use).

Rare Trismus

General disorders and administration site conditions
Very rare Malignant hyperthermia (see Warnings and Precautions).

Investigations
Common Transient blood potassium increase.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie .

4.9 Overdose

Symptoms and signs:
Apnoea and prolonged muscle paralysis are the main and serious effects of overdosage.

Management:
In such cases it is essential to maintain a patent airway together with assisted ventilation until spontaneous respiration returns.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peripherally acting muscle relaxants, choline derivatives
ATC code M03AB01

Mechanism of action:
Suxamethonium is an ultra-short acting, depolarising, neuromuscular blocking agent.

Pharmacodynamic effects:
Suxamethonium, an analogue of acetylcholine, inhibits neuromuscular transmission by depolarising the motor end plates in skeletal muscle. The depolarisation may be observed as fasciculation. Subsequent neuromuscular transmission is inhibited as long as an adequate concentration of suxamethonium remains at the receptor site. Onset of flaccid paralysis occurs within 30-60 seconds of intravenous injection and with single administration persists for 2-6 minutes.

The paralysis following administration of suxamethonium is progressive, with differing sensitivities of different muscles. This initially involves consecutively the levator muscles of the face, muscles of the glottis and finally the intercostals and the diaphragm and all other skeletal muscles.

The short duration of suxamethonium is considered to be due to its rapid metabolism in the blood. Suxamethonium is rapidly hydrolysed by plasma cholinesterase to succinylcholine (which possesses clinically insignificant depolarising muscle relaxant properties) and then more slowly to succinic acid and choline.

5.2 Pharmacokinetic properties

Absorption:
The pharmacokinetics of a bolus dose of suxamethonium have been studied in anaesthetised adult patients using a high performance liquid chromatographic assay.
Distribution:
The pharmacokinetic parameters for suxamethonium 1mg/kg and 2mg/kg respectively are:
apparent volume of distribution 16.4 ± 14.7ml/kg and 5.6 ± 6.8ml/kg; area under the plasma concentration-time curve 124.3 ± 163.2 and 695 ±1008.9 minutes/microgram/ml.

The arterial blood suxamethonium concentration at 30 and 120 seconds following injection of suxamethonium 1mg/kg are 79.5 ± 108.4 and 3.3 ± 6.7 micrograms/ml, and following injection of 2mg/kg suxamethonium are 336.2 ± 512.5 and 7.2 ±13.0 micrograms/ml, respectively.

Elimination:
The pharmacokinetic parameters for suxamethonium 1mg/kg and 2mg/kg respectively are: total body clearance 40.5 ± 38.7 and 15.0 ± 14.8 litre/min and elimination half-life 16.6 ± 4.8 and 11.7 ± 4.5 seconds.

Suxamethonium was not detectable 150 seconds after administration of either 1mg/kg or 2mg/kg suxamethonium.

5.3 Preclinical safety data

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

6.1 List of excipients

Water for injections

6.2 Incompatibilities

Anectine injection should not be mixed with other medicinal products prior to its administration except those mentioned in section 6.6.

Anectine injection is acidic and should not be mixed with highly alkaline solutions, e.g. barbiturates.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store between 2-8°C. Store in the original container. Do not freeze.

6.5 Nature and contents of container

2 ml neutral clear glass ampoules. Each pack contains 5 ampoules.

6.6 Special precautions for disposal and other handling

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

Anectine injection may be administered by intravenous infusion as a 0.1% (1mg/ml) or 0.2% (2 mg/ml) Solution of suxamethonium chloride dihydrate in sterile 5% glucose solution or sterile 0.9% w/v saline solution.

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

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

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

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