

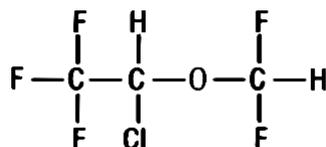
AERRANE

NAME OF THE MEDICINE

Isoflurane USP

Chemical Structure: 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether.

Molecular Formula:



DESCRIPTION

CAS Number: - 26675-46-7.

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5°C (uncorr.)
Refractive index		1.2990 - 1.3005
Specific gravity 25°/25°C		1.496
Vapour pressure (mm Hg)	20°C	238
	25°C	295
	30°C	367
	35°C	450

Isoflurane is a clear, colourless, stable volatile liquid containing no additives or chemical stabilisers: it has a mildly pungent, musty, ethereal odour.

Isoflurane does not decompose in the presence of soda lime, and does not attack aluminium, tin, brass, iron or copper.

PHARMACOLOGY

Pharmacodynamic properties

AERRANE is an inhalation-type anaesthetic, belonging to the group of halogenated anaesthetics. Induction and recovery from anaesthesia rapidly take place with AERRANE.

AERRANE has the slightly irritating odour of ether, which can limit the speed of induction.

Pharyngeal and laryngeal reflexes are rapidly diminished as a result of which tracheal intubation is rendered easy.

Pharmacokinetic properties

AERRANE is metabolised minimally in comparison to other halogenated anaesthetics such as enflurane or halothane. On average 95% of the AERRANE is recovered in the expired air; 0.2% of the AERRANE that is taken up with the body is metabolised. The principal metabolite is trifluoroacetic acid. The average serum level of inorganic fluoride in patients administered AERRANE anaesthesia is between 3 and 4 $\mu\text{mol/L}$.

In patients anaesthetised with AERRANE, the mean peak serum concentration of inorganic fluorides is usually less than 5 $\mu\text{mol/L}$ and occurs about four hours after anaesthesia, returning to normal levels within 24 hours. This should not alter renal function in a normal subject.

INDICATIONS

AERRANE is a volatile halogenated anaesthetic for general inhalation anaesthesia.

CONTRAINDICATIONS

AERRANE is contraindicated in those patients:

- with known hypersensitivity to isoflurane or to other halogenated anaesthetics
- with known or suspected genetic disposition toward malignant hyperthermia
- with a history of malignant hyperthermia, or in whom liver dysfunction, jaundice or unexplained fever, leukocytosis and/or eosinophilia has occurred after a previous isoflurane or other halogenated anaesthetic administration
- with a history of confirmed hepatitis due to a halogenated inhalational anaesthetic
- in whom general anaesthesia is contraindicated
- undergoing an obstetric operation
- with concomitant nonselective MAOIs (See **Interactions with Other Medicines**)

PRECAUTIONS

AERRANE must only be used by a licensed anaesthetist. Since the depth of anaesthesia can change easily and rapidly with AERRANE, only vaporisers that have been specially calibrated for this product may be used. The extent of blood pressure reduction and respiratory depression can be an indication of the extent or depth of anaesthesia; decreases may respond to reducing the inspired concentration of isoflurane.

Spontaneous respiration must be carefully and continuously monitored and must be assisted if necessary.

With the use of halogenated anaesthetics, disruption of the liver function, icterus, and fatal liver necrosis have been reported. Such reactions appear to indicate hypersensitivity reactions to anaesthetics. Cirrhosis, viral hepatitis, or other pre-existing liver disease can be a reason to select

an anaesthetic other than a halogenated anaesthetic.

Relatively little metabolism of AERRANE occurs in the human body. In the post operation period only 0.17% of the AERRANE taken up can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5 $\mu\text{mol/L}$ and occur about four hours after anaesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after AERRANE administration.

There is insufficient experience of use in repeated anaesthesia to make a definite recommendation in this regard. As with all halogenated anaesthetics repeat anaesthesia within a short period of time should be approached with caution.

It is recommended that ventilation be controlled in neurosurgery patients: cerebral blood flow remains unchanged in the course of light anaesthesia, but tends to rise in the course of deeper anaesthesia. An increase in intracranial pressure may be averted or abolished by hyperventilation of the subject before or during anaesthesia. AERRANE should not be administered to patients who can develop bronchoconstriction since bronchospasms can occur. In the case of neurosurgical operations, respiration should be adequately checked. As with other halogenated anaesthetics, AERRANE increases the flow of blood through the brain and is accompanied by a transient increase in cerebrospinal fluid pressure. In most cases, this pressure increase can be prevented by hyperventilation.

In light of the fact that AERRANE acts in an irritating manner on the mucous membranes, the product is difficult to use if inhalation anaesthesia is applied via mask. During the induction of anaesthesia in children, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm.

In the case of patients who have undergone an abortion, an increased loss of blood has been found. A transient increase in bromsulphthalein retention, blood glucose, and serum creatinine with a decrease in the serum urea level, serum cholesterol level, and alkaline phosphatase level, has been observed.

Malignant hyperthermia

In susceptible individuals, isoflurane anaesthesia may trigger a skeletal muscle hypermetabolic state in the skeletal muscle, leading to high oxygen consumption and the clinical syndrome known as malignant hyperthermia.

The clinical syndrome is signalled by hypercapnia and may include nonspecific features such as muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and/or unstable blood pressure. It should also be noted that many of these nonspecific signs may appear with light anaesthesia: acute hypoxia and hypovolaemia. An increase in overall metabolism may be reflected in an elevated temperature, (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot canister). PaO₂ and pH may decrease, and hyperkalaemia and a base deficit may appear.

Treatment of malignant hyperthermia includes discontinuance of triggering agents (eg. isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to decrease the patient's body temperature, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements

(consult Prescribing Information for dantrolene sodium intravenous for additional information on patient management). Renal failure may appear later, and urine flow should be monitored and sustained if possible. Fatal outcome of malignant hyperthermia has been reported with isoflurane (see **Contraindications**).

Perioperative hyperkalaemia

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatinine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Hepatic Reactions

Cases of mild, moderate, and severe postoperative hepatic dysfunction or hepatitis with or without jaundice, including fatal hepatic necrosis and hepatic failure, have been reported with isoflurane. Such reactions can represent hypersensitivity hepatitis, a known risk of exposure to halogenated anaesthetics, including isoflurane. Clinical judgment should be exercised when isoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction (see **Contraindications**). As with all halogenated anaesthetics, repeated anaesthesia within a short period of time should be approached with caution.

Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with isoflurane. Manifestations of such reactions have included hypotension, rash, difficulty breathing and cardiovascular collapse.

QT prolongation

Reports of QT prolongation, very rare associated with torsade de pointes, have been received. Caution should be exercised when administering isoflurane to susceptible patients.

General monitoring

All patients anesthetized with isoflurane should be continuously monitored (eg. monitoring of the electrocardiogram, blood pressure, oxygen saturation, and end tidal CO₂).

Respiratory Reactions

Isoflurane is a profound respiratory depressant whose effect is accentuated by narcotic premedication or concurrent use of narcotics or other respiratory depressants. Excessive respiratory depression may be related to depth of anaesthesia and respond to decreasing the inspired concentration of isoflurane. The depressant effect is accentuated by concurrent use of narcotics and other respiratory depressants. Respiration should be closely monitored and assisted or controlled ventilation employed when necessary.

Patients with Myasthenia Gravis are extremely sensitive to drugs that produce respiratory

depression. These effects are potentiated with some general anaesthetics. AERRANE should be used with caution in these patients.

Use in Hypovolemic, Hypotensive or Haemodynamically compromised patients

Isoflurane causes a dose-dependent reduction in systemic vascular resistance and blood pressure. Particular care must be taken when selecting the dosage for patients who are hypovolemic, hypotensive, or otherwise haemodynamically compromised eg. due to concomitant medications.

Use in patients with Coronary Artery Disease

In patients with coronary artery disease, maintenance of normal haemodynamics is important in order to avoid myocardial ischaemia. Isoflurane, like some other coronary arteriolar dilators, can cause dose-dependent coronary vasodilation and has been shown to divert blood at the arteriolar level from collateral-dependent myocardium to normally perfused areas in selected animal models (“coronary steal”). The extent to which coronary steal occurs in patients with steal-prone coronary anatomy is unclear. Clinical studies to date evaluating myocardial ischaemia, infarction and death as outcome parameters have not established that the coronary arteriolar dilation property of AERRANE is associated with coronary steal or myocardial ischaemia in patients with coronary artery disease. However, due to the phenomenon of coronary steal, isoflurane should be used with caution in patients with coronary artery disease. In particular, patients with subendocardial ischaemia may be considered to be more susceptible.

Use in patients with or at risk of elevations of Intracranial Pressure

In patients with or at risk for elevations of intracranial pressure (ICP), isoflurane should be administered cautiously and in conjunction with ICP-reducing measures.

Reaction with CO₂ absorbents

AERRANE, as with other halogenated anaesthetics, has been reported to interact with dry carbon dioxide absorbents to form carbon monoxide. In order to minimise the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, fresh (moist) carbon dioxide absorbents should be used. In addition, consideration should be given to direct measurement of carboxyhaemoglobin levels in patients on closed circuit anaesthesia with isoflurane, if oxygen desaturation develops which does not respond to usual corrective steps.

Barium hydroxide lime and soda lime become desiccated when fresh gases are passed through the CO₂ absorber canister at high flow rates over many hours or days. When a clinician suspects that CO₂ absorbent may be desiccated, it should be replaced before the administration of isoflurane.

The colour indicator of most CO₂ absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant colour change should not be taken as an assurance of adequate hydration. CO₂ absorbents should be replaced routinely regardless of the state of the colour indicator, following current guidelines for use of anaesthesiology equipment.

Decrease in Intellectual function

Isoflurane may cause a decrease in intellectual function as well as changes in mood for several days after general anaesthesia.

General

The following reactions have been reported following occupational exposure to isoflurane: dyspnoea, bronchospasm, stridor, cough, dizziness, paresthesia, hepatic reactions, flushing, rash, contact dermatitis, erythema, periorbital oedema, eye irritation, conjunctival hyperaemia, and headache (See *Adverse Reactions*).

Use in Pregnancy (Category B3)

All general anaesthetics cross the placenta and carry the potential to produce central nervous system and respiratory depression in the newborn infant. In routine practice, this does not appear to be a problem, however in the compromised foetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

Isoflurane exerts a relaxant effect on uterine smooth muscle. This can lead to increased blood loss in situations where uterine muscle contraction aids haemostasis such as in obstetric surgery and in patients undergoing abortions or uterine curettage.

Concerning the use of this substance in pregnancy, in the case of humans, adequate data do not exist in order to judge possible injuriousness. In regard to effects in animal tests, in published fetal rhesus macaque studies, isoflurane exposed in utero, resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring. Studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits.

In light of the fact that it has not been established that AERRANE can be used safely in pregnant women, the use of this product must be avoided during pregnancy.

Insufficient information is available to recommend use in pregnancy or obstetrics.

Use in Lactation

Breast feeding should not be given for up to 12 hours after the termination of anaesthesia. Because there is insufficient information regarding the excretion of isoflurane in human milk, the potential risks and benefits for each specific patient should be carefully considered before isoflurane is administered to nursing women.

Effects on Ability to Drive and Use Machines

Following anaesthesia with AERRANE, patients should be advised that performance of activities requiring mental alertness may be impaired for some time. Patients must not undertake hazardous tasks such as driving or operating machinery for at least 24 hours following administration of a general anaesthetic. The patient should only be sent home with an escort and should not consume any alcohol.

INTERACTIONS WITH OTHER MEDICINES

The simultaneous administration of AERRANE and the following products requires strict supervision of the clinical and biologic condition of the patient.

Opioids

Opioids decrease the Minimum Alveolar Concentration (MAC) of isoflurane. Opioids such as fentanyl and its analogues, when combined with isoflurane, may lead to a synergistic fall in blood pressure and respiratory rate.

Nitrous Oxide

N₂O decreases the MAC of isoflurane (See **Dosage and Administration**).

Neuromuscular blocking agents

Isoflurane decreases the required doses of neuromuscular blocking agents. If added relaxation is required, supplemental doses of muscle relaxants may be used.

St John's Wort

Severe hypotension and delayed emergence from anaesthesia with halogenated inhalational anaesthetics have been reported in patients treated long-term with St John's Wort.

Contraindicated combination:

Nonselective Mono Amine Oxidase Inhibitors (MAOIs): Risk of haemodynamic instability and crisis during the operation or medical procedure. Treatment should be stopped 15 days prior to surgery.

Combinations advised against:

Beta-sympathomimetics (isoprenaline) and alpha- and beta-sympathomimetics (adrenaline; noradrenaline): risk of serious ventricular arrhythmia as a result of an increase in heart rate.

Combinations requiring precautions in using:

In the majority of cases where a drug treatment is indispensable, there is no reason to suspend it before general anaesthesia. It suffices to inform the anaesthetist about it.

Beta-blockers: Concomitant use may exaggerate the cardiovascular effects of inhalational anaesthetics as there is a risk of blockage of the cardiovascular compensation mechanism, resulting in intensified hypotension and negative inotropic effects (see **Precautions**). The action of beta-blockers can be suppressed during the operation with the use of beta-sympathomimetic agents. In general, any medication with a beta-blocker need not be stopped but any abrupt reductions of the dosage should be avoided.

Isoniazid: Risk of potentiating the hepatotoxic effect, with increased formation of toxic metabolites of isoniazid. Treatment with isoniazid should be suspended one week before the operation and should not be resumed until 15 days afterward.

Adrenaline utilised for its local haemostatic action, by subcutaneous or gingival injections: risk of multiple and serious ventricular arrhythmia as a consequence of increased heart rate. Isoflurane is similar to sevoflurane in myocardium sensitisation to the arrhythmogenic effect of exogenous adrenaline, whereas myocardial sensitivity with adrenaline is lower with AERRANE than with other halogenated anaesthetics. Doses of adrenaline greater than 5 µg/kg, when administered submucosally, may produce multiple ventricular arrhythmias. Thus, the dosage should be limited to,

for example, 0.1 mg adrenaline wimaothin 10 minutes or 0.3 mg within one hour in adults.

Indirect sympathomimetics (amphetamines and their derivatives; psychostimulants, appetite suppressants, ephedrine and its derivatives): risk of intraoperative hypersensitivity episode. In the case of a planned operation, it is preferable to interrupt the treatment a few days before the operation.

Muscle relaxing agents: Concomitant use increases the risk of intensification of the action of depolarising relaxants and in particular, non-depolarising relaxants. The disappearance of the myoneural effect takes longer with AERRANE than with other conventional anaesthetics. If such combinations are used and additional relaxation is required, supplemental doses of muscle relaxants should be administered with caution.

Neuromuscular blocking agents: In general, isoflurane decreases the required doses of neuromuscular blocking agents; it is recommended that approximately 1/3 to 1/2 of the usual dose of these substances is administered. Anaesthetic concentrations of isoflurane at equilibrium reduce the ED95 of succinylcholine, atracurium, pancuronium, rocuronium and vecuronium by approximately 25 - 40% or more compared to N₂O/ opioid anaesthesia. Neostigmine has an effect on the non-depolarising relaxants, but has no effect on the relaxing action of AERRANE itself.

Morphine analgesics: these products potentiate the depressive action of AERRANE on respiration.

Calcium antagonists: AERRANE may lead to marked hypotension in patients treated with calcium antagonists, particularly dihydropyridine derivatives.

ADVERSE EFFECTS

The following adverse reactions were identified from controlled clinical studies of adult and paediatric patients using a variety of premedications, other anaesthetics and surgical procedures of varying lengths:

Cardiac disorders: Intraoperative arterial hypotension or hypertension: This was dependent on the dose; postoperative hypotension (uncommon); postoperative hypertension (rare).

Increase in heart rate: This was intensified in case of the existence of hypercapnia. Serious ventricular rhythm disorders, including arrhythmias (postoperatively) and atrial, ventricular or nodal arrhythmias (intraoperatively), can arise commonly.

Respiratory, thoracic, and mediastinal disorders: The pungency of AERRANE can give rise to an irritating action on the mucous membranes during the induction of anaesthesia, which can be accompanied by respiratory depression, coughing (very common), secretions (uncommon), and a tendency toward laryngospasm (common) or bronchospasm (rare). Breath-holding was very commonly observed.

Hepatobiliary disorders: Disturbance of the liver function and liver damage (including blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, bromsulphthalein clearance decreased and blood lactate

dehydrogenase increased), and jaundice were observed.

Metabolism and nutrition disorders: Blood glucose increased

General disorders and administration site conditions: Chills/ shivering (very common); asthenia and fatigue; malignant hyperthermia (see Precautions).

Psychiatric disorders: Delirium (common); mood changes and nightmares (uncommon); confusional state and nervousness.

Nervous system disorders: Agitation during induction (very common); movements during maintenance (common); convulsive pattern on ECG (uncommon); seizures (rare); ataxia, intellectual function decreased, dizziness and drowsiness.

Gastrointestinal disorders: Nausea on recovery (very common); vomiting on induction (uncommon) or recovery (common); and retching during induction (uncommon), maintenance (uncommon) or postoperatively.

Blood and lymphatic system disorders: The number of white blood cells increased very commonly (postoperatively), even in the absence of surgical stress.

Skin and subcutaneous tissue disorders: Diaphoresis (uncommon); rash.

Musculoskeletal connective tissue and bone disorders: Myalgia

The following adverse reactions have been reported in post-marketing experience:

Blood and lymphatic system disorders: Carboxyhaemoglobin increased

Immune system disorders: Anaphylactic reaction

Metabolism and nutrition disorders: Hyperkalaemia

Psychiatric disorders: Withdrawal syndrome (following multi-day exposure; symptoms included seizure, hallucination, ataxia, agitation, confusion)

Nervous system disorders: Brain oedema, intracranial pressure increased, migraine, myoclonus, nystagmus, pupils unequal, headache

Cardiac disorders: Cardiac arrest, ventricular fibrillation, torsade de pointes, myocardial infarction, myocardial ischaemia, atrioventricular block complete, atrioventricular block second degree, atrial fibrillation, ECG QT prolonged, atrioventricular block first degree, ventricular tachycardia, ventricular extrasystoles, tachycardia, bradycardia, cardiac output decreased

Vascular disorders: Flushing

Respiratory, thoracic, and mediastinal disorders: Apnoea, hypoxia, bronchospasm, airway obstruction, respiratory depression, hypercapnia, stridor, hiccups

Gastrointestinal disorders: Pancreatitis

Hepatobiliary disorders: Hepatic failure, hepatic necrosis, hepatitis fulminant, cholestatic hepatitis, hepatitis, hepatic steatosis, jaundice, gammaglutamyltransferase increased

Skin and subcutaneous tissue disorders: Rash

Musculoskeletal, connective tissue and bone disorders: Rhabdomyolysis

Renal and urinary disorders: Acute renal failure**, oliguria**

General disorders and administration site conditions: Malignant hyperthermia, hypothermia

Injury, poisoning, and procedural complications*: Unwanted awareness during anaesthesia, dyspnoea, bronchospasm, stridor, cough, dizziness, paresthesia, hepatic reactions, flushing, rash, contact dermatitis, erythema, periorbital oedema, eye irritation, conjunctival hyperaemia, headache

*All reactions categorized in this section, with the exception of *unwanted awareness during anaesthesia*, were from occupational exposure in non-patients.

**Cases of acute renal failure and oliguria have been reported after isoflurane anaesthesia. These events may be secondary to hypotension or other effects of isoflurane.

DOSAGE AND ADMINISTRATION

Isoflurane should be administered only by persons trained in the administration of general anaesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available.

In order to be able to accurately control the precise concentration of AERRANE, vaporisers that have been specially designed and calibrated for isoflurane should be used. Dosage for induction and maintenance must be individualized and titrated to the desired effect according to the patient's age and clinical status.

With the exception of neonates, the minimum alveolar concentration (MAC) of isoflurane decreases with increasing patient age.

Minimum alveolar concentration (MAC) of AERRANE in humans:

<u>Age (years)</u>	<u>O₂ – 100%</u>	<u>O₂ + N₂O</u>
Neonates	1.60	-
1-6 months	1.87	-
7-11 months	1.80	-
1-2 years	1.60	-
3-5 years	1.62	-
6-10 years	1.40	0.58
10-15 years	1.16	0.53

<u>Age (years)</u>	<u>O₂ – 100%</u>	<u>O₂ + N₂O (70%)</u>
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of anaesthesia

When using isoflurane for induction, it should be considered that the risk of coughing, breath holding, laryngospasm, and bronchospasm during induction increases with the concentration of isoflurane.

If AERRANE is used for induction of anaesthesia, a starting concentration of 0.5% administered by inhalation is recommended. Concentrations of 1.3 - 3.0% usually bring about surgical anaesthesia within 7 to 10 minutes.

It is recommended that use be made of a hypnotic dose of a short acting barbiturate or another product such as propofol, etomidate, or midazolam in order to avoid coughing or laryngospasm, which can arise if induction is carried out with AERRANE alone or in combination with oxygen or with an oxygen-nitrous oxide mixture.

Maintenance of anaesthesia

Anaesthesia can be maintained during surgery using a concentration of 1.0 - 2.5% administered by inhalation, with the simultaneous administration of N₂O and O₂.

A higher concentration of 1.5 - 3.5% of AERRANE is necessary if AERRANE is administered with pure oxygen.

Recovery

The concentration of AERRANE administered by inhalation must be reduced to 0.5% at the end of the operation, or to 0% during closure of the wound to allow prompt recovery.

If all administration of anaesthetic agents has been stopped, the air passages of the patient should be ventilated several times with 100% oxygen until complete awakening occurs.

If the vector gas is a mixture of 50% O₂ and 50% N₂O, the volume of the minimum alveolar concentration of AERRANE is approximately 0.65%.

OVERDOSAGE

In case of overdose, stop administration of the anaesthetic agent, check whether air passages are open, and depending on the circumstances, continue with assisted or controlled respiration using pure oxygen. Support and maintain adequate haemodynamics.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

AERRANE is supplied in 100 mL and 250 mL amber coloured glass bottles.

Storage

Store bottle in an upright position. To avoid leakage, apply bottle cap firmly but not too tightly.

AERRANE must be kept in the original container until immediately prior to use.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Baxter Healthcare Pty Ltd
1 Baxter Drive, Old Toongabbie, NSW 2146, Australia

POISONS SCHEDULE: Schedule 4

DATE OF THE FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG): 1 July 1996

DATE OF MOST RECENT AMENDMENT: 19 June 2017

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