

NEW ZEALAND DATA SHEET

NORCURON

Vecuronium bromide 4mg and 10mg injections

Presentation

NORCURON contains as active substance vecuronium bromide. It is supplied in a citrate-phosphate buffered freeze-dried white to off-white dry cake or powder. No preservative has been added.

Norcuron 4mg, powder for solution for injection

Addition of 1mL water for injections results in a clear to almost clear isotonic solution with pH 4 containing 4mg vecuronium bromide per mL (4mg/mL).

Norcuron 10mg, powder for solution for injection

Addition of 5mL water for injections results in a clear to almost clear isotonic solution with pH 4 containing 2mg vecuronium bromide per mL (2mg/mL)

Uses

Actions

Pharmacotherapeutic group: muscle relaxants, peripherally acting agents, ATC code: M03A C03
NORCURON (vecuronium bromide) is a non-depolarising neuromuscular blocking agent, chemically designated as the aminosteroid 1-(3 α , 17 β -diacetoxy-2 β piperidino-5 α -androstan-16 β -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 suxamethonium, NORCURON does not cause muscle fasciculations.

Within the clinical dosage range, NORCURON exerts no vagolytic nor ganglion blocking activity.

Tracheal intubation

Within 90 to 120 seconds following intravenous administration of a dose of 0.08 to 0.10mg vecuronium bromide per kg body weight, good to excellent conditions for tracheal 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 24 to 60 minutes. The time to 95% recovery of control twitch height following this dose is approximately 60 to 80 minutes.

With higher dosages of NORCURON, onset time to maximal block is shortened and duration of action is prolonged.

Continuous intravenous infusion

In case NORCURON is administered by continuous intravenous infusion, a steady state neuromuscular blockade of 90% can be maintained at a constant rate of 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 given in succession.

The abovementioned properties mean that NORCURON can be used equally as well in short, as in long lasting surgical procedures.

Reversal of neuromuscular block

The action of vecuronium can be antagonized either by sugammadex or by acetylcholinesterase inhibitors, such as neostigmine, pyridostigmine or edrophonium. Sugammadex can be given for routine reversal at 1-2 post-tetanic counts to reappearance of T₂. Acetylcholinesterase inhibitors can be administered at reappearance of T₂ or at the first signs of clinical recovery.

Use in paediatrics

Neonates and infants:

In neonates and infants the ED₉₅ dose of vecuronium bromide under nitrous oxide in oxygen anaesthesia was found to be approximately the same (approx. 47 μ g/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 relatively large 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 ED₉₅ dose of vecuronium bromide under nitrous oxide in oxygen anaesthesia was found to be higher than in adults (0.081 vs 0.043mg/kg body weight, respectively). 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.

Pharmacokinetics

After intravenous administration of 0.1-0.15mg/kg vecuronium, the distribution half-life of vecuronium amounts to 1.2-1.4 minutes. Vecuronium is mainly distributed in the extracellular fluid compartment. At steady state, the volume of distribution is 0.19-0.51L/kg in adult patients.

The plasma clearance of vecuronium amounts to 3.0-6.4 mL/kg/min and its plasma elimination half-life is 36-117 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 is formed in the liver. In patients not suffering from renal nor hepatic failure, the plasma concentration of this derivative is below the limit of detection, 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 60% of the dose administered is excreted into the bile as monoquaternary compounds. Approximately 95% of these monoquaternary compounds is unchanged vecuronium and less than 5% is 3-hydroxy vecuronium. Prolonged duration of action has been observed in patients with liver disease and/or biliary tract disease, probably as a result of decreased clearance leading to an increased elimination half-life.

Renal elimination is relatively low. The amount of monoquaternary compounds excreted in the urine collected by intravesical catheter for 24 hours following NORCURON administration is 20-30% of the dose administered. In patients with renal failure, the duration of action may be prolonged. This is probably the result of an increased sensitivity to vecuronium, but it could also be the result of a reduced plasma clearance.

Indications

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

Dosage And Administration

Dosage

Like 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 agents. Like with 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 medicines 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 an appropriate neuromuscular monitoring technique is recommended to monitor neuromuscular block and recovery. Inhalational anaesthetics do potentiate the neuromuscular blocking effects of NORCURON. 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 NORCURON should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of NORCURON during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (see **Interactions**).

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.

Tracheal intubation

The standard intubating dose during routine anaesthesia is 0.08 to 0.1mg vecuronium bromide per kg body weight, after which adequate intubation conditions are established within 90 to 120 seconds in nearly all patients.

Dosages of NORCURON for surgical procedures after intubation with suxamethonium:

Recommended doses:

0.03 to 0.05mg vecuronium bromide per kg body weight.

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

Maintenance dosing:

The recommended maintenance dose is 0.02 to 0.03mg vecuronium bromide per kg body weight. These maintenance doses should best be given when twitch height has recovered to 25% of control twitch height.

Dose requirements for administration of NORCURON by continuous infusion

If NORCURON is administered by continuous infusion, it is recommended to give a loading dose first (see 'Tracheal intubation') and, when neuromuscular block starts to recover, to start administration of NORCURON 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, the infusion rate required to maintain neuromuscular block at this level, ranges from 0.8 to 1.4µg vecuronium bromide/kg/min. For neonates and infants, see below. Repeat monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Dosing in elderly patients

The same intubation and maintenance doses as for younger adults (0.08-0.1mg/kg and 0.02-0.03mg/kg, respectively) can be used. However, the duration of action is prolonged in elderly compared to younger subjects due to changes in pharmacokinetic mechanisms. The onset time in elderly is similar to younger adults.

Dosing in paediatric patients

Because of the possible variation of the sensitivity of the neuromuscular junction, especially in neonates (up to 4 weeks) and probably in infants up to 4 months of age, an initial test dose of 0.01 to 0.02mg vecuronium bromide per kg body weight followed by incremental doses until 90 to 95% depression of twitch response is achieved is recommended. In neonatal surgery the dose should not exceed 0.1mg/kg. Dose requirements in neonates and infants (1-12 months) 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 are required less frequently (See 'paediatric patients').

Dose requirements in children (2-10 years) are higher (see 'paediatric patients' in **Actions**).

However, the same intubation and maintenance doses as for adults (0.08-0.1mg/kg and 0.02-0.03mg/kg, respectively) are usually sufficient. Since the duration of action is shorter in children, maintenance doses are required more frequently.

Although there is very little information on dosage in adolescents, it is advised to use the same dose as in adults, based on the physiological development at this age.

Dosing in 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 an ideal body weight.

Higher doses

- Should there be reason for selection of larger doses in individual patients, initial doses ranging from 0.15mg up to 0.30mg 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.

Administration

NORCURON should be administered following reconstitution. NORCURON is administered intravenously either as a bolus injection or as a continuous infusion (see also **Pharmaceutical**

Precautions).

Reconstitution

Norcuron 4mg

Addition of 1mL water for injections results in an isotonic solution of pH 4 containing 4mg vecuronium bromide per mL (4mg/mL)

Norcuron 10mg

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

Alternatively, in order to obtain a solution with a lower concentration, NORCURON 4mg and NORCURON 10mg may be reconstituted with a volume up to 4mL and 10mL, 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

Contraindications

Hypersensitivity to vecuronium or the bromide ion or any of the excipients of NORCURON.

Warnings And Precautions

Since NORCURON causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this medicine until adequate spontaneous respiration is restored.

As with other neuromuscular blocking agents, residual curarization has been reported for NORCURON. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual curarization after extubation in the post-operative phase (such as medicine interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of sugammadex or another reversal agent should be considered, especially in those cases where residual curarization 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 muscle relaxants, special precautions should be taken since allergic cross-reactivity to muscle relaxants 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 medicines 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 medicines with known vagal stimulatory effects are used, ophthalmic, abdominal or anorectal surgery, etc).

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 overdose it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants 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 non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported frequently. 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.

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

Hepatic and/or biliary tract disease and renal failure

Because vecuronium is excreted in bile and in urine, NORCURON 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, especially when high doses of vecuronium (0.15-0.2mg/kg bodyweight) were administered in patients with hepatic disease.

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. The duration of action may also be prolonged due to a reduced plasma clearance.

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 increased and the duration is prolonged.

Obesity

Like other neuromuscular blocking agents, NORCURON 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-depolarizing agents. It is recommended that the dose is titrated to response.

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.

Use During Pregnancy And Lactation

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 0.1mg/kg, have shown its safety for use in caesarean section. In caesarean section the dose should not exceed 0.1mg/kg. In several clinical studies NORCURON did not affect Apgar score, foetal muscle tonus or cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only very little placental transfer of NORCURON occurs which did not lead to the observation of any clinical adverse effect in the newborn.

Note

Reversal of a NORCURON-induced neuromuscular block may be inhibited or unsatisfactory in patients receiving magnesium sulphate for toxemia of pregnancy because magnesium salts enhance neuromuscular block. Therefore, in patients receiving magnesium sulphate, the dosage of NORCURON should be reduced and be carefully titrated to twitch response.

Lactation

There are no human data on the use of NORCURON during lactation. NORCURON should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

Effects On Ability To Drive And Use Machinery

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

Adverse Effects

Adverse Drug Reactions (ADRs) are rare (<1/1000). The most commonly occurring ADRs include changes in vital signs and prolonged neuromuscular block. The most frequently reported ADR during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms (reporting frequency <1/100,000). See also the explanations below the table.

MedDRA SOC	Preferred term ¹	
	Uncommon/rare (<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

Respiratory, thoracic and mediastinal disorders		Bronchospasm
Skin and subcutaneous tissue disorders		Angioneurotic oedema Urticaria Rash Erythematous rash
Musculoskeletal and connective tissue disorders		Muscular weakness ² Steroid myopathy ²
General disorders and administration site conditions	Drug ineffective Decreased drug effect/therapeutic response Increased drug effect/therapeutic response	Face oedema 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 After long-term use in the ICU

Prolonged Neuromuscular Block

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the medicine'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 apnoea. A few cases of myopathy have been reported after NORCURON was used in the ICU in combination with corticosteroids (see **Warnings and Precautions**).

Anaphylactic And Histaminoid Reactions

Anaphylactic Reactions

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including NORCURON, have been reported. Anaphylactic/anaphylactoid reactions usually comprise of several signs or symptoms, e.g. 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 should always be taken into consideration when administering these agents (see also **Anaphylactic Reactions** above).

Experimental studies with intradermal injection of NORCURON have demonstrated that this medicine has only a weak capacity for inducing local histamine release.

Controlled studies in humans failed to demonstrate any significant rise in plasma histamine levels after intravenous administration of NORCURON. Still, such cases have rarely been reported during large scale use of NORCURON.

Interactions

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

Effect of Other Agents on Norcuron

Increased Effect

- Halogenated volatile anaesthetics potentiate the neuromuscular block of NORCURON. The effect only becomes apparent with maintenance dosing (see also **Dosage and Administration**). Reversal of the block with anticholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see **Dosage and Administration**)
- Long-term concomitant use of corticosteroids and NORCURON in the ICU may result in prolonged duration of neuromuscular block or myopathy (see also **Warnings and Precautions and Adverse Effects**).

Other medicines

- antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylaminopenicillin antibiotics.
- diuretics, quinidine, magnesium salts, calcium channel blocking agents, lithium salts, cimetidine, lidocaine and acute administration of phenytoin or β -blocking agents
- Recurarization has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine and magnesium salts (see **Warnings and Precautions**)

Decreased Effect (possible higher dose requirements)

- prior chronic administration of phenytoin or carbamazepine

Variable Effect

- Administration of other non-depolarizing neuromuscular blocking agents in combination with NORCURON 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 NORCURON may produce potentiation or attenuation of the neuromuscular blocking effect of NORCURON.

Effect of Norcuron on other agents

Effect of Norcuron on lidocaine

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

Overdosage

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. In this situation there are two options for the reversal of neuromuscular block: (1) Sugammadex can be used for reversal of intense (profound) and deep block. The dose of sugammadex to be administered depends on the level of neuromuscular block. (2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) can be used at reappearance of T₂ or at the first signs of clinical recovery and should be administered in adequate doses.

When administration of an acetylcholinesterase-inhibiting agent fails to reverse the neuromuscular effects of NORCURON, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

Pharmaceutical Precautions

Special Precautions For Storage

NORCURON should be stored at a temperature not above 25°C in the outer carton.

Shelf-Life

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 4mg – 3 years

NORCURON 10mg – 2 years

Chemical and physical in-use (i.e. following reconstitution) stability has been demonstrated for 24 hours at 15 to 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

The date mentioned behind “exp.:" on the label of the ampoule or vial is the expiry date up to which NORCURON may be used.

Compatibility

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 40mg/litre:

- 0.9% NaCl solution
- 5% glucose solution
- Ringer's solution
- Ringer's glucose

The abovementioned reconstituted solution can also be injected into 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

Compatibility studies with other infusion fluids have not been performed.

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

Except for those solutions with which NORCURON has shown to be compatible, it is not recommended to mix NORCURON with other solutions, or agents in the same syringe or bag.

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

Medicine Classification

Prescription Medicine.

Package Quantities

Norcuron 4mg*

Package of 50 ampoules each containing 4mg vecuronium bromide and 50 ampoules each containing 1mL water for injections (solvent).

Package of 10 ampoules each containing 4 mg vecuronium bromide.

Norcuron 10mg

Package of 10 vials each containing 10mg vecuronium bromide.

**Note: Norcuron 4mg presentation is currently not available in New Zealand.*

Further Information

Qualitative And Quantitative Composition

NORCURON is supplied as a freeze dried powder containing citric acid monohydrate, disodium phosphate dihydrate, mannitol (E421), sodium hydroxide and phosphoric acid (for pH correction). No preservative has been added.

Preclinical Safety Data

Vecuronium bromide showed no genotoxic, embryotoxic or teratogenic potential. Single and repeated dose toxicity studies in rats, dogs and cats revealed no special hazard for humans.

Name and Address

Merck Sharp & Dohme (NZ) Ltd
P O Box 99 851
Newmarket
Auckland

Tel: 0800 500 673

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