NOTRIXUM 50
Injection 50 MG/5ML

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5mL Notrixum injection contains 50 mg of Atracurium Besylate

PHARMACEUTICAL FORM
Solution for injection.
Clear colourless solution and practically free from visible particles with a pH of 3.00 - 3.65.

CLINICAL PARTICULARS
Indications
NOTRIXUM is a highly selective, competitive or non-depolarising neuromuscular blocking agent which is used as an adjunct to general anaesthesia to enable tracheal intubation to be performed and to relax skeletal muscles during surgery or controlled ventilation during a wide range of medical procedures.

Dosage and Administration
In common with all neuromuscular blocking agents monitoring of neuromuscular function is recommended during the use of NOTRIXUM in order to individualise dosage requirements.

- **Use by injection in adults**
  NOTRIXUM is administered by intravenous (i.v.) injection. The dosage range for adults is 0.3 to 0.6 mg/kg (depending on the duration of full block required) and will provide adequate relaxation for 15 to 35 minutes.
  Endotracheal intubation can usually be accomplished within 90 seconds from the i.v. injection of 0.5 to 0.6 mg/kg.
  Full block can be prolonged with supplementary doses of 0.1 to 0.2 mg/kg as required. Successive supplementary dosing does not give rise to accumulation of neuromuscular blocking effect.
  Spontaneous recovery from the end of full block occurs in about 35 minutes as measured by the restoration of the tetanic response to 95% of normal neuromuscular function.
  The neuromuscular block produced by NOTRIXUM can be rapidly reversed by standard doses of anticholinesterase agents, such as neostigmine and edrophonium, accompanied or preceded by atropine, with no evidence of recurarisation.
- **Use as an infusion in adults**
  After an initial bolus dose of 0.3 to 0.6 mg/kg, NOTRIXUM can be used to maintain neuromuscular block during long surgical procedures by administration as a continuous infusion at rates of 0.3 to 0.6 mg/kg/h.
  NOTRIXUM can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25°C to 26°C reduces the rate of inactivation of NOTRIXUM, therefore full neuromuscular block may be maintained by approximately half the original infusion rate at these low temperatures.
  NOTRIXUM is compatible with the following infusion solutions for the times stated below:

Infusion Solution	Period of stability
Sodium Chloride I.V. Infusion British Pharmacopeia (BP) (0.9% w/v)	24 hours
Glucose I.V. Infusion BP (5% w/v)	8 hours
Ringer's Injection United States Pharmacopeia (USP)	8 hours
Sodium Chloride (0.18% w/v) and Glucose (4% w/v) I.V. Infusion BP	8 hours
Compound Sodium Lactate I.V. Infusion BP (Hartmann's Solution for Injection)	4 hours

  Chemical and physical in-use stability has been demonstrated for the stated periods at temperature of up to 30°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 dilution has taken place in controlled and validated aseptic conditions.
- **Use in children**
  The dosage in children over the age of 1 month is the same as that in adults on a bodyweight basis.
- Use in the elderly
  NOTRIXUM may be used at standard dosage in elderly patients.
  It is recommended, however, that the initial dose be at the lower end of the range and that it be administered slowly.
- Use in patients with reduced renal and/or hepatic function
  NOTRIXUM may be used at standard dosage at all levels of renal or hepatic function, including end-stage failure.
- Use in patients with cardiovascular disease
  In patients with clinically significant cardiovascular disease, the initial dose of NOTRIXUM should be administered over a period of 60 seconds.

Contraindications
NOTRIXUM is contraindicated in patients known to be hypersensitive to atracurium, cisatracurium or benzenesulfonic acid.

Warnings and Precautions
In common with all the other neuromuscular blocking agents NOTRIXUM paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness.
NOTRIXUM should be administered only with adequate general anaesthesia and only by or under the close supervision of an experienced anaesthetist with adequate facilities for endotracheal intubation and artificial ventilation.
The potential for histamine release exists in susceptible patients during NOTRIXUM administration. Caution should be exercised in administering NOTRIXUM to patients with a history suggestive of an increased sensitivity to the effects of histamine.
Caution should also be exercised when administering NOTRIXUM 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 (see Contraindications).
NOTRIXUM does not have significant vagal or ganglionic blocking properties in the recommended dosage range.
Consequently, NOTRIXUM has no clinically significant effects on heart rate in the recommended dosage range and it will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery.
In common with other non-depolarising neuromuscular blocking agents, increased sensitivity to NOTRIXUM may be expected in patients with myasthenia gravis, other forms of neuromuscular disease and severe electrolyte imbalance.
NOTRIXUM should be administered over a period of 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who are hypovolaemic.
NOTRIXUM is inactivated by high pH and so must not be mixed in the same syringe with thiopentone or any alkaline agent.
When a small vein is selected as the injection site, NOTRIXUM should be flushed through the vein with physiological saline after injection. When other anaesthetic drugs are administered through the same in-dwelling needle or cannula as NOTRIXUM it is important that each drug is flushed through with an adequate volume of physiological saline.
NOTRIXUM is hypotonic and must not be administered into the infusion line of a blood transfusion.
Studies in malignant hyperthermia in susceptible animals (swine) and clinical studies in patients susceptible to malignant hyperthermia indicate that NOTRIXUM does not trigger this syndrome.
In common with other non-depolarising neuromuscular blocking agents, resistance may develop in patients suffering from burns.
Such patients may require increased doses dependent on the time elapsed since the burn injury and the extent of the burn.
Injection:
Intensive Care Unit (ICU) Patients: When administered to laboratory animals in high doses, laudanosine, a metabolite of atracurium, has been associated with transient hypotension and in some species, cerebral excitatory effects. Although seizures have been seen in ICU patients receiving NOTRIXUM, a causal relationship to laudanosine has not been established (see Adverse Reactions).

Interactions
The neuromuscular block produced by NOTRIXUM may be increased by the concomitant use of inhalational anaesthetics such as halothane, isoflurane and enflurane.
In common with all non-depolarising neuromuscular blocking agents the magnitude and/or duration of a non-depolarising neuromuscular block may be increased as a result of interaction with:
– antibiotics: including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin
– antiarrhythmic drugs: propranolol, calcium channel blockers, lidocaine, procainamide and quinidine
– diuretics: furosemide and possibly mannitol, thiazide diuretics and acetazolamide
– magnesium sulphate
– ketamine
– lithium salts
– ganglion blocking agents: trimetaphan, hexamethonium.
Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to NOTRIXUM would be consequent on such a development. Such drugs include various antibiotics, beta-blockers (propranolol, oxprenolol), antiarrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.
The onset of non-depolarising neuromuscular block is likely to be lengthened and the duration of block shortened in patients receiving chronic anticonvulsant therapy.
The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with NOTRIXUM may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of NOTRIXUM administered. Any synergistic effect may vary between different drug combinations.
A depolarising muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarising agents such as NOTRIXUM, as this may result in a prolonged and complex block which can be difficult to reverse with anti-cholinesterase drugs.
Treatment with anticholinesterases, commonly used in the treatment of Alzheimer's disease e.g. donepezil, may shorten the duration and diminish the magnitude of neuromuscular blockade with atracurium.

Pregnancy and Lactation
Fertility
Fertility studies have not been performed.
Pregnancy
Use in Pregnancy: Atracurium has been shown to cross the placenta to a limited degree although the transfer of metabolites may be greater. Animal studies of teratogenic potential are limited to a single study in which pregnant rabbits received subcutaneous doses of 0.15 mg/kg once daily or 0.1 mg/kg twice daily during the period of organogenesis. There was no clear evidence of teratogenic activity at these doses, which are less than those used clinically, although there was some indication of fetotoxicity manifest as slight increases in the incidences of minor skeletal and visceral anomalies. There are no adequate and well controlled studies in pregnant women. In common with all neuromuscular blocking agents, NOTRIXUM should be used in pregnant women only if in the opinion of the physician, the potential benefit outweighs any potential risk to the foetus.
Obstetrics
In an open study, atracurium was administered (0.3 mg/kg) to 26 pregnant women during delivery

by Caesarean section. No harmful effects were attributable to atracurium in any of the newborn infants, although atracurium was shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following Caesarean section during which a neuromuscular blocking agent has been administered.
In patients receiving magnesium sulphate, the reversal of neuromuscular blockade may be unsatisfactory and NOTRIXUM dose should be lowered as indicated.
In common with all neuromuscular blocking agents, NOTRIXUM should be used during pregnancy only if the potential benefit to the mother outweighs any potential risk to the foetus.
NOTRIXUM is suitable for maintenance of muscle relaxation during Caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses.

Lactation
It is not known whether atracurium is excreted in human milk.

Effects on Ability to Drive and Use Machines
This precaution is not relevant to the use of NOTRIXUM.
NOTRIXUM will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following anaesthesia apply.

Adverse Reactions
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 (≥1/1000 to < 1/100), rare (≥1/10,000 to < 1/1000), very rare (< 1/10,000). Very common, common, and uncommon frequencies were determined from clinical trial data. Rare and very rare frequencies were generally derived from spontaneous data. The frequency classification "Not known" has been applied to those reactions where a frequency could not be estimated from the available data.

Clinical Trial Data
Vascular Disorders
Events which have been attributed to histamine release are indicated by a hash (#).
Common: Hypotension (mild, transient)#, Skin flushing#
Respiratory, thoracic and mediastinal disorders
Events which have been attributed to histamine release are indicated by a hash (#).
Uncommon: Bronchospasm#

Post-Marketing Data
Immune system disorders
Very rare: **Anaphylactic reaction, anaphylactoid reaction**
Very rarely, severe anaphylactoid or anaphylactic reactions have been reported in patients receiving NOTRIXUM in conjunction with one or more anaesthetic agents.
Nervous system disorder
Not known: Seizures
There have been reports of seizures in ICU patients who have been receiving atracurium concurrently with several other agents.
These patients usually had one or more medical conditions predisposing to seizures (e.g. cranial trauma, cerebral oedema, viral encephalitis, hypoxic encephalopathy, uraemia). A causal relationship to laudanosine has not been established. In clinical trials, there appears to be no correlation between plasma laudanosine concentration and the occurrence of seizures.
Skin and subcutaneous tissue disorders
Rare: Urticaria
Musculoskeletal and connective tissue disorders
Not known: Myopathy, muscle weakness
There have been some reports of muscle weakness and/or myopathy following prolonged use of muscle relaxants in severely ill patients in the ICU. Most patients were receiving concomitant corticosteroids.
These events have been seen infrequently in association with atracurium and a causal relationship has not been established.

Overdose
Symptoms and Signs
Prolonged muscle paralysis and its consequences are the main signs of overdosage.
Treatment
It is essential to maintain a patent airway together with assisted positive pressure ventilation until spontaneous respiration is adequate.
Full sedation will be required since consciousness is not impaired.
Recovery may be hastened by the administration of anticholinesterase agents accompanied by atropine or glycopyrrolate, once evidence of spontaneous recovery is present.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Mechanism of Action
Atracurium is a highly selective, competitive or non-depolarising neuromuscular blocking agent.
Pharmacodynamic Effects
NOTRIXUM has no direct effect on intra-ocular pressure, and is therefore suitable for use in ophthalmic surgery.

Pharmacokinetics
Metabolism
Atracurium is inactivated by Hofmann elimination, a non-enzymatic process which occurs at physiological pH and temperature, and by ester hydrolysis catalysed by non-specific esterases.
Tests with plasma from patients with low levels of pseudocholinesterase show that the inactivation of atracurium proceeds unaffected.
Variations in the blood pH and body temperature of the patient within the physiological range will not significantly alter the duration of action of atracurium.

Elimination
The termination of the neuromuscular blocking action of NOTRIXUM is not dependent on its hepatic or renal metabolism or excretion. Its duration of action, therefore, is unlikely to be affected by impaired renal, hepatic or circulatory function.
The elimination half-life of atracurium is approximately 20 minutes, and the volume of distribution is 0.16 L/kg. Atracurium is 82% bound to plasma proteins.

Special Patient Populations
Injection:
Haemofiltration and haemodiafiltration have a minimal effect on plasma levels of atracurium and its metabolites, including laudanosine. The effects of haemodialysis and haemoperfusion on plasma levels of atracurium and its metabolites are unknown.
Concentrations of metabolites are higher in ICU patients with abnormal renal and/or hepatic function (see Warnings and Precautions). These metabolites do not contribute to neuromuscular block.

Long-Term Use in the Intensive Care Unit (ICU)
NOTRIXUM has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the risk-benefit ratio of neuromuscular blockade must be considered.
For NOTRIXUM, as with other neuromuscular blocking agents used in intensive care units, available evidence suggests that there is wide interpatient variability in dosage requirements and that requirements may change with time. Limited data suggest that NOTRIXUM infusion requirements may increase with prolonged administration in the ICU. The effects of haemodialysis, haemoperfusion and haemofilitration on plasma levels of atracurium and its metabolites are unknown.
One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. No pharmacological effects of laudanosine have been demonstrated in humans even after days/weeks of prolonged infusion.

PHARMACEUTICAL PARTICULARS
List of Excipients
– Benzenesulfonic Acid
– Water for Injection
– Nitrogen, Low Oxygen

Special Precautions for Storage
Store between 2°and 8°C to preserve potency.
Do not freeze.
Protect from light.
Upon removal from refrigerator to room temperature storage conditions (below 30°C), use Notrixum injection within 14 days.
Any unused NOTRIXUM injection from opened ampoules should be discarded.

Instructions for Use/Handling
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Presentation
Box, 5 ampoules @ 5 mL

PRESCRIPTION ONLY MEDICINE

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Manufactured by:
NOVELL PHARMACEUTICAL LABORATORIES
PT. Novell Pharmaceutical Laboratories
Jl. Wanaherang No.35, Tlajung Udik,
Gunung Putri, Bogor 16962, Indonesia

Distributed by:
GOLDPLUS UNIVERSAL
Goldplus Universal Pte Ltd
103 Kallang Avenue #06-02,
Singapore 339504

Pack. Code