



Atracurium
Atracurium Besilate
10 mg/ml Solution for Injection

Reference Market: UK

AfME Markets using same as LPD:

Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atracurium Besilate 10 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atracurium besilate 10 mg/ml (equivalent to atracurium 7.5 mg/ml)

2.5 ml of solution contains 25 mg atracurium besilate

5 ml of solution contains 50 mg atracurium besilate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

A clear colourless or faint yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atracurium Besilate Injection is indicated as an adjunct to general anaesthesia during surgery to relax skeletal muscles, and to facilitate endotracheal intubation and mechanical ventilation. It is also indicated to facilitate mechanical ventilation in intensive care unit (ICU) patients.

4.2 Posology and method of administration

Use as an adjunct to general anaesthesia

Atracurium Besilate Injection should only be administered by intravenous injection. **Do not give Atracurium Besilate Injection intramuscularly** since this may result in tissue irritation and there are no clinical data to support this route of administration.

To avoid distress to the patient, Atracurium Besilate Injection should not be administered before unconsciousness has been induced.

Atracurium Besilate Injection should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g. barbiturate solutions).

See section 6.6 for a list of compatible infusion solutions.

In common with all neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of Atracurium Besilate Injection in order to individualise dosage requirements.

Initial bolus doses for intubation

An initial atracurium besilate dose of 0.3 to 0.6 mg/kg (depending on the duration of full block required), given as an intravenous bolus injection, is recommended. This will provide adequate relaxation for about 15 to 35 minutes.

Endotracheal intubation can usually be accomplished within 90 to 120 seconds of the intravenous injection of 0.5 to 0.6 mg/kg. Maximum neuromuscular blockade is generally achieved approximately 3 to 5 minutes after administration. 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.

Maintenance doses

Intermittent IV injection: During prolonged surgical procedures neuromuscular blockade may be maintained with atracurium besilate maintenance doses of 0.1 to 0.2 mg/kg. Successive supplementary dosing does not give rise to accumulation of neuromuscular blocking effect.

Use as an infusion: After the initial atracurium bolus dose, neuromuscular blockade may be maintained during prolonged surgical procedures by administering atracurium besilate as a continuous intravenous infusion at a rate of 0.3 to 0.6 mg/kg/hour. The infusion should not be commenced until early spontaneous recovery from the initial atracurium bolus dose is evident.

Atracurium Besilate Injection can be administered by infusion during cardiopulmonary bypass surgery at the recommended infusion rates. Induced hypothermia to a body temperature of 25 to 26°C reduces the rate of inactivation of atracurium, and therefore full neuromuscular block may be maintained with approximately half the original infusion rate at these temperatures.

Reversal of neuromuscular blockade

The neuromuscular blockade induced by atracurium can be reversed with an anticholinesterase agent such as neostigmine or pyridostigmine, usually in conjunction with an anticholinergic agent such as atropine or glycopyrronium to prevent the adverse muscarinic effects of the anticholinesterase. Under balanced anaesthesia, reversal can usually be attempted approximately 20 to 35 minutes after the initial atracurium dose, or approximately 10 to 30 minutes after the last atracurium maintenance dose, when recovery of muscle twitch has started. Complete reversal of neuromuscular blockade is usually achieved within 8 to 10 minutes after administration of the reversing agents.

Rare instances of breathing difficulties, possibly related to incomplete reversal, have been reported following attempted pharmacological antagonism of atracurium induced neuromuscular blockade. As with other agents in this class, the tendency for residual neuromuscular block is increased if reversal is attempted at deep levels of blockade or if inadequate doses of reversal agents are employed.

Facilitation of mechanical ventilation in intensive care unit (ICU) patients

After an optional initial bolus dose of 0.3 to 0.6 mg/kg, neuromuscular block may be maintained by administering a continuous atracurium besilate infusion at rates of between 11 and 13 microgram/kg/min (0.65 to 0.78 mg/kg/hr). There may be wide inter-patient variability in dosage requirements and these may increase or decrease with time. Infusion rates as low as 4.5 microgram/kg/min (0.27 mg/kg/hr) or as high

as 29.5 microgram/kg/min (1.77 mg/kg/hr) are required in some patients.

The rate of spontaneous recovery from neuromuscular block after infusion of atracurium besilate in ICU patients is independent of the duration of administration.

Spontaneous recovery to a train-of-four ratio >0.75 (the ratio of the height of the fourth to the first twitch in a train-of-four) can be expected to occur in approximately 60 minutes. A range of 32 to 108 minutes has been observed in clinical trials.

Dosage considerations

Use in children: The dosage in children over the age of 1 month is similar to that in adults on a body weight basis, however, large individual variability in the neuromuscular response in paediatric patients indicates that neuromuscular monitoring is essential.

Use in neonates: The use of Atracurium is not recommended in neonates since there are insufficient data available (see section 5.1).

Use in the elderly: The standard dose of atracurium may be used in elderly patients, however, it is recommended that the initial dose be at the lower end of the range and it should be administered slowly

Use in patients with reduced renal and/or hepatic function: Standard dosages may be used at all levels of renal or hepatic function, including endstage failure.

Use in patients with cardiovascular disease: In patients with significant cardiovascular disease the initial dose of atracurium should be administered over a period of at least 60 seconds.

See also “Special warnings and special precautions for use”.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Atracurium Besilate Injection should be used only by those skilled in the management of artificial respiration and only when facilities are immediately available for endotracheal intubation and for providing adequate ventilation support, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. The clinician must be prepared to assist or control ventilation, and anticholinesterase agents should be immediately available for reversal of neuromuscular blockade.

Atracurium has no known effect on consciousness, pain threshold, or cerebation. In surgery, it should be used only with adequate general anaesthesia.

In common with other neuromuscular blocking agents, the potential for histamine release exists in susceptible patients during administration of atracurium besilate. Caution should be exercised in patients with a history suggestive of an increased sensitivity to the effects of histamine.

Do not give Atracurium Besilate Injection by intramuscular administration.

Atracurium Besilate Injection has an acid pH and therefore should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Atracurium Besilate Injection may be inactivated and a free acid may be precipitated.

When a small vein is selected as the injection site, Atracurium Besilate Injection should be flushed through the vein with physiological saline after injection. When other anaesthetic drugs are administered through the same indwelling needle or cannula as Atracurium Besilate Injection, it is important that each drug is flushed through with an adequate volume of physiological saline.

Atracurium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of non-depolarising agents has been noted. A reduced dosage of atracurium and the use of a peripheral nerve stimulator for assessing neuromuscular blockade is especially important in these patients. Similar precautions should be taken in patients with severe electrolyte disorders.

Atracurium does not have significant vagal or ganglion blocking properties in the recommended dosage range. Consequently, atracurium will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery. Therefore, bradycardia during anaesthesia may be more common with atracurium than with other muscle relaxants.

As with other non-depolarising neuromuscular blocking agents, resistance to atracurium may develop in patients suffering from burns. Such patients may require increased doses of atracurium depending on the time elapsed since the burn injury and the extent of the burn.

Atracurium Besilate Injection should be administered over a period of at least 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who are hypovolaemic.

Atracurium Besilate Injection is hypotonic and must not be applied into the infusion line of a blood transfusion.

Monitoring of serial creatine phosphokinase (CPK) values should be considered in asthmatic patients receiving high dose corticosteroids and neuromuscular blocking agents in intensive care units.

Special precautions should be taken in patients with known anaphylactic reactions to curares, as cross-reactivity may be possible with this product.

4.5 Interaction with other medicinal products and other forms of interaction

As with other non-depolarising neuromuscular blocking agents, the magnitude and/or duration of atracurium's effects may be increased as a result of an interaction with the following agents.

Inhalation anaesthetics: atracurium is potentiated by isoflurane, desflurane, sevoflurane and enflurane anaesthesia, and only marginally potentiated by halothane anaesthesia.

Antibiotics: including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin, clindamycin and vancomycin.

Anticonvulsants (acute administration only): phenytoin, carbamazepine.

Antiarrhythmic drugs: local anaesthetics such as lidocaine, procainamide, quinidine.

Beta-blockers: propranolol, oxprenolol

Antirheumatic drugs: chloroquine, d-penicillamine

Calcium channel blockers: diltiazem, nicardipine, nifedipine, verapamil.

Diuretics: frusemide, thiazides, acetazolamide and possibly mannitol.

Ganglion blocking agents: trimetaphan, hexamethonium.

Others: dantrolene, parenteral magnesium sulphate, chlorpromazine, steroids, ketamine, lithium salts and quinine.

Rarely, some of the above drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome. In these situations a consequent increased sensitivity to atracurium would be expected.

The administration of combinations of non-depolarising neuromuscular blocking agents in conjunction with atracurium may produce a degree of neuromuscular blockade in excess of that which might be expected were an equipotent total dose of atracurium 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 blocking agents such as atracurium, as this may result in a prolonged and complex block which can be difficult to reverse with anticholinesterase drugs.

The prior use of suxamethonium reduces the onset (to maximum blockade) by approximately 2 to 3 minutes and may increase the depth of neuromuscular blockade induced by atracurium. Therefore, the initial atracurium dose should be reduced and the reduced dose should not be administered until the patient has recovered from the neuromuscular blocking effects of suxamethonium.

The use of intravenous corticosteroids with neuromuscular blocking agents has been reported to antagonise neuromuscular blockades. In addition, prolonged co-administration of these agents may increase the risk and/or severity of myopathy resulting in prolonged flaccid paralysis following discontinuation of the neuromuscular blocking agent. The myopathy is usually reversible with recovery in several months.

The onset of neuromuscular blockade is likely to be lengthened and the duration of blockade shortened in patients receiving chronic anticonvulsant therapy (e.g. carbamazepine, phenytoin). However, if the anticonvulsants are given acutely, the neuromuscular blocking effects may be increased.

In principle, maintaining neuromuscular monitoring until complete reversal of neuromuscular blockade should permit detection of most interactions. Nevertheless, recurrence of neuromuscular blockade may occur, for example, upon treatment with post surgical antibiotics.

4.6 Fertility, pregnancy and lactation

Fertility

No fertility data are available

Pregnancy

Atracurium crosses the placenta but there have been no demonstrated adverse effects in the foetus or newborn infant. Animal studies have indicated that atracurium has no adverse effects on foetal development. As with all neuromuscular blocking agents, the use of atracurium in the first three months of pregnancy should be avoided and it should not be used during the second and third trimesters unless clearly necessary.

Atracurium is suitable for maintenance of muscle relaxation during caesarean section as it does not cross the placenta in clinically significant amounts following recommended doses. In an open study, atracurium besilate (0.3 mg/kg) was administered to 26 pregnant women during delivery by caesarean section. No harmful effects were attributable to atracurium in any of the newborn infants, although small amounts of atracurium were 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.

Anaesthesia during the third trimester of pregnancy exposes the mother to Mendelson syndrome (acid pneumopathy due to gastric acid aspiration). If a muscle relaxant is used at induction of anaesthesia, one should be chosen with a short onset and duration of action and low placental transfer and used in the lowest dose required to induce adequate neuromuscular relaxation. In patients receiving magnesium sulphate, the reversal of neuromuscular blockade may be unsatisfactory and the atracurium dose should be lowered as indicated.

Breastfeeding

Atracurium has a relatively high molecular weight and is highly ionized at physiologic pH, both factors that markedly reduce transfer into milk. In addition, even though milk is slightly more acidic than plasma, any atracurium transferred into milk would be rapidly degraded. Nevertheless, in view of the potential respiratory depressant effect on the neonate, especially if premature, it is recommended that if breastfeeding is started within 24 hours after administration of atracurium, the neonate is closely monitored.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The adverse effects are reported in decreasing order of frequency within each system order class (SOC).

As with most neuromuscular blocking agents, the potential exists for undesirable effects suggestive of histamine release in susceptible patients. In clinical trials (875 patients) reports of skin flushing ranged from 1% at doses up to 0.3 mg/kg, to 29% at doses of 0.6 mg/kg or greater. The incidence of transient hypotension ranged from 1 to 14% respectively for the corresponding dosages.

Table for frequency of adverse reactions for Atracurium Besilate 10 mg/ml Solution for injection

SOC	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $<1/10$)	Uncommon ($\geq 1/1000$ to $<1/100$)	Rare ($\geq 1/10,000$ to $<1/1000$)	Very rare ($<1/10,000$)	Not known (cannot be estimated from the available data).
Cardiac disorders		Tachycardia, bradycardia (observed in 1% of patients)		Severe allergic reactions (e.g. shock, cardiac failure, cardiac arrest)		
General disorders and administration site condition		Reaction at injection site				
Immune system disorders					Allergic reactions (i.e. anaphylactic or anaphylactoid responses) Anaphylactoid reactions	
Injury, poisoning and procedural complications						Prolonged block
Respiratory, thoracic and mediastinal disorders		Wheezing,	Bronchospasm (0.2% of patients)	Dyspnea, laryngospasm	hypoxemia	Bronchial secretions
Skin and subcutaneous tissue		Localized skin reactions,	Generalized Erythema,	Angioneurotic oedema,		

disorders		rash, itching,	Hives,	urticaria		
Nervous system disorders						Inadequate block
Vascular disorders		Hypertension (observed in approximately 1% of patients), Hypotension, vasodilatation (flushing)- each occurred in approximately 2-3% of patients)				

After prolonged administration of atracurium besilate in severely ill patients under intensive care, some incidences of muscle weakness and/or myopathy occurred. Most patients were concomitantly treated with corticosteroids. A causal relationship with atracurium therapy has not been established.

There have been rare 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). In clinical trials, there appears to be no correlation between plasma laudanosine concentration and the occurrence of seizures.

Reporting suspected adverse reactions after marketing authorization 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 according to their local country requirements.

To Report side effects

- Saudi Arabia

National Pharmacovigilance and Drug Safety Centre (NPC)

- Fax: +966 11 205 7662
- Call NPC at 00966 11 2038222, Exts: 2317-2356-2353-2354-2334-2340
- Toll-Free phone: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

4.9 Overdose

Prolonged muscle paralysis and its consequences are the main signs of overdose.

There is limited experience with atracurium overdosage following parenteral administration. The possibility of iatrogenic overdosage can be minimised by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of atracurium are likely to produce symptoms consistent with extensions of the usual pharmacological effects. Overdosage may increase the risk of histamine release and adverse cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this should include proper positioning, fluid administration, and the use of vasopressor agents if necessary. It is essential to maintain a patent airway with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation will be required since consciousness is not impaired. The duration of neuromuscular blockade may be prolonged and a peripheral nerve stimulator should be used to monitor recovery. Recovery may be hastened by the administration of an anticholinesterase agent such as neostigmine or pyridostigmine in conjunction with an anticholinergic agent such as atropine, once evidence of spontaneous recovery is present.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Atracurium besilate is a non-depolarising neuromuscular blocking agent (ATC code M03A C04) with an intermediate duration of action, administered intravenously to produce skeletal muscle relaxation.

Non-depolarising neuromuscular blocking agents antagonise the action of the neurotransmitter acetylcholine by competitively binding with cholinergic receptor sites on the motor endplate of the myoneural junction. These effects may be inhibited or reversed by the administration of anticholinesterases such as neostigmine or pyridostigmine.

As with other non-depolarising neuromuscular blocking agents, the time to onset or paralysis is reduced, and the duration of maximum effect prolonged, with increasing atracurium doses.

Once recovery from atracurium's neuromuscular blocking effect begins, it proceeds more rapidly than recovery from tubocurarine, alcuronium, and pancuronium. Regardless of the atracurium dose, the time from start of recovery (from complete block) to complete recovery (as measured by restoration of the tetanic response to 95% of normal) is approximately 30 minutes under balanced anaesthesia, and approximately 40 minutes under halothane, enflurane or isoflurane anaesthesia. Repeated doses have no cumulative effect on recovery rate.

With initial atracurium besilate doses up to 0.5 mg/kg, plasma histamine levels were shown to increase by 15% in a dose dependant way, but haemodynamic changes were minor within this dose range. Following the administration of 0.6 mg/kg of atracurium besilate, histamine levels were shown to increase by 92%, and were shown to correlate with a transient (5 minutes) decrease in blood pressure and a brief (2 to 3

minutes) episode of skin flushing. While these effects are of little clinical significance in most patients, the possibility of substantial histamine release at recommended doses must be considered in sensitive individuals, or in patients in whom substantial histamine release would be especially hazardous (e.g. patients with significant respiratory or cardiovascular disease).

Studies in malignant hyperthermia-susceptible pigs indicated that atracurium besilate does not trigger this syndrome. Clinical studies in patients with a history of malignant hyperthermia revealed the same results.

Atracurium besilate does not appear to affect intraocular pressure, therefore, it is a suitable agent for ophthalmic surgery.

Paediatric population:

The limited data in neonates from literature reports suggest variability in the time to onset and duration of action of atracurium in this population as compared to children (see section 4.2).

5.2 Pharmacokinetic properties

The pharmacokinetics of atracurium besilate in humans are essentially linear within the dose range of 0.3 to 0.6 mg/kg. The elimination half-life is approximately 20 minutes. The protein binding of atracurium is approximately 82%. The volume of distribution of atracurium is 0.16 l/kg and plasma clearance of atracurium is about 6.5 ml/min/kg. Some placental transfer occurs in humans. The umbilical venous to maternal venous drug concentration ratios are between 0.03 and 0.33 (mean 0.12 \pm 0.04).

The duration of neuromuscular blockade produced by atracurium does not correlate with plasma pseudocholinesterase levels and is not altered by the absence of renal function. This is consistent with the results of *in vitro* studies which have shown that atracurium is inactivated in plasma via two non-oxidative pathways: ester hydrolysis, catalysed by non-specific esterases; and Hofmann elimination, a non-enzymatic chemical process which occurs at physiological pH and body temperature. The rate of Hofmann elimination, which is the principal route of elimination for atracurium, is increased at a higher pH or at higher temperatures, and reduced at a lower pH or lower temperatures.

Limited clinical experience on long term administration of atracurium besilate show only minimal effects of haemofiltration or haemodialysis on plasma levels of atracurium and its metabolites. The effects of haemoperfusion on plasma levels of atracurium and its metabolites are not known.

5.3 Preclinical safety data

Carcinogenicity / Mutagenicity: Carcinogenicity studies have not been performed. Atracurium yielded negative results for gene mutation in bacteria, and chromosomal damage in bone marrow of rats. A positive response in the mouse lymphoma assay was observed only at highly cytotoxic concentrations. This single positive response is not considered to be of clinical relevance.

Reproductive toxicity:- Animal studies have indicated that atracurium has no adverse effect on foetal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzenesulphonic acid

Water for Injections

6.2 Incompatibilities

Atracurium Besilate Solution for Injection has an acid pH and therefore should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle.

6.3 Shelf life

Atracurium must not be used after the expiry date which is stated on the ampoule label and carton after 'EXP'. Where only a month and year is stated, the expiry date refers to the last day of that month.

Information is presented below on chemical and physical stability following dilution with a number of infusion solutions:

Atracurium Besilate Injection diluted to 0.5 mg/ml with the following infusion solutions, and stored at 30°C protected from light, was shown to be stable for the times stated below.

Infusion Solution	Period of stability (hours)
Sodium Chloride 0.9% Intravenous Infusion	24
Glucose 5% Intravenous Infusion	24
Glucose 4% and Sodium Chloride 0.18% Intravenous Infusion	24
Ringer's Injection USP	24
Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution for Injection)	4

Atracurium Besilate Injection diluted to 5 mg/ml with the following infusion solutions, and stored at 30°C protected from light in 50 ml plastic syringes, was shown to be stable for the times stated below.

Infusion Solution	Period of stability (hours)
Sodium Chloride 0.9% Intravenous Infusion	24
Glucose 5% Intravenous Infusion	24
Glucose 4% and Sodium Chloride 0.18%	24

Intravenous Infusion	
Ringer's Injection USP	24
Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution for Injection)	8

However, 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.

Discard residue immediately after use.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep container in the outer carton.

6.5 Nature and contents of container

2.5 ml: Type I glass ampoule in packs of 5 ampoules.

5 ml: Type I glass ampoule in packs of 5 ampoules.

6.6 Special precautions for disposal and other handling

Contains no preservative. Discard residue immediately after use.

Do not use if cloudiness or precipitate is observed.

Atracurium besilate infusion solutions may be prepared by admixing Atracurium Besilate Injection with an appropriate diluent (see below) to give an atracurium besilate concentration of 0.5 mg/ml to 5 mg/ml.

Infusion Solutions

Sodium Chloride 0.9% Intravenous Infusion

Glucose 5% Intravenous Infusion

Glucose 4% and Sodium Chloride 0.18% Intravenous Infusion

Ringer's Injection USP

Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution for Injection)

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Horizon, Honey Lane., Hurley,
Maidenhead,

SL6 6RJ
UK

10 DATE OF REVISION OF THE TEXT

January 2017

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers

Union of Arabic Pharmacists