PROFESSIONAL INFORMATION

TRAKEZE

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

TRAKEZE (solution for injection/infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of TRAKEZE contains 10 mg rocuronium bromide. Each vial has a total content of 50 mg rocuronium bromide per 5 ml solution.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

The solution that is clear, colourless up to pale brown-yellowish pH: 3,5 – 4,5; osmolarity: 270 – 330 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TRAKEZE is indicated as an adjunct:

- to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, and to provide skeletal muscle relaxation during surgery;
- in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation for up to 3 days in adults 18 to 65 years.

4.2 Posology and method of administration

Posology

TRAKEZE should be administered only by experienced doctors familiar with the use of neuromuscular blocking medicines.

The dosage of TRAKEZE should be individualised in each patient. The method of anaesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other medicines that are administered concomitantly, and the condition of the patient should be considered when determining the dose.

The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of the neuromuscular block and recovery.

Inhalation anaesthetics potentiate the neuromuscular blocking effects of TRAKEZE (see section 4.5). This potentiation becomes clinically relevant during the course of anaesthesia when a certain tissue concentration of the volatile medicines is reached. Consequently, adjustments should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of TRAKEZE during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (see section 4.5).

Risk of medication errors

Accidental administration of neuromuscular blocking medicines may result in serious adverse events, including fatal outcomes. Store TRAKEZE with the cap and ferrule intact and in a manner that minimises the possibility of selecting the wrong product (see section 4.4).

In adult patients the following dosage recommendations may serve as a general guidance for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the ICU.

Surgical procedures

Tracheal intubation

The standard intubating dose during routine anaesthesia is 0,6 mg rocuronium bromide per kg body mass, which results in adequate intubation conditions within 90 seconds in nearly all patients.

A dose of 1,0 mg TRAKEZE per kg body mass is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia, after which adequate intubation conditions are also established within 60 seconds in nearly all patients.

Higher doses

Should there be a reason for selection of larger doses in individual patients, initial doses up to 2 mg/kg TRAKEZE have been administered during surgery. The use of these high doses of TRAKEZE decreases the onset time and increases the duration of action (see section 5.2).

Maintenance dosing

The recommended maintenance dose is 0,15 mg TRAKEZE per kg body mass. In the case of long-term inhalational anaesthesia, this should be reduced to 0,075 to 0,1 mg/kg TRAKEZE. The maintenance doses should be given as a bolus when twitch height has recovered to 25 % of control twitch height, or when 2 to 3 responses to train-of-four stimulation (TOF) are present (see section 5.2).

No cumulative effect (progressive increase in duration of action) with repetitive maintenance dosing at the recommended level has been observed.

Continuous infusion

If TRAKEZE is administered by continuous infusion, it is recommended to give a loading dose of 0,6 mg TRAKEZE per kg body mass and, when the neuromuscular block starts to recover, to start administration 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 under intravenous anaesthesia, the infusion rate required to maintain the neuromuscular block at this level ranges from 0,3 to 0,6 mg/kg per hour. Under inhalational anaesthesia the infusion rate ranges from 0,3 to 0,4 mg/kg per hour.

Continuous monitoring of the neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Dosage in paediatric patients

For infants (28 days to 23 months), children (2 to 14 years) and adolescents (12 to 18 years) the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those in adults.

For continuous infusion in paediatrics the infusion rates, with exception of children, are the same as for adults. For children higher infusion rates might be necessary. For children the same initial infusion rates as for adults are recommended, and this should be adjusted to maintain twitch response at 10 % of control twitch height, or to maintain 1 or 2 responses to train-of-four stimulation during the procedure.

The experience with TRAKEZE in rapid sequence induction in paediatric patients is limited. TRAKEZE is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Elderly patients and patients with hepatic and/or biliary tract disease and/or renal failure

The standard intubation dose for elderly patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0,6 mg/kg TRAKEZE.

Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0,075 to 0,1 mg/kg TRAKEZE and the recommended infusion rate is 0,3 to 0,4 mg/kg per hour (see “Continuous infusion”).

Dosage 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 mass) doses should be reduced considering a lean body mass.

Intensive care procedures

Tracheal intubation

For tracheal intubation, the same doses should be used as described above under surgical procedures.

Maintenance dosing

The use of an initial loading dose of 0,6 mg TRAKEZE per kg body mass is recommended, followed by a continuous infusion as soon as twitch height recovers to 10 % or upon reappearance of 1 to 2 twitches to train-of-four (TOF) stimulation. Dosage should always be titrated to effect in the individual

patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80 to 90 % (1 to 2 twitches to TOF stimulation) in adult patients is 0,3 to 0,6 mg/kg per hour during the first hour of administration, which will need to be decreased during the following 6 to 12 hours, according to individual response. Thereafter, individual dose requirements remain relatively constant.

A large interpatient variability in hourly infusion rates has been found, with mean hourly infusion rates ranging from 0,2 to 0,5 mg/kg per hour depending on nature and extent of organ failure(s), concomitant medicine and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Safety and efficacy beyond 3 days has not been established.

Following continuous infusion in the ICU, the time to recovery of the TOF ratio to 0,7 depends on the level of block at the end of the infusion. After a continuous infusion for 20 hours or more the median (range) time between return of T_2 to TOF stimulation and recovery of the TOF ratio to 0,7 approximates 1,5 (1 to 5) hours in patients without multiple organ failure and 4 (1 to 25) hours in patients with multiple organ failure.

Method of administration

TRAKEZE is for single use only.

TRAKEZE is administered intravenously either as a bolus injection or as a continuous infusion (see section 6.6 for compatible infusion fluids). Administration should begin immediately after mixing and should be completed within 24 hours. Unused solutions should be discarded.

4.3 Contraindications

- TRAKEZE is contraindicated in patients with hypersensitivity to rocuronium bromide, or to the bromide ion, or to any of the excipient of TRAKEZE;
- There is inadequate data to support the use of TRAKEZE in neonates (0 to 1 month);
- TRAKEZE is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and elderly patients due to a lack of data on safety and efficacy.

4.4 Special warnings and precautions for use

TRAKEZE causes paralysis of the respiratory muscles. Ventilatory support is therefore mandatory for patients treated with TRAKEZE until adequate spontaneous respiration is restored. It is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

Residual neuromuscular blockade

Residual neuromuscular blockade has been reported for rocuronium bromide, as in TRAKEZE – see section 4.8. To prevent complications, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual neuromuscular blockade after extubation in the post-operative phase (such as medicine interactions or the condition of the patient) should also be considered. If not used as part of standard clinical practice, the use of a reversal medicine should be considered, especially in those cases where residual neuromuscular blockade is more likely to occur.

It is essential to ensure that the patient is breathing spontaneously, deeply and regularly before leaving the theatre after anaesthesia.

Hypersensitivity/anaphylaxis

Severe anaphylactic and anaphylactoid reactions, which may be fatal, can occur after the administration of TRAKEZE (see section 4.8 (c)).

High rates of cross-reactivity between neuromuscular blocking medicines have been reported. Therefore, where possible, before administering TRAKEZE, hypersensitivity to other neuromuscular blocking medicines should be excluded. TRAKEZE should only be used when absolutely essential in susceptible patients. Patients who experience a hypersensitivity reaction under general anaesthesia should be tested subsequently for hypersensitivity to other neuromuscular blockers.

Histamine release and histaminoid reactions

Since neuromuscular blocking substances 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 (see section 4.8), should always be taken into consideration when administering TRAKEZE.

Cardiac effects

TRAKEZE may increase the heart rate (see section 4.8).

Prolonged neuromuscular blockage

Prolonged paralysis and/or skeletal muscle weakness has been noted after long-term use of TRAKEZE in the ICU (see section 4.8).

In order to help preclude possible prolongation of neuromuscular blockage and/or overdose, it is strongly recommended that neuromuscular transmission is monitored throughout the use of TRAKEZE.

Patients should also receive adequate analgesia and sedation. TRAKEZE should furthermore be titrated to effect in the individual patients, or under the supervision of experienced medical practitioners who are familiar with its actions and with appropriate neuromuscular monitoring techniques.

Myopathy

Myopathy has been reported regularly after long-term administration of TRAKEZE in the ICU, in combination with corticosteroids.

In patients receiving both TRAKEZE and corticosteroids, treatment with TRAKEZE should be limited as much as possible.

Suxamethonium

If suxamethonium is used for intubation, the administration of TRAKEZE should be delayed until the patient has clinically recovered from the neuromuscular blockade induced by suxamethonium (see section 4.5).

Malignant hyperthermia

Because TRAKEZE is always used with other medicines and because of the possibility of the occurrence of malignant hyperthermia during anaesthesia, even in the absence of known triggering medicines, medical practitioners should be familiar with the early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anaesthesia. Cases of malignant hyperthermia with rocuronium (as in TRAKEZE) have been reported during post- marketing surveillance; however, a causal association has not been proven.

Risk of death due to medication errors

Administration of TRAKEZE results in paralysis, which may lead to respiratory arrest and death, a progression that may be more likely to occur in a patient for whom it is not intended. Confirm proper selection of intended product and avoid confusion with other injectable solutions that are present in critical care and other clinical settings. If another healthcare provider is administering the product, ensure that the intended dose is clearly labelled and communicated.

<u>The following conditions may influence the pharmacokinetics and/or pharmacodynamics of TRAKEZE:</u>

Hepatic and/or biliary tract disease and renal failure

Rocuronium bromide, as contained in TRAKEZE, is excreted in bile and urine (see section 5.2). Prolongation of action has been reported with doses of 0,6 mg/kg TRAKEZE in patients with clinically significant hepatic and/or biliary disease, or with renal failure/impairment. Therefore, TRAKEZE should be used with caution in these patients.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular diseases, old age and oedematous states resulting in an increased volume of distribution, may contribute to a slower onset of the effect. The duration of action may also be prolonged due to reduced plasma clearance.

Neuromuscular disease

TRAKEZE should be used with extreme caution in patients with neuromuscular disease or after

poliomyelitis, since the response to neuromuscular blocking medicines may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of rocuronium bromide may have profound effects and TRAKEZE should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking effect of TRAKEZE is increased and the duration prolonged.

Obesity

TRAKEZE may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body mass.

Burns

Patients with burns are known to develop resistance to non-depolarising neuromuscular blocking medicines. It is recommended that the dose is titrated to the response.

Conditions which may increase the effects of TRAKEZE

Hypokalaemia (e.g. after severe vomiting, diarrhoea, or diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia and cachexia.

Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

4.5 Interactions with other medicines and other forms of interaction

The following medicines have been shown to influence the extent and/or duration of the effect of TRAKEZE:

Increased effect

- Halogenated volatile anaesthetics potentiate the neuromuscular block of TRAKEZE. The effect

only becomes apparent with maintenance dosing (see section 4.2, “Surgical procedures, *Maintenance dosing”*). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.

- After intubation with suxamethonium (see section 4.2 and 4.8).
- Long-term concomitant use of corticosteroids and TRAKEZE in the ICU may result in prolonged duration of neuromuscular block or myopathy. See section 4.4 and 4.8.

Other medicines:

- Antibiotics: aminoglycosides, lincosamides (e.g. lincomycin and clindamycin), polypeptide antibiotics, acylamino-penicillin antibiotics.
- Diuretics, quinidine, quinine, magnesium salts, calcium channel blocking medicines, lithium salts, local anaesthetics (lidocaine I.V., bupivacaine epidural) and acute administration of phenytoin of ß-blocking medicines.

Recurarisation (increase in neuromuscular block after a variable period of recovery) has been reported after post-operative administration of aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see section 4.4).

Decreased effect

- Prior chronic administration of phenytoin or carbamazepine
- Calcium chloride, potassium chloride
- Protease inhibitor homologues (such as gabexate and ulinastatin)
- Neostigmine, edrophonium, pyridostigmine, aminopyridine derivatives

Variable effect

Administration of other non-depolarising neuromuscular blocking medicines in combination with TRAKEZE may produce attenuation of potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking medicines used.

Suxamethonium given after the administration of TRAKEZE may produce potentiation or attenuation of the neuromuscular blocking effect of TRAKEZE.

Effect of TRAKEZE on other medicines

Combined use of TRAKEZE with lidocaine could result in a quicker onset of action of lidocaine.

Paediatric population

No formal interaction studies have been reported.

4.6 Pregnancy and lactation

Pregnancy

The safety of use of TRAKEZE in pregnancy has not been established.

Caesarean section

In patients undergoing Caesarean section, TRAKEZE can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic medicine is administered or following suxamethonium facilitated intubation.

However, TRAKEZE, administered in doses of 0,6 mg/kg may not produce adequate conditions for intubation until 90 seconds after administration. This dose has been shown to be safe in patients undergoing Caesarean section. TRAKEZE does not affect Apgar score, foetal muscle tone or cardiorespiratory adaptation.

From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs which does not lead to the observation of clinical adverse effects in the new-born.

Doses of 1,0 mg/kg have not been investigated in Caesarean section patients. Therefore, only a dose of 0,6 mg/kg is recommended in this patient group.

Reversal of neuromuscular block induced by neuromuscular blocking medicines may be inhibited or unsatisfactory in patients receiving magnesium salts for toxaemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of TRAKEZE should be reduced and be titrated to twitch response.

Breastfeeding

The safety of use of TRAKEZE in lactation has not been established.

4.7 Effects on ability to drive and use machinery

Patients should be warned not to handle potentially dangerous machinery or drive a car within 24 hours after the full recovery from the neuromuscular blocking action of TRAKEZE.

4.8 Undesirable effects

a) Summary of the safety profile

The most common undesirable effects are pain/reaction around injection site, changes in vital functions and prolonged neuromuscular block. The most frequently reported serious adverse medicine reactions during post-marketing surveillance is anaphylactic and anaphylactoid reactions and associated symptoms.

b) Tabulated list of adverse reactions

Immune system disorders	
Less frequent:	Hypersensitivity, anaphylactic reaction (sometimes fatal), anaphylactic shock, anaphylactoid reaction (see section 4.4), angioedema
Nervous system disorders	
Less frequent:	Flaccid paralysis
Cardiac disorders	
Less frequent:	Tachycardia
Vascular disorders	
Less frequent:	Hypotension, circulatory collapse and shock, flushing
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Bronchospasm
Frequency unknown:	Apnoea, respiratory failure
Skin and subcutaneous tissue disorders	
Less frequent:	Urticaria, rash, erythematous rash, itching
Musculoskeletal, connective tissue and bone disorders	
Less frequent:	Muscular weakness, steroid myopathy (see section 4.4)

General disorders and administration site conditions	
Less frequent:	Medicine ineffective, decreased medicine effect/therapeutic response, increased medicine effect/therapeutic response, injection site pain, injection site reaction, facial oedema
Frequency unknown:	Malignant hyperthermia
Injury, poisoning and procedural complication	
Less frequent:	Prolonged neuromuscular block (see section 4.4), delayed recovery from anaesthesia, airway complication of anaesthesia

c) Discussion of selected adverse reactions

Anaphylaxis

Severe anaphylactic reactions to neuromuscular blocking medicines, including TRAKEZE, have been reported (see section 4.8). Anaphylactic/ anaphylactoid reactions are 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.

Clinical study reports mention a slight increase in mean plasma histamine level following rapid bolus administration of 0,3 – 0,9 mg rocuronium bromide per kg body weight.

Prolonged neuromuscular block

The most frequent adverse reaction to non-depolarising blocking medicines 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 (see section 4.4).

Myopathy

Myopathy has been reported after the use of various neuromuscular blocking medicines in the ICU in combination with corticosteroids (see section 4.4).

Local injection site reactions

During rapid sequence induction of anaesthesia, pain on injection has been reported, especially when

the patient has not yet completely lost consciousness and particularly when propofol is used for induction. Clinical study reports mention pain on injection in 16 % of the patients who underwent rapid sequence induction of anaesthesia with propofol and in less than 0,5 % of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

Paediatric patients

A meta-analysis of 11 clinical studies in paediatric patients (n=704) with rocuronium bromide (up to 1 mg/kg) showed that tachycardia was identified as an adverse medicine reaction with a frequency of 1,4 %.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms of overdose

In overdose, side effects can be precipitated and/or be of increased severity. See section 4.8.

Treatment of overdose

In the event of overdose and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. Upon start of spontaneous recovery, suggamadex or an acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting medicine fails to reverse the neuromuscular effects of TRAKEZE, artificial ventilation must be continued until spontaneous breathing is restored. Repeated dosages of an acetylcholinesterase inhibitor can be dangerous.

Further treatment is symptomatic and supportive.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Category and class: A 17.1 Peripherally acting muscle relaxants

Rocuronium bromide is a non-depolarising neuromuscular blocking medicine. It acts by competing for nicotinic ACh (acetylcholine) receptors at the motor end-plate. The latter action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

The ED_{90} (dose required to produce 90 % depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anaesthesia is approximately 0,3 mg/kg rocuronium bromide. The ED_{90} in infants is lower than in adults and children (0,25, 0,35 and 0,40 mg/kg, respectively).

The clinical duration (the duration until spontaneous recovery to 25 % of control twitch height) with 0,6 mg/kg rocuronium bromide is 30 to 40 minutes. The total duration (time until spontaneous recovery to 90 % of control twitch height) is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75% (recovery index) after a bolus dose of 0,6 mg/kg rocuronium bromide is 14 minutes.

With lower dosages of 0,3 to 0,45 mg/kg rocuronium bromide (1 to 1,5 x ED_{90}), onset of action is slower and duration of action is shorter. With high doses of 2 mg/kg, clinical duration is 110 minutes.

Cardiovascular surgery

In patients scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum block following 0,6 to 0,9 mg/kg rocuronium bromide are an increase in heart rate up to 9 % and an increase in mean arterial blood pressure up to 16 % from the control values.

Special populations

The mean onset time in infants and children at an intubation dose of 0,6 mg/kg is slightly shorter than in adults. The duration of relaxation and the time to recovery tend to be shorter in children compared

to infants and adults.

Reversal of muscle relaxation

Administration of acetylcholinesterase inhibitors, (neostigmine, pyridostigmine or edrophonium) at reappearance of T_2 or at the first signs of clinical recovery, antagonises the action of rocuronium bromide.

5.2 Pharmacokinetic properties

Absorption and distribution

After intravenous administration of a single bolus dose, the plasma concentration time course runs in three exponential phases. In normal adults, the mean (95 % CI) elimination half-life is 73 (66 to 80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193 to 214) ml/kg and the plasma clearance is 3,7 (3,5 to 3,9) ml/kg per minute.

Elimination

When administered as a continuous infusion to facilitate mechanical ventilation for 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A large variability amongst patients exists, related to nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure the mean (± SD) elimination half-life is 21,5 (± 3,3) hours, the (apparent) volume of distribution at steady state is 1,5 (± 0,8) l/kg and the plasma clearance rate is 2,1 (± 0,8) ml/kg per minute.

Rocuronium is excreted in urine and bile. Excretion in urine is nearly 40 % within 12 to 24 hours. After injection of a radio-labelled dose of rocuronium bromide, excretion of the radiolabel is on average 47 % in urine and 43 % in faeces after 9 days. About 50 % is recovered as the parent compound.

Infants and children

In infants (3 months to 1 year), the apparent volume of distribution at steady state conditions is increased compared to adults and children (1 to 8 years). In older children (3 to 8 years), a trend is seen towards higher clearance and shorter elimination half-life (approximately 20 minutes) compared

to adults, younger children and infants.

Elderly patients and patients with renal or hepatic disease

The plasma clearance in elderly patients and in patients with renal dysfunction is reduced but does not reach the level of statistical significance. In patients with hepatic disease, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml/kg per minute.

6 Pharmaceutical particulars

6.1 List of excipients

TRAKEZE contains the following excipients:

Acetic acid 99 % (E260) (for pH adjustment)

Acetic acid 30 % (E260) (for pH adjustment)

Sodium acetate trihydrate (E262)

Sodium chloride

Water for injections.

No preservatives have been added.

6.2 Incompatibilities

Physical incompatibility has been documented for TRAKEZE when added to solutions containing the following active substances: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, intralipid, methohexital, methylprednisone, prednisolone sodium succinate, thiopental, trimethoprim, and vancomycin.

TRAKEZE must not be mixed with other medicines except those mentioned in section 6.6.

If TRAKEZE 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 TRAKEZE and other medicines.

6.3 Shelf life

TRAKEZE has a shelf life of 3 years, if stored as described in section 6.4.

Since TRAKEZE does not contain a preservative, the solution should be used immediately after opening the vial.

From a microbiological point of view, the diluted product should therefore 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 ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 to 8 ºC). Do not freeze. Protect from light.

If stored out of a refrigerator:

TRAKEZE may be stored outside the refrigerator at a temperature of up to 25 °C for a maximum of 12 weeks, after which it should be discarded. TRAKEZE should not be placed back in the refrigerator, once it has been kept outside. The storage period must not exceed the shelf life.

Storage conditions after opening of the vial:

See section 6.3.

6.5 Nature and contents of the container

TRAKEZE is packaged in a clear Type I 10 ml glass vial containing 5 ml solution, with a vial neck of 20 mm, closed with a bromobutyl rubber stopper and a polypropylene flip-off cap.

Folding boxes contain 10 vials each.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

TRAKEZE is compatible with water for injection, 0,9 % sodium chloride, 5 % glucose, sodium chloride 0,3 % and glucose 3,3 %, sodium chloride 0,45 % in glucose 2,5 % and lactated Ringer's solution.

Administration should begin immediately after mixing and should be completed within 24 hours.

Do not use TRAKEZE if you notice that the solution is not clear and not free from particles.

For single use only. Unused solutions should be discarded.

7 Holder of the certificate of registration

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8 Registration number

A53/17.1/0159.158

9 Date of first authorisation/renewal of the authorisation

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10 Date of revision of the text

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