1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

IMMAROC (injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

Each 5 ml vial contains 50 mg rocuronium bromide. For the full list of excipients, see section 6.1.

Each ml IMMAROC contains 3.30 mg of sodium

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

IMMAROC 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. IMMAROC is also indicated as an adjunct in the Intensive Care Unit 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

IMMAROC should only be administered by, or under supervision of, experienced medical practitioners who are familiar with the action and use of these medicines.

The dosage of IMMAROC 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 medication that is administered concomitantly, 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 for the evaluation of neuromuscular block and recovery.

Inhalational anaesthetics potentiate the neuromuscular blocking effects of IMMAROC. 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 IMMAROC should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of IMMAROC during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (see section 4.5).

Risk of Medication Errors: Accidental administration of neuromuscular blocking agents may result in serious adverse events, including fatal outcomes. Store IMMAROC with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product (see section 4.4).

In adult patients the following dosage recommendations serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the Intensive Care Unit.

Surgical Procedures

Tracheal intubation

The standard intubating dose during routine anaesthesia is 0,6 mg/kg IMMAROC, after which adequate intubation conditions are established within 90 seconds.

A dose of 1 mg/kg IMMAROC is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia. At this dose adequate intubation conditions are established within 60 seconds in nearly all patients.

Higher doses

Should there be reason for selection of larger doses in individual patients, initial doses up to 2 mg/kg IMMAROC have been administered during surgery without adverse cardiovascular effects being noted. The use of these high dosages of IMMAROC decreases the onset time and increases the duration of action (see section 5.1).

Maintenance dosing

The recommended maintenance dose is 0,15 mg/kg IMMAROC. In the case of long-term inhalational anaesthesia, this should be reduced to 0,075 to 0,1 mg/kg IMMAROC. The maintenance doses should best 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 are present (see section 5.1).

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

Continuous infusion

If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg/kg rocuronium bromide and, when 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 neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h (300-600 micrograms/kg/h) and under inhalational anaesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Paediatric population

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

For children higher infusion rates might be necessary.

Thus, for children the same initial infusion rates as for adults are recommended and then 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 rocuronium bromide in rapid sequence induction in paediatric patients is limited. Rocuronium bromide 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 rocuronium bromide. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg/kg rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg/kg/h (see Continuous infusion). (See also section 4.4.)

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 ideal body weight.

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/kg rocuronium bromide 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 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 80-90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3-0.6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6-12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant.

A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5 mg/kg/h depending on nature and extent of organ failure(s), concomitant medication 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 Intensive Care Unit, the time to recovery of the train of four 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 train of four stimulation and recovery of the train of four 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.

Special populations

IMMAROC 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.

Method of administration

IMMAROC is administered intravenously either as a bolus injection or as a continuous infusion (see section 6.6).

4.3 Contraindications

Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients.

There is insufficient data to support recommendations for the use of IMMAROC in neonates (0 to 1 month).

IMMAROC 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.

Safety in pregnancy and lactation has not been demonstrated (see section 4.6)

4.4 Special warnings and precautions for use

Anaphylaxis

Anaphylactic and anaphylactoid reactions may occur. Precautions for treating such reactions should always be taken, particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, since allergic cross-reactivity to neuromuscular blocking agents has been reported.

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 medicines.

In clinical studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0,3 to 0,9 mg/kg IMMAROC.

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

Appropriate Administration and Monitoring

Since IMMAROC causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this medicine 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 Curarisation

Residual curarisation has been reported for IMMAROC. In order to prevent complications resulting from residual curarisation, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Elderly patients (65 years or older) may be at increased risk for residual neuromuscular block. Other factors which could cause residual curarisation 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 a reversal agent should be considered, especially in those cases where residual curarisation is more likely to occur.

Long-Term Use in an Intensive Care Unit

Following long term use of IMMAROC in the Intensive Care Unit, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of IMMAROC.

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

Myopathy after long-term administration of IMMAROC in the Intensive Care Unit, in combination with corticosteroid therapy, has been reported. Therefore, for patients receiving both IMMAROC and corticosteroids, the period of use of IMMAROC should be limited as much as possible.

Use with Suxamethonium

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

Risk of Death due to Medication Errors

Administration of IMMAROC 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.

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

Hepatic and/or biliary tract disease and renal failure

Because rocuronium is excreted in urine and bile, it 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 with doses of 0.6 mg/kg rocuronium bromide.

Prolonged circulation time

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

Neuromuscular disease

IMMAROC should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents 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 IMMAROC may have profound effects and IMMAROC should be titrated to the response.

Hypothermia

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

Obesity

IMMAROC 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-depolarising neuromuscular blocking agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of IMMAROC

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

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

4.5 Interaction with other medicines and other forms of interaction

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

Effect of other medicines on IMMAROC

Increased effect:

• Halogenated volatile anaesthetics potentiate the neuromuscular block of IMMAROC. The effect only becomes apparent with maintenance dosing (see section 4.2). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.

• After intubation with suxamethonium (see section 4.4).

• Long-term concomitant use of corticosteroids and IMMAROC in the ICU may result in prolonged duration of neuromuscular block or myopathy (see section 4.4 and 4.8).

Other medicines:

• antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.

• diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lidocaine i.v, bupivacaine epidural) and acute administration of phenytoin or ß-blocking agents.

Recurarisation 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 inhibitors (gabexate, ulinastatin).

Variable effect:

• Administration of other non-depolarising neuromuscular blocking agents in combination with IMMAROC 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 IMMAROC may produce potentiation or attenuation of the neuromuscular blocking effect of IMMAROC.

Effect of IMMAROC on other medicines

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

Paediatric population

No formal interaction studies have been performed. The above mentioned interactions for adults and their special warnings and precautions for use (see section 4.4) should be taken into account for paediatric patients.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been demonstrated.

Caesarean Section

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

Doses of 1,0 mg/kg have been investigated during rapid sequence induction of anaesthesia, but not 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 agents 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 IMMAROC should be reduced and be titrated to twitch response.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms. See also the explanations below the table.

Tabulated list of adverse reactions

MedDRA SOC	**FREQUENCY**
	Less Frequent
Immune system disorders	Hypersensitivity Angioedema
	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	Urticaria
	Rash
	Erythematous rash
Musculoskeletal and connective tissue disorders	Muscular weakness
	Steroid myopathy
General disorders and administration site conditions	Medicine ineffective
	Face oedema
	Medicine effect/ therapeutic response decreased
	Malignant hyperthemia
	Medicine effect/ therapeutic response increased
	Injection site pain
	Injection site reaction
Injury, poisoning and procedural	Prolonged neuromuscular block

complications	Airway complication of anaesthesia
	Delayed recovery from anaesthesia

Anaphylaxis

Severe anaphylactic reactions to neuromuscular blocking agents, including IMMAROC, have been reported. 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.

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 reaction at the site of injection and/or generalised histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these medicines.

In clinical studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0.3-0.9 mg/kg rocuronium bromide.

Prolonged neuromuscular block

The most frequent adverse reaction to nondepolarising blocking agents as a class consists of an extension of the drug'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 apnea.

Myopathy

Myopathy has been reported after the use of various neuromuscular blocking agents 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.

Paediatric population

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 adverse drug reaction with a frequency of 1.4%

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents, ATC code: M03AC09.

Mechanism of Action

IMMAROC (rocuronium bromide) is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of medicines (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

The ED90 (dose required to produce 90 % depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0,3 mg/kg rocuronium bromide. The ED90 in infants is lower than in adults and children (0,25, 0,35 and 0,40 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 ED90), onset of action is slower and duration of action is shorter (13 to 26 minutes). With high doses of 2 mg/kg the 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

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 T2 or at the first signs of clinical recovery, antagonises the action of rocuronium bromide.

5.2 Pharmacokinetic properties

After intravenous administration of a single bolus dose of rocuronium bromide 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 plasma clearance is 3,7 (3,5 to 3,9) ml/kg/min.

The plasma clearance in elderly patients and in patients with renal dysfunction was reduced, in most studies however without reaching 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/min.

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.

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 between patient variability is found in controlled clinical studies, related to nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean (+- SD) elimination half-life of 21,5 (+- 3,3) hours, a (apparent) volume of distribution at steady state of 1,5 (+- 0,8) l/kg and a plasma clearance of 2,1 (+- 0,8) ml/kg/min were found.

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

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

There is no proper animal model to mimic the usually extremely complex clinical situation of the ICU patient. Therefore the safety of IMMAROC when used to facilitate mechanical ventilation in the Intensive Care Unit is mainly based on results obtained in clinical studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium chloride

sodium acetate trihydrate

glacial acetic acid

6.2 Incompatibilities

Physical incompatibility has been documented for IMMAROC when added to solutions containing the following medicines: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide,

hydrocortisone sodium succinate, insulin, intralipid, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin.

IMMAROC must not be mixed with other medicinal products except those mentioned in section 6.6.

If IMMAROC 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 IMMAROC and medicines for which incompatibility with IMMAROC has been demonstrated or for which compatibility with IMMAROC has not been established.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at 2^0 to 8^0 C.

Protect from light.

IMMAROC may be stored at a temperature not exceeding 30^0 C, for a maximum period of 12 weeks. After first removal from the refrigerator, the 12 week shelf life applies.

After opening of the container the solution is chemically stable for 24 hours at room temperature. Since IMMAROC does not contain a preservative, any unused solution should be discarded.

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 has taken place in controlled and validated aseptic conditions.

Keep out of reach of children.

6.5 Nature and contents of container

A clear colourless to yellow orange solution in a pack of 5mL clear USP Type-I glass vial with 20 mm plain grey bromobutyl rubber stopper having 20 mm super green colored aluminium flip-off seal in a carton. Pack size of 1, 5, 10, 20

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Compatibility studies with the following infusion fluids have been performed: In nominal concentrations of 0.5 mg/ml and 2.0 mg/ml IMMAROC has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in saline, sterile water for injections, Lactated Ringers and Haemaccel.

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

Any unused solution should be discarded.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (PTY) LTD

Unit 1, 96 Hartley Road

Durban, 4091

8 REGISTRATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT