SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Caffeine Citrate 10mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Caffeine Citrate 10mg/ml

Each 1ml of solution contains, 10mg Caffeine Citrate, equivalent to 5mg of Caffeine.

Each 2ml of solution contains, 20mg Caffeine Citrate, equivalent to 10mg of Caffeine.

Excipient(s) with known effect

1ml of the solution contains 3.04mg sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

Appearance: clear and colourless.

pH = 2.0-3.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of apnoea of prematurity.

4.2 Posology and method of administration

Treatment with caffeine citrate should be initiated under the supervision of a physician experienced in neonatal intensive care. Treatment should be administered only in a neonatal intensive care unit in which adequate facilities are available for patient surveillance and monitoring.

Posology

The recommended doses of Caffeine Citrate 10mg/ml Solution for Injection are expressed below. Please note:

(a) the dose expressed as caffeine citrate is twice the dose expressed as caffeine base.

(b) given orally or intravenously, caffeine is clinically effective within 4 hours. If the patient fails to respond within this time, a second loading dose may be given. If there is no clinical response to the second loading dose, caffeine blood levels should be measured (see 'special warnings and precautions for use' section 4.4 below)

(c) Caffeine Citrate 10mg/ml Solution for Injection is also effective when administered orally, and this route may be used alternatively without adjusting the dose.

(d) because of the slow elimination of caffeine in this patient population, there is no requirement for dose tapering on cessation of treatment.

(e) Infants must be of sufficient respiratory maturity not to require positive pressure ventilation.

	Dose of Caffeine Citrate 10mg/ml Solution for Injection	**Dose Expressed as Caffeine Citrate**	**Dose Expressed as Caffeine Base**	**Route**	**Frequency**
Loading Dose **See (b) above**	**2ml/kg**	**20 mg/kg**	**10mg/kg**	**Intravenous** (over 30 min) or oral**	**Once**
Maintenance Dose	**0.5-1ml/kg***	**5-10mg/kg***	**2.5-5.0mg/kg***	**Intravenous** (over 10 min) or oral**	**Every 24 hours*****

* In some cases maintenance doses higher than 10mg/kg/day (expressed as caffeine citrate) may be required to achieve maximal efficacy (eg in continuing apnoeic episodes where plasma levels indicate the dose may be safely increased)

** By intravenous infusion

*** Beginning 24 hours after the loading dose(s)

Dosage, adjustments and monitoring

Plasma concentrations of caffeine may need to be monitored periodically throughout treatment in cases of incomplete clinical response or signs of toxicity.
Additionally, doses may need to be adjusted according to medical judgment following routine monitoring of caffeine plasma concentrations in at risk situations such as:
- very premature infants (< 28 weeks gestational age and/or body weight <1000 g) particularly when receiving parenteral nutrition
- infants with hepatic and renal impairment (see sections 4.4 and 5.2)
- infants with seizure disorders
- infants with known and clinically significant cardiac disease
- infants receiving co-administration of medicinal products known to interfere with caffeine metabolism (see section 4.5)
- infants whose mothers consume caffeine while providing breast milk for feeding.
It is advisable to measure baseline caffeine levels in:
- infants whose mothers may have ingested large quantities of caffeine prior to delivery (see section 4.4)
- infants who have previously been treated with theophylline, which is metabolized to caffeine.
Caffeine has a prolonged half-life in premature newborn infants and there is potential for accumulation which may necessitate monitoring infants treated for an extended period (see section 5.2). Blood samples for monitoring should be taken just before the next dose in the case of therapeutic failure and 2 to 4 hours after the previous dose when suspecting toxicity.
Although a therapeutic plasma concentration range of caffeine has not been determined in the literature, caffeine levels in studies associated with clinical benefit ranged from 8 to 30 mg/l and no safety concerns have normally been raised with plasma levels below 50 mg/l.

Duration of treatment
The optimal duration of treatment has not been established. In a recent large multicentre study on preterm newborn infants a median treatment period of 37 days was reported.

Treatment should be continued until the child has reached a gestational age of 37 weeks, by which time apnoea of prematurity usually resolves spontaneously. This limit may however be revised according to clinical judgement in individual cases depending on response to treatment, the continuing presence of apnoeic episodes despite treatment, or other clinical considerations.

Please see Section 4.4 below regarding use of the filter straws.

It is recommended that caffeine citrate administration should be stopped when the patient has 5-7 days without a significant apnoeic attack. If the patient has recurrent apnoea, caffeine citrate administration can be restarted with either a

maintenance dose or a half loading dose, depending upon the time interval from stopping caffeine citrate to recurrence of apnoea.
Because of the slow elimination of caffeine in this patient population, there is no requirement for dose tapering on cessation of treatment.
As there is a risk for recurrence of apnoeas after cessation of caffeine citrate treatment monitoring of the patient should be continued for approximately one week.

Hepatic and renal impairment
There is limited experience in patients with renal and hepatic impairment. In a post authorisation safety study, the frequency of adverse reactions in a small number of very premature infants with renal/hepatic impairment appeared to be higher as compared to premature infants without organ impairment (see sections 4.4 and 4.8).

In the presence of renal impairment, a reduced daily maintenance dose of caffeine is required and the dose should be guided by blood caffeine measurements. There is increased potential for accumulation.

In very premature infants, clearance of caffeine does not depend on hepatic function. Hepatic caffeine metabolism develops progressively in the weeks following birth and for the older infant, hepatic disease may indicate a need for monitoring plasma levels and may require dose adjustments (see sections 4.4 and 5.2).

Adults and Children

Not applicable

Elderly

Not applicable

Method of administration
Caffeine Citrate 10mg/ml Injection should not be given intramuscularly; being acidic, i.m. injection is likely to be painful. When given intravenously, it should be given as a slow infusion rather than a bolus injection; there is evidence that bolus administration may cause sudden changes in blood pressure.

4.3 Contraindications
Hypersensitivity to caffeine citrate or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Apnoea

Apnoea of prematurity is a diagnosis of exclusion. Other causes of apnoea (e.g., central nervous system disorders, primary lung disease, anaemia, sepsis, metabolic disturbances, cardiovascular abnormalities, or obstructive apnoea) should be ruled out or properly treated prior to initiation of treatment with caffeine citrate.

It is advisable to monitor plasma levels of caffeine periodically. However, at the recommended doses, frequent (more than weekly) monitoring of plasma levels is not normally necessary unless there are concerns regarding lack of efficacy or possible toxicity. In premature neonates, caffeine has a prolonged half-life. If higher maintenance dosages are used, the clinician should recognise this potential for accumulation and monitor plasma caffeine levels (see also Section 5.2).

If there is inadequate clinical response to the first loading dose, a second dose may be given, but if there is continued inadequate response, the plasma levels should be confirmed before further doses are given, as the failure to respond could be an indication of another cause of apnoea. Plasma levels should not normally exceed 50micrograms/ml (optimally 10-30micrograms/ml).

Caffeine consumption

In newborn infants born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate, since caffeine readily crosses the placenta into the foetal circulation (see sections 4.2 and 5.2). Breast-feeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine-containing foods and beverages or medicinal products containing caffeine (see section 4.6), since caffeine is excreted into breast milk (see section 5.2).

Theophylline

In newborns previously treated with theophylline, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate because preterm infants metabolise theophylline to caffeine.

Seizures

Caffeine is a central nervous system stimulant and seizures have been reported in cases of caffeine overdose. Extreme caution must be exercised if caffeine citrate is used in newborns with seizure disorders.

Cardiovascular reactions

Caffeine has been shown to increase heart rate, left ventricular output, and stroke volume in published studies. Therefore, caffeine citrate should be used with caution in newborns with known cardiovascular disease. There is

evidence that caffeine causes tachyarrhythmias in susceptible individuals. In newborns this is usually a simple sinus tachycardia. If there have been any unusual rhythm disturbances on a cardiotocograph (CTG) trace before the baby is
born, caffeine citrate should be administered with caution.

Renal and hepatic impairment
Caffeine citrate should be administered with caution in preterm newborn infants with impaired renal or hepatic function. In a post-authorisation safety study, the frequency of adverse reactions in a small number of very premature infants with renal/hepatic impairment appeared to be higher as compared to premature infants without organ impairment (see sections 4.2, 4.8 and 5.2). Doses should be adjusted by monitoring of caffeine plasma concentrations to avoid toxicity in this population.

Necrotising enterocolitis
Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for the development of necrotising enterocolitis (see section 4.8).
Caffeine citrate should be used with caution in infants suffering gastro-oesophageal reflux, as the treatment may exacerbate this condition.
Caffeine citrate causes a generalised increase in metabolism, which may result in higher energy and nutrition requirements during therapy.
The diuresis and electrolyte loss induced by caffeine citrate may necessitate correction of fluid and electrolyte disturbances.

Use of filter straws

Opening the ampoules may introduce glass particles into this solution. It is recommended that the solution be filtered prior to use by means of a suitable filter device.

Caffeine Citrate 10mg/ml Injection contains sodium

This medicinal product contains 3.04mg sodium per 1ml of the solution. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 1A2 (CYP1A2) is the major enzyme involved in the metabolism of caffeine in humans. Therefore, caffeine has the potential to interact with active substances that are substrates for CYP1A2, inhibit

CYP1A2, or induce CYP1A2. However, caffeine metabolism in preterm newborn infants is limited due to their immature hepatic enzyme systems.

Interconversion between caffeine and other xanthines such as theophylline has been reported in premature neonates. Therefore the concurrent use of these drugs should be avoided. Baseline serum levels of caffeine should be measured in patients previously treated with theophylline.

Although few data exist on interactions of caffeine with other active substances in preterm newborn infants, lower doses of caffeine citrate may be needed following co-administration of active substances which are reported to decrease caffeine elimination in adults (e.g., cimetidine and ketoconazole) and higher caffeine citrate doses may be needed following co-administration of active substances that increase caffeine elimination (e.g., phenobarbital and phenytoin). Where doubt exists about possible interactions, plasma caffeine concentrations should be measured.
As bacterial overgrowth in the gut is associated with the development of necrotising enterocolitis, co-administration of caffeine citrate with medicinal products that suppress gastric acid secretion (antihistamine H2 receptor blockers or proton-pump inhibitors) may in theory increase the risk of necrotising enterocolitis (see section 4.4 and 4.8).
Concurrent use of caffeine and doxapram might potentiate their stimulatory effects on the cardio-respiratory and central nervous system. If concurrent use is indicated, cardiac rhythm and blood pressure must be carefully monitored.

4.6 Fertility, pregnancy and lactation

Fertility

Effects on reproductive performance observed in animals are not relevant to its indication in the preterm newborn infants (see section 5.3).

Pregnancy

Caffeine in animal studies, at high doses, was shown to be embryotoxic and teratogenic. These effects are not relevant with regard to short term administration in the preterm infant population (see section 5.3).

Breast-feeding

Caffeine is excreted into breast milk and readily crosses the placenta into the foetal circulation (see section 5.2).
Breast-feeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine-containing foods, beverages or medicinal products containing caffeine.
In newborn infants born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate (see section 4.4).

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Summary of the safety profile

The known pharmacology and toxicology of caffeine and other methylxanthines predict the likely adverse reactions to caffeine citrate. Effects described include central nervous system (CNS) stimulation such as convulsion, irritability, restlessness and jitteriness, cardiac effects such as tachycardia, arrhythmia, hypertension and increased stroke volume, metabolism and nutrition disorders such as hyperglycaemia. These effects are dose related and may necessitate measurement of plasma levels and dose reduction.

They are generally, although not exclusively, associated with serum caffeine concentrations ≥50micrograms/ml.

Tabulated list of adverse reactions

The adverse reactions described in the short- and long-term published literature and obtained from a post-authorisation safety study that can be associated with caffeine citrate are listed below by System Organ Class and Preferred Term (MedDRA).
Frequency is defined as: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Sepsis	Not known
Immune system disorders	Hypersensitivity reaction	Rare
Metabolism and nutrition disorders	Hyperglycaemia	Common
	Hypoglycaemia, failure to thrive, feeding intolerance	Not known
Nervous system disorders	Convulsion	Uncommon
	Irritability, jitteriness, restlessness, brain injury	Not known
Ear and labyrinth disorders	Deafness	Not known
Cardiac disorders	Tachycardia	Common
	Arrhythmia	Uncommon
	Increased left ventricular output and increased stroke volume	Not known
Gastrointestinal disorders	Regurgitation, increased gastric	Not known

	aspirate, necrotising enterocolitis	
General disorders and administration site conditions	Infusion site phlebitis, infusion site inflammation	Common
Investigations	Urine output increased, urine sodium and calcium increased, haemoglobin decreased, thyroxine decreased	Not known

Description of selected adverse reactions
Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established.

In a double-blind placebo-controlled study of caffeine citrate in 85 preterm infants (see section 5.1), necrotising enterocolitis was diagnosed in the blinded phase of the study in two infants on active treatment and one on placebo, and in three infants on caffeine during the open-label phase of the study. Three of the infants who developed necrotising enterocolitis during the study died. A large multicentre study (n=2006) investigating long-term outcome of premature infants treated with caffeine citrate (see section 5.1) did not show an increased frequency of necrotising enterocolitis in the caffeine group when compared to placebo. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for the development of necrotising enterocolitis (see section 4.4). Brain injury, convulsion and deafness were observed but they were more frequent in the placebo group.

Caffeine may suppress erythropoietin synthesis and hence reduce haemoglobin concentration with prolonged treatment.

Transient falls in thyroxine (T4) have been recorded in infants at the start of therapy but these are not sustained with maintained therapy.

Available evidence does not indicate any adverse long-term reactions of neonatal caffeine therapy as regards neurodevelopmental outcome, failure to thrive or on the cardiovascular, gastrointestinal or endocrine systems. Caffeine does not appear to aggravate cerebral hypoxia or to exacerbate any resulting damage, although the possibility cannot be ruled out.
Other special populations
In a post-authorisation safety study on 506 preterm infants treated with Peyona, safety data have been collected in 31 very premature infants with renal/hepatic impairment. Adverse reactions appeared to be more frequent in this subgroup with organ impairment than in other observed infants without organ impairment. Cardiac disorders (tachycardia, including one single case of arrhythmia) were mostly reported.

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 via:
UK: Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Following overdose, published plasma caffeine levels have ranged from approximately 50 mg/l to 350 mg/l.

Symptoms

Signs and symptoms of overdosage from these reports include jitteriness, tachycardia, tachypnoea, tremor, opisthotonos, rigidity and tonic-clonic movements, hypokalaemia, , restlessness, , gastric irritation, gastro-intestinal haemorrhage, increased white blood cell count, non-purposeful jaw and lip movements. One case of caffeine overdose complicated by development of intraventricular haemorrhage and long-term neurological sequelae has been reported. In one case of overdose the patient developed compromised circulation, vomiting and seizures. Other reported effects of gross overdose include fever, agitation, hyperexcitability, hypertonia, gastric residues, distended abdomen, metabolic acidosis, hyperglycaemia and elevated urea levels. No deaths associated with caffeine overdose have been reported in preterm infants.

Management

Treatment of overdosage should include monitoring of blood levels of caffeine and supportive measures. Plasma potassium and glucose concentrations should be monitored and hypokalaemia and hyperglycaemia corrected.

Previous cases reported resolved satisfactorily.

In severe cases of overdose, exchange transfusion should be considered. In one case, this was found to reduce plasma caffeine levels by 40mg/L per transfusion.

Convulsions may be treated with intravenous administration of anticonvulsants (diazepam or a barbiturate such as pentobarbital sodium or phenobarbital).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics xanthine derivatives

ATC code: N06BC01

Mechanism of action

Caffeine is structurally related to the methylxanthines theophylline and theobromine. Most of its effects have been attributed to antagonism of adenosine receptors, both A_1 and A_{2A} subtypes, demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically in this indication.

Pharmacodynamic effects

The desired respirogenic activity of caffeine is an expression of its central nervous system stimulation, although it may also increase the sensitivity of respiratory response to carbon dioxide levels. Caffeine increases both tidal volume and frequency of ventilation.

In the premature infant, caffeine produced increased minute ventilation, mainly due to an increase in inspiratory drive as shown by an increased mean respiratory flow (V_T/T_1). Caffeine regularises the breathing pattern, indicating that it stabilises the oscillation of the respiratory control system.

Caffeine also inhibits phosphodiesterase, but this effect only occurs at concentrations associated with toxicity, and not at therapeutic concentrations.

Caffeine increases metabolic rate, heart rate, cardiac contractility and output. It also increases blood flow to the kidneys, and prevents sodium and chloride from reabsorbing at the proximal tubules, so mild diuresis can occur.

Adenosine is a vasodilator and therefore caffeine, as its antagonist, can cause vasoconstriction. Hence it is a vasoconstrictor in the cerebral and splanchnic circulations. Elsewhere, it has a vasodilator effect due to an effect on vascular smooth muscle.

The stimulant effect may affect sleep patterns.

Clinical efficacy and safety

The clinical efficacy of caffeine citrate was assessed in a multicentre, randomised, double-blind study that compared caffeine citrate to placebo in 85 preterm infants (gestational age 28 to < 33 weeks) with apnoea of prematurity. Infants received 20 mg/kg caffeine citrate loading dose intravenously. A maintenance daily dose of 5 mg/kg caffeine citrate was then administered either intravenously or orally (through a feeding tube) for up to 10-12 days. The protocol allowed infants to be “rescued” with open-label caffeine citrate

treatment if their apnoea remained uncontrolled. In that case, infants received a second loading dose of 20 mg/kg caffeine citrate after treatment day 1 and before treatment day 8.
There were more days without any apnoea under caffeine citrate treatment (3.0 days, versus 1.2 days for placebo; p=0.005); also, there was a higher percentage of patients with no apnoeas for $\geq$ 8 days (caffeine 22% versus placebo 0%).
A recent large placebo-controlled multicentre study (n=2006) investigated short-term and long-term (18-21 months) outcomes of premature infants treated with caffeine citrate. Infants randomised to caffeine citrate received an intravenous loading dose of 20 mg/kg, followed by a daily maintenance dose of 5 mg/kg. If apnoeas persisted, the daily maintenance dose could be increased to a maximum of 10 mg/kg of caffeine citrate. The maintenance doses were adjusted weekly for changes in body weight and could be given orally once an infant tolerated full enteral feedings. Caffeine therapy reduced the rate of bronchopulmonary dysplasia [odds ratio (95%CI) 0.63 (0.52 to 0-76)] and improved the rate of survival without neurodevelopmental disability [odds ratio (95%CI) 0.77 (0.64 to 0.93)].
The size and direction of caffeine effect on death and disability differed depending on the degree of respiratory support infants needed at randomisation, indicating more benefit for the supported infants [odds ratio (95%CI) for death and disability, see table below].
Death or disability according to subgroup of respiratory support at entry to study

Subgroups	**Odds ratio (95% CI)**
No support	1.32 (0.81 to 2.14)
Non invasive support	0.73 (0.52 to 1.03)
Endotracheal tube	0.73 (0.57 to 0.94)

5.2 Pharmacokinetic properties

Caffeine citrate readily dissociates in aqueous solution. The citrate moiety is rapidly metabolized on infusion or ingestion.

Absorption

The onset of action of caffeine from caffeine citrate is within minutes of commencement of infusion. In neonates, orally administered caffeine has been shown to be rapidly and completely absorbed. After oral administration of 10 mg caffeine base/kg body weight to preterm newborn infants, the peak plasma caffeine concentration (C_{max}) ranged from 6 to 10 mg/l and the mean time to reach peak concentration (t_{max}) ranged from 30 min to 2 h. The extent of absorption is not affected by formula feeding but t_{max} may be prolonged.

Distribution

Caffeine is rapidly distributed into the brain following caffeine citrate administration. Caffeine concentrations in the cerebrospinal fluid of preterm newborn infants approximate to their plasma levels. The mean volume of distribution (Vd) of caffeine in infants (0.8-0.9 l/kg) is slightly higher than that in adults (0.6 L/kg). Plasma protein binding data are not available for newborn

infants or infants. In adults, the mean plasma protein binding in vitro is reported to be approximately 36%.
Caffeine readily crosses the placenta into the fetal circulation and is excreted into breast milk.

Biotransformation
Caffeine metabolism in preterm newborn infants is very limited due to their immature hepatic enzyme systems and most of the active substance is eliminated in urine. Hepatic cytochrome P450 1A2 (CYP1A2) is involved in caffeine biotransformation in older individuals.
Inter-conversion between caffeine and theophylline has been reported in preterm newborn infants; caffeine levels are approximately 25% of theophylline levels after theophylline administration and approximately 3-8% of caffeine administered would be expected to convert to theophylline.

Elimination
In young infants, the elimination of caffeine is much slower than that in adults due to immature hepatic and/or renal function. In newborn infants, caffeine clearance is almost entirely by renal excretion. Mean half-life ($t_{1/2}$) and fraction excreted unchanged in urine (A_e) of caffeine in infants are inversely related to gestational / postmenstrual age. In newborn infants, the $t_{1/2}$ is approximately 3-4 days and the A_e is approximately 86% (within 6 days). By 9 months of age, the metabolism of caffeine approximates to that seen in adults ($t_{1/2}$ = 5 hours and A_e = 1%).
Studies examining the pharmacokinetics of caffeine in newborn infants with hepatic or renal insufficiency have not been conducted.
In the presence of significant renal impairment, considering the increased potential for accumulation, a reduced daily maintenance dose of caffeine is required and the doses should be guided by blood caffeine measurements. In premature infants with cholestatic hepatitis a prolonged caffeine elimination half-life with an increase of plasma levels above the normal limit of variation has been found suggesting a particular caution in the dosage of these patients (see sections 4.2 and 4.4).

5.3 Preclinical safety data
Non- clinical data revealed no major hazard for humans based on studies of repeated dose toxicity of caffeine. However, at high doses convulsions in rodents were induced. At therapeutic doses some behavioural changes in newborn rats were induced, most likely as a consequence of increased adenosine receptor expression that persisted into adulthood. Caffeine was shown to be devoid of mutagenic and oncogenic risk. Teratogenic potential and effects on reproductive performance observed in animals are not relevant to its indication in the preterm infant population.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

Sodium Hydroxide

Dilute Hydrochloric Acid

Sodium Chloride

Citric Acid

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

3 years

After opening the ampoule, the medicinal product should be used immediately.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Type I clear glass ampoule containing 1ml or 2ml in packs of 10 ampoules.

6.6 Special precautions for disposal and other handling

Only clear solution without particulate matter should be used. For single use only. Any unused solution should be discarded.

There was no detectable degradation of the solution when diluted 50/50 with commercial glucose 5%, glucose 4% saline 0.18%, and sodium chloride 0.9% infusions, when stored in disposable plastic syringes at room temperature for 4 hours.

7 MARKETING AUTHORISATION HOLDER

Macarthys Laboratories Limited T/A Martindale Pharma,
Bampton Road,
Harold Hill,
Romford,
Essex,
RM3 8UG,
United Kingdom

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