

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KAFESIT 20 mg/ml solution for infusion and oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Each ml contains 20 mg caffeine citrate equivalent to 10 mg caffeine.

Each 3 ml vial contains 60 mg caffeine citrate equivalent to 30 mg caffeine.

Excipients:

Sodium citrate dihydrate 8.3 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile solution for infusion and oral solution.

Clear, colorless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

KAFESIT is used for the short-term treatment of premature apnea in infants with 28 to < 33 weeks gestational age

4.2. Posology and method of administration

Posology/frequency and duration 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.

The recommended dose regimen in previously untreated infants is a loading dose of 20 mg caffeine citrate per kg body weight administered by slow intravenous infusion over 30 minutes, using a syringe infusion pump or other metered infusion device. After an interval of 24 hours, maintenance doses of 5 mg per kg body weight may be administered by slow intravenous infusion over 10 minutes every 24 hours. Alternatively, maintenance doses of 5 mg per kg body weight may be administered by oral administration, such as through a nasogastric tube every 24 hours.

The recommended loading dose and maintenance doses of caffeine citrate are provided in the following table which clarifies the relationship between injection volumes and administered doses expressed as caffeine citrate.

The dose expressed as caffeine base is one-half the dose when expressed as caffeine citrate (20 mg caffeine citrate are equivalent to 10 mg caffeine base).

	Dose of caffeine citrate (Volume)	Dose of caffeine citrate (mg/kg body weight)	Route of administration	Frequency
Loading dose	1.0 ml/kg body weight	20 mg/kg body weight	Intravenous* infusion (over 30 minutes) or by oral administration	Once
Maintenance dose	0.25 ml/kg body weight	5 mg/kg body weight	Intravenous* infusion (over 10 minutes) or by oral administration	Every 24 hours**

* using a syringe infusion pump

** Beginning 24 hours after the loading dose

In preterm newborn infants with insufficient clinical response to the recommended loading dose, a second loading dose of 10 -20 mg/kg maximum may be given after 24 hours.

Higher maintenance doses of 10 mg/kg body weight could be considered in case of insufficient response, taking into account the potential for accumulation of caffeine due to the long half- life in preterm newborn infants and the progressively increasing capacity to metabolize caffeine in relation to post-menstrual age (see section 5.2). Where clinically indicated, caffeine plasma levels should be monitored. The diagnosis of apnea of prematurity may need to be reconsidered if patients do not respond adequately to a second loading dose or maintenance dose of 10 mg/kg/day (see section 4.4).

When given intravenously, caffeine citrate should be administered by controlled intravenous infusion, using a syringe infusion pump or other metered infusion device only. Caffeine citrate can be either used without dilution or diluted in sterile solutions for infusion such as glucose 50 mg/ml (5%), or sodium chloride 9 mg/ml (0.9%) or calcium gluconate 100 mg/ml (10%) immediately after withdrawal from the vial (see section 6.6).

Routine monitoring of plasma caffeine levels is not required in the majority of preterm infants. However, 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 multicenter study on preterm newborn infants a median treatment period of 37 days was reported. In clinical practice, treatment is usually continued until the infant has reached a post-menstrual age of 37 weeks, by which time apnea of prematurity usually resolves spontaneously. This limit may however be revised according to clinical judgment in individual cases depending on the response to treatment, the continuing presence of apneic episodes despite treatment, or other clinical considerations. It is recommended that caffeine citrate administration should be stopped when the patient has 5-7 days without a significant apneic attack.

If the patient has recurrent apnea, 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 apnea.

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 apneas after cessation of caffeine citrate treatment monitoring of the patient should be continued for approximately one week.

Method of administration:

Caffeine citrate can be administered by intravenous infusion and by the oral route. The product must not be administered by intramuscular, subcutaneous, intrathecal or intraperitoneal injection.

If it will be administered orally, doses may be given orally or through a feeding tube every 24 hours.

Additional information on special populations:

Renal/Hepatic failure:

There is limited experience with patients with renal and hepatic failure. In a post-marketing safety study, the incidence of adverse reactions was higher in a small number of premature

infants with renal / hepatic failure compared to premature infants without organ failure (see sections 4.4 and 4.8).

In the presence of renal impairment, there is increased potential for accumulation. A reduced daily maintenance dose of caffeine citrate is required and the dose should be guided by plasma caffeine measurements.

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 infants, hepatic disease may indicate a need for monitoring caffeine plasma levels and may require dose adjustments (see sections 4.4 and 5.2).

Pediatric population:

KAFESIT is intended for use in newborn infants.

Geriatric population:

No data are available.

4.3. Contraindications

KAFESIT is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

4.4. Special warnings and precautions for use

Apnea of prematurity is a diagnosis of exclusion of the other causes of apnea. Other causes of apnea (e.g., central nervous system disorders, primary lung disease, anemia, sepsis, metabolic disturbances, cardiovascular abnormalities, or obstructive apnea) should be ruled out or properly treated prior to initiation of treatment with caffeine citrate. Failure to respond to caffeine treatment (confirmed if necessary by measurement of plasma levels) could be an indication of another cause of apnea.

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).

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

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.

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.

Caffeine citrate should be administered with caution in preterm newborn infants with impaired renal or hepatic function. In a post-marketing safety study, the incidence of adverse reactions was higher in a small number of premature infants with renal / hepatic failure compared to premature infants without organ failure (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.

Necrotizing 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 necrotizing enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotizing enterocolitis has not been established. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for the development of necrotizing enterocolitis (see section 4.8).

Caffeine citrate should be used with caution in infants suffering gastro-esophageal reflux, as the treatment may exacerbate this condition.

Caffeine citrate causes a generalized 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.

This medicinal product contains less than 1 mmol (23 mg) of sodium per each dose, i.e. essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

Inter-conversion between caffeine and theophylline occurs in preterm newborn infants. These active substances should not be used concurrently.

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.

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.*

KAFESIT should not be used in combination with acyclovir, furosemide, ibuprofen lysine, lorazepam, nitroglycerin and oxacillin.

4.6. Pregnancy and lactation

General recommendation:

Pregnancy category: C

Women of childbearing potential/Contraception:

No data are available.

Pregnancy:

There is not sufficient data on the use of KAFESIT in pregnant women. Studies conducted on animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown.

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).

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).

Lactation:

Caffeine is excreted into breast milk and readily crosses the placenta into the fetal 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.

Reproductive ability/Fertility:

No data are available.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

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 pulse volume, metabolism and nutrition disorders such as hyperglycemia. These effects are dose related and may necessitate measurement of plasma levels and dose reduction.*

The adverse reactions described in the short- and long-term published literature that can be associated with caffeine citrate and obtained from a post-authorization safety study are listed below by System Organ Class and Preferred Term (MedDRA)

Frequency is defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$), very rare ($<1/10,000$) and not known (cannot be estimated from the available data).

Infections and infestations

Not known: Sepsis

Immune system disorders

Rare: Hypersensitivity reaction

Metabolism and nutrition disorders

Common: Hyperglycemia

Not known: Hypoglycemia, failure to thrive, feeding intolerance

Nervous system disorders

Uncommon: Convulsion*

Not known: Irritability, jitteriness, restlessness, brain injury*

Ear and internal ear disorders

Not known: Deafness*

Cardiac disorders

Common: Tachycardia

Uncommon: Arrhythmia

Not known: Increased left ventricular output and increased pulse volume

Gastrointestinal disorders

Not known: Regurgitation, increased gastric aspirate, necrotizing enterocolitis**

General disorders and administration site conditions

Common: Infusion site phlebitis, infusion site inflammation

Laboratory parameters

Not known: Urine output increased, urine sodium and calcium increased, hemoglobin decreased, thyroxine decreased

*Brain injury, convulsion and deafness were observed but they were more frequent in the placebo group.

**See below.

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

Transient falls in thyroxine 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 and resulting brain damage, although the possibility cannot be ruled out.

Necrotizing enterocolitis

Necrotizing 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 necrotizing 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), necrotizing 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 necrotizing enterocolitis during the study died. A large multicenter 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 necrotizing 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 necrotizing enterocolitis (see section 4.4).

Other special populations

In a post-authorization safety study conducted on 506 preterm infants treated with caffeine citrate, safety data were collected in 31 preterm infants with renal / hepatic failure. Adverse reactions were more common in infants in the sub-group with organ failure compared to infants without organ failure. Mostly heart diseases (tachycardia, arrhythmia in a single case) have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 800 314 00 08; fax: 0 312 218 35 99)

4.9. Overdose

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

Signs and symptoms reported in the literature after caffeine overdose in preterm infants include hyperglycemia, hypokalemia, fine tremor of the extremities, restlessness, hypertonia, opisthotonus (prolonged contraction state), tonic clonic movements, seizures, tachypnea, tachycardia, vomiting, gastric irritation, gastro-intestinal hemorrhage, pyrexia, jitteriness, increased blood urea and increased white blood cell count, non-purposeful jaw and lip movements. One case of caffeine overdose complicated by development of intraventricular hemorrhage and long-term neurological sequelae has been reported. No deaths associated with caffeine overdose have been reported in preterm infants.

Treatment of caffeine overdose is primarily symptomatic and supportive. Plasma potassium and glucose concentrations should be monitored and hypokalemia and hyperglycemia

corrected. Plasma caffeine concentrations have been shown to decrease after exchange 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: Xanthine Derivatives (CNS stimulants)

ATC code: N06BC01

Caffeine is structurally related to the methylxanthines theophylline and theobromine.

Most of its effects have been attributed to antagonism of adenosine receptors, both A1 and A2A subtypes, demonstrated in receptor binding assays and observed at concentrations approximating those achieved therapeutically in this indication.

Caffeine's main action is as a central nervous system stimulant. This is the basis of caffeine's effect in apnea of prematurity, for which several mechanisms have been proposed for its actions including: (1) respiratory center stimulation, (2) increased minute ventilation, (3) decreased threshold to hypercapnia, (4) increased response to hypercapnia, (5) increased skeletal muscle tone, (6) decreased diaphragmatic fatigue, (7) increased metabolic rate, and (8) increased oxygen consumption.

The clinical efficacy of caffeine citrate was assessed in a multicenter, randomized, double-blind study that compared caffeine citrate to placebo in 85 preterm infants (gestational age 28 to <33 weeks) with apnea 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 transfer of infants to open-label caffeine citrate treatment if their apnea 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 apnea 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 apneas for > 8 days (caffeine 22% versus placebo 0%).

A recent large placebo-controlled multicenter study ($n=2006$) investigated short-term and long-term (18-22 months) outcomes of premature infants treated with caffeine citrate. Infants randomized to caffeine citrate received an intravenous loading dose of 20 mg/kg, followed by a daily maintenance dose of 5 mg/kg.

If apneas 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% Confidence interval) 0.63 (0.52 to 0.76)] and improved the rate of survival without neurodevelopmental disability [odds ratio (95% Confidence interval) 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 randomization, indicating more benefit for the supported infants [odds ratio (95% Confidence interval) for death and disability, see table below].

Death or disability according to respiratory support at entry to study

Subgroups	Odds ratio (95% Confidence interval)
No support	1.32 (0.81-2.14)
Noninvasive support	0.73 (0.52-1.03)
Endotracheal tube	0.73 (0.57-0.94)

5.2 Pharmacokinetic properties

General characteristics

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. 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 (V_d) 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 behavioral 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

Citric acid monohydrate
Sodium citrate dihydrate
Water for injections

6.2. Incompatibilities

This medicinal product must not be mixed or concomitantly administered in the same intravenous line with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

60 months

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

From a microbiological point of view, when administered with solutions for infusion the medicinal product should be used immediately after dilution by aseptic technique.

6.4. Special precautions for storage

Store at room temperature under 25°C.

For storage conditions of the diluted medicinal product see section 6.3.

6.5. Nature and contents of container

KAFESIT is presented in the colorless glass (Type I) vial closed with a teflon-coated rubber stopper and flip-off aluminum cap.

Each box contains 1 or 10 vials of 3 ml.

6.6. Special precautions for disposal and other handling

Aseptic technique must be strictly observed throughout handling of the medicinal product since no preservative is present.

Caffeine citrate should be inspected visually for particulate matter and discoloration prior to administration. Vials containing discolored solution or visible particulate matter should be discarded.

Caffeine citrate can be either used without dilution or diluted in sterile solutions for infusion such as glucose 50 mg/ml (5%) or sodium chloride 9 mg/ml (0.9%) or calcium gluconate 100 mg/ml (10%) immediately after withdrawal from the vial.

The diluted solution must be clear and colorless. All parenteral solutions must be inspected visually for particulate matter and discoloration prior to administration. The solution must not be used if it is discolored or foreign particulate matter is present

For single use only. Any unused portion left in the vial should be discarded.

Unused portions should not be saved for later administration.

No special requirements for disposal.

Unused products or waste materials must be discarded in accordance with the “Regulation on control of the medical waste” and “Regulations on control of the packaging wastes.

7. MARKETING AUTHORISATION HOLDER

Berko İlaç ve Kimya Sanayi A.Ş.

Yenişehir Mah. Özgür Sok. No: 16-18 Ataşehir/İstanbul

0 216 456 65 70 (Pbx)

0 216 456 65 79 (Fax)

info@berko.com.tr

8. MARKETING AUTHORISATION NUMBER

241/95

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 26.04.2012

Date of latest renewal: 29.03.2019

10. DATE OF REVISION OF THE TEXT

30.06.2018