SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

POLAMİNOFEN 10 mg/ml Solution for I.V. Infusion

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Paracetamol 10 mg/ml

Excipient(s):

Mannitol ..... 38.5 mg/ml

Disodium phosphate dihydrate..... 0.13 mg/ml

Sodium hydroxide (pH adjustment) ..... q.s.

For a full list of excipients, see section 6.1

Electrolyte density (For each Litre)

Sodium:1.46 mmol

Phosphate: 0.73 mmol

Chloride:1.4 mmol

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colorless or slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

POLAMINOFEN is indicated for the short-term treatment of moderate pain (especially following surgery), and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

4.2 Posology and method of administration

It is recommended that a suitable analgesic oral treatment be used as soon as the patient can receive drugs via this route of administration.

The 100 ml bag is restricted to adults, adolescents, and children weighing more than 33 kg.

Single dose or repeat doses can be administered for acute pain or fever.

Posology/frequency and duration of administration:

The paracetamol solution is administered as a 15-minute intravenous infusion.

It is recommended as 10-15 mg/kg/dose (500 mg once a day for over children 30 kg) for every 6 hours, 60 mg/kg (maximum 2 g daily maximum dose for children over 30 kg). Minimum dose range should be 4 hours and not be given more than 4 times in a day.

Dosing based on patient weight. Recommended dose adjustments are listed in the table below.

Patient weight	Dose per administration	Volume per administration	Maximum dose (based on upper weight limit)	Maximum Daily Dose**
≤10 kg *	7.5 mg/kg	0.75 ml/kg	7.5 ml	30 mg/kg
>10 kg and ≤33kg	15 mg/kg	1.5 ml/kg	49.5 ml	60 mg/kg maximum 2 g
>33 kg and ≤50kg	15 mg/kg	1.5 ml/kg	75 ml	60 mg/kg maximum 3 g
>50kg with additional risk factors for hepatotoxicity	1 g	100 ml	100 ml	3 g
>50kg and no additional risk factors for hepatotoxicity	1 g	100 ml	100 ml	4 g

*Data on the use in newborn infants is very limited and the definitive dose has not been established. Use in preterm infants less than 32-weeks old is not recommended.
In patients with creatinine clearance ≤30 mL/min, the daily dose should be reduced and the interval between each administration should be increased.

**The minimum interval between each dose should be 4 hours. In patients with renal impairment, this interval should not be less than 6 hours. The number of doses administered within 24 hours shall not exceed 4.
Severe Renal Impairment:
When giving paracetamol to patients with severe renal impairment (creatinine clearance ≤30 mL/min), the minimum interval between each administration should be increased to 6 hours (See section 5.2).
In adults with hepatocellular impairment, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration: Maximum daily dose should be 3 g (See section 4.4).

Entire bag of 100 ml (1000 mg) should not be used in patients under 50 kg, as it can cause dosing error (overdose).
Pediatric doses up to 60 ml are administered over a period of 15-minutes, using a syringe.

Method of administration:
The paracetamol solution is administered as a 15-minute intravenous infusion.

When prescribing POLAMINOFEN, care should be exercised to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and/or death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both, the total dose in mg and the total dose in volume.

In order to prevent dosing errors in the newborn and infants (≤ 10 kg) and to avoid confusing milligrams (mg) and milliliters (mL) for each other, it is recommended to determine the volume to be administered in milliliters (mL). The volume (10 mg/mL) of POLAMINOFEN administered in patients in this group of weight should never exceed 7.5 mL. Very small volumes will be required in the newborn and infants (≤ 10 kg).

A 5 or 10 mL syringe should be used to measure the dose as appropriate for the weight of the child and the desired volume.

The entire product should not be connected to the infusion kit as this would result in overdose in patients ≤ 10 kg. The volume to be administered should be withdrawn to the syringe and diluted in a 0.9% sodium chloride solution or 5% glucose solution up to one ninth (1 volume POLAMINOFEN into 9 volumes diluent) and administered via infusion over minimum 15 minutes.
As with all solutions for infusion presented in polypropylene bags, close monitoring is recommended particularly at the end of the infusion. Monitoring near the end of the infusion applies particularly for infusions via the central venous route, in order to avoid air embolism.

Additional information on special populations:
Renal insufficiency: In patients with severe renal impairment (creatinine clearance ≤30 mL/min), the minimum interval between each administration should be 6 hours (see *Section 5.2*).
Hepatic insufficiency: Dose should not exceed 3 g/day in patients with chronic or active hepatic disease, and particularly patients with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserve of hepatic glutathione), and dehydration (*see Section 5.2*).

Pediatric population: The 100 ml bag is restricted to children weighing more than 33 kg.
Data on the use in newborn infants is very limited and the definitive dose has not been established. Use in preterm infants less than 32-weeks old is not recommended.

In order to prevent dosing errors in the newborn and infants (≤ 10 kg) and to avoid confusing milligrams (mg) and milliliters (mL) for each other, it is recommended to determine the volume to be administered in milliliters (mL). The volume (10 mg/mL) of POLAMINOFEN administered in patients in this group of weight should never exceed 7.5 mL. Very small volumes will be required in the newborn and infants (≤ 10 kg).

A 5 or 10 mL syringe should be used to measure the dose as appropriate for the weight of the child and the desired volume.

Geriatric population: No dose adjustment is necessary in elderly patients (*see Section 5.2*.)
The daily dose of paracetamol should not exceed 2000 mg due to the risk of hepatotoxicity in alcohol users.
Alcohol: Due to the risk of hepatotoxicity, the dose of paracetamol administered to individuals who consume alcohol should not exceed 2 g/day.

4.3 Contraindications

POLAMINOFEN is contraindicated in:

- Patients with hypersensitivity to paracetamol, propacetamol hydrochloride (prodrug of paracetamol), or any of the excipients
- Cases of severe hepatic insufficiency or active hepatic disease.

4.4 Special warnings and precautions for use

Risk of Treatment Error: Care should be exercised to avoid dosing errors due to confusion between milligram (mg) and milliliter (mL), which could result in accidental overdose and death.

It is recommended that a suitable analgesic oral treatment be used as soon as this route of administration is possible.

In order to avoid the risk of overdose, it should be checked that no other medicines containing paracetamol are administered at the same time.

Doses higher than those recommended entail the risk of very serious liver damage. Initial clinical signs and symptoms of liver damage are usually seen after two days, and up to a maximum of 4-6 days after. Treatment with antidote should be given as soon as possible (*see section 4.9*.).

Rash, urticaria or a skin infection may occur in patients using paracetamol for the first time or with a history of paracetamol. In this case, the drug should be discontinued and an alternative treatment should be switched after consulting with a doctor. Patients who experience skin reactions with paracetamol should not use this drug or any other drug containing paracetamol. This can lead to severe and fatal skin reactions, including Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).

Paracetamol should be used carefully in:

- Hepatic insufficiency,
- Severe renal insufficiency (creatinine clearance ≤30 mL/min) (*see Section 4.2 and Section 5.2*),
- Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency (may cause hemolytic anemia),
- Chronic alcoholism, excess alcohol consumption (3 or more glasses of alcoholic drinks/day),
- Anorexia, bulimia or cachexia, chronic malnutrition (low reserves of hepatic glutathione),
- Dehydration, hypovolemia
- It should be used with caution under doctor's supervision in patients with anemia, lung disease, liver and kidney dysfunction.
- Acute high dose causes serious liver toxicity.
- In adults, chronic daily doses may cause liver damage.
- It should be used with caution in alcoholic liver patients.

Use with caution and under supervision of a doctor in patients with anemia, hepatic and renal dysfunction.

Acute high doses result in severe hepatotoxicity.
Daily doses in adults can result in hepatic damage.

Care should be exercised when used in hepatic patients with alcoholism.
Due to the risk of hepatotoxicity, the dose of paracetamol administered to individuals who consume alcohol should not exceed 2000 mg/day.

This medicinal product contains <1 mmol sodium (23 mg) in each 100 mL, i.e., essentially "sodium-free."

4.5 Interactions with other medicinal products and other forms of interaction

Concomitant administration of POLAMINOFEN with other medicines can increase the risk of undesirable effects.

Concomitant administration with phenytoin may reduce the efficacy of paracetamol and increase the risk of hepatotoxicity. Administration of high doses and/or chronic paracetamol

should be avoided in patients receiving fenitoin treatment. Patients should be monitored in terms of hepatotoxicity.

Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction in the paracetamol dose should be considered if it is to be used concomitantly with probenecid.

Salicylamide may prolong the elimination half-life of paracetamol. For short-term use, it is recommended that the combined dose of paracetamol and salicylates does not exceed the recommended dose of paracetamol or salicylate alone. Diflunisal may increase paracetamol-induced hepatotoxicity risk by increasing the plasma concentration of paracetamol by 50%.

Care should be exercised when taking together enzyme-inducing substances. Without limitation, these substances may include barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin+clavulanic acid, and ethanol.

Anticonvulsants such as phenytoin, barbiturates, and carbamazepine may increase paracetamol-induced hepatotoxicity due to increased conversion of paracetamol to hepatotoxic metabolites. There is an increased risk of paracetamol-induced hepatotoxicity in patients receiving paracetamol higher than the recommended doses during anticonvulsant use.

Patients with chronic alcoholism should be cautioned against regular and overuse of paracetamol, or avoiding chronic alcohol consumption, since there is a set of evidence that excessive consumption of alcohol increases the risk of paracetamol-induced hepatotoxicity.
Prolonged co-administration of paracetamol with anticoagulants (coumarin or indanthion derivatives) at high doses can potentially increase anticoagulant activity due to reduced hepatic synthesis of procoagulant factors. Anticoagulant dose adjustment may be necessary if prolonged prothrombin time is observed when paracetamol therapy is initiated or terminated. This does not apply in rare cases of use or chronic doses below 2 g/day.

Although the mechanism of its interaction is not fully understood, concomitant use of isoniazid with paracetamol may increase the risk of hepatotoxicity.

Anticoagulants: Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to variations of INR values. In this case, increased monitoring of INR values should be conducted during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: B

Women with childbearing potential/Birth control (Contraception)

There is insufficient data on the use of POLAMINOFEN in women with childbearing potential.

Pregnancy

There is insufficient data on the exposure during pregnancy for intravenous use of paracetamol.

Studies on animals do not show any direct or indirect harmful effects on pregnancy/embryonic/fetal development/birth or postnatal development.

Caution should be exercised when administering to pregnant women.

The use of POLAMINOFEN during pregnancy is recommended only if the benefit outweighs the possible risks.

During pregnancy, the recommended posology and duration must be strictly observed.

Prospective data on pregnancies exposed to overdose do not demonstrate increased risk of malformation.

Breast-feeding

After oral administration, paracetamol is excreted into breast milk (passes into the milk) in small quantities. No undesirable effects on nursing infants have been reported. Care should be exercised when using POLAMINOFEN in nursing mothers.

Reproducibility/Fertility

No reproductive studies with the intravenous form of paracetamol have been performed in animals. There is no sufficient data to demonstrate whether paracetamol has any effect on fertility.

4.7 Effects on ability to drive and use machines

It is not known whether POLAMINOFEN affects the ability to drive and use machines. However, it may cause nausea or vomiting in some individuals (*see Section 4.8*). Therefore, patients should be cautioned.

4.8 Undesirable effects

Clinical experience

As with other medicines containing paracetamol, adverse reactions reported in clinical trials with POLAMINOFEN were also rare or very rare:

The frequency is defined using the following convention:

Very common (≥ 1/10); common (≥ 1/100 to 1/10); uncommon (≥ 1/1,000 to 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very Rare: Thrombocytopenia, Leucopenia, Neutropenia

Cardiac disorders

Rare: Hypotension

Hepatobiliary disorders

Rare: Increased levels of hepatic transaminases

General disorders and administration site conditions

Rare: Malaise

Very Rare: Hypersensitivity reaction

Post-marketing experience

The adverse effects listed below have been reported during post-marketing experience, but their incidence is unknown:

Blood and lymphatic system disorders

Not known: Thrombocytopenia

Immune system disorders

Not known: Anaphylactic shock, anaphylaxis, hypersensitivity reaction, angioneurotic (Quincke's) edema

Cardiac disorders

Not known: Tachycardia

Gastrointestinal disorders

Not known: Nausea, vomit

Hepatobiliary disorders

Not known: Fulminant hepatitis, hepatic necrosis, liver failure, liver enzymes increased

Skin and subcutaneous tissue disorders

Rare: Skin rash, itching, urticaria, allergic edema and angioedema, acute generalized exanthematous pustulosis, erythema multiforme, Steven-Johnson syndrome and toxic necrolysis (including fatal outcome).

General disorders and administration site conditions

Not known: Administration site reactions

4.9 Overdose and management

There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdosing may be fatal in these cases.

Overdose, 7.5 g or more of paracetamol in a single administration in adults or 140 mg/kg of body weight in a single administration in children, causes hepatic cytolysis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Moreover, the damage caused by overdosing is greater in subjects with non-cirrhotic alcoholic liver disease. The paracetamol half-life, which is around 2 hours in normal adults with paracetamol overdose with liver cell damage, usually lasts for 4 hours or more. Diminution of $^{14}CO_2$ excretion after ^{14}C-aminopyridine has been reported. This correlates better with liver cell damage in paracetamol overdosage than does either plasma paracetamol concentration or half-life, or conventional liver function test measurements.

Development of acute tubular necrosis after paracetamol-induced fulminant liver failure can result in acute renal failure. However, incidence is less common in this group of patients when compared with patients with fulminant hepatic failure due to other reasons. Rarely, renal tubular necrosis can occur with minimal hepatic toxicity only 2-10 days after taking the drug. Chronic alcohol consumption of a patient with paracetamol overdose has been reported to contribute to acute pancreatitis. In addition to acute overdose, liver damage and nephrotoxic effects have been reported after daily overdose of paracetamol.

Signs and symptoms: Common early symptoms (generally appear within the first 24 hours) of paracetamol overdose comprise nausea, vomiting, anorexia, pallor and abdominal pain. Hepatic necrosis is a dose-related complication of paracetamol overdose. While hepatic enzymes (hepatic transaminase level (AST, ALT), lactate dehydrogenase, and bilirubin) may elevate and prothrombin may be prolonged within 12 to 48 hours, no clinical symptoms may appear for 1 to 6 days following drug ingestion.

Clinical symptoms of liver damage usually occur within 2 days and reach maximum levels within 4-6 days.

Management: Patient should be immediately hospitalized. Before beginning treatment, take a blood sample for plasma paracetamol assay, as soon as possible after the overdose. The paracetamol overdose should be treated immediately to protect the patient against delayed hepatotoxicity. The treatment includes administration of N-acetylcysteine by the i.v route (if possible before the 10th hour) or oral methionine after decreasing absorption (gastric lavage or active charcoal). Methionine should not be used if there is vomiting or if the patient has already been treated with activated charcoal. Peak plasma concentrations of paracetamol may be delayed for up to 4 hours following the overdose. For this reason, plasma paracetamol levels should be measured at least 4 hours after drug ingestion to determine the risk of hepatotoxicity. Additional treatment (supplemental oral methionine or intravenous N-Acetylcysteine) should be considered for serum paracetamol levels and the time since drug intake. Treatment of fulminant hepatic insufficiency which may develop after paracetamol overdose may require specialization. Symptomatic treatment should be applied.
Hepatic tests should be performed at the beginning of treatment and repeated for every 24 hours. In many cases, hepatic transaminase levels return to normal within 1 to 2 weeks. Very severe conditions may require liver transplant.

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic particulars

Pharmacotherapeutic group: Other analgesics and antipyretics
ATC code: N02BE01

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

POLAMONIFEN provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.

POLAMONIFEN reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

5.2 Pharmacodynamic particulars

Mechanism of action

Absorption:

The bioavailability of paracetamol following infusion of 1g of paracetamol is similar to that observed following infusion of propacetamol (containing 1 g paracetamol).

The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15-minute intravenous infusion of 1 g of paracetamol is about 30µg/ml.

Distribution:

The volume of distribution of paracetamol is approximately 1 L/kg and it is not extensively bound to plasma proteins. Following infusion of 1 g paracetamol, significant concentrations of paracetamol (about 1.5µg/mL) were observed in the cerebrospinal fluid at and after the 20th minute following infusion.

Metabolism:

Paracetamol in the adults is metabolized mainly in the liver following two major hepatic pathways; glucuronic acid conjugation and sulfuric acid conjugation. The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine). This, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, during massive overdosing, the quantity of this toxic metabolite is increased.

Elimination:

The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted within 24 hours, mainly as glucuronide (60-80%) and sulphate (20-30%) conjugates. Less than 5% is eliminated unchanged.

Plasma half-life is 2.7 hours and total body clearance is 18 L/h.

Linearity/non-linearity:

Paracetamol pharmacokinetics is linear up to 2 g following single administration and repeated administrations within 24 hours.

Special populations

Renal insufficiency: In cases of severe renal impairment (creatinine clearance ≤ 10-30 mL/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulfate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, when giving paracetamol to patients with severe renal impairment (creatinine clearance ≤30mL/min), the minimum interval between each administration should be increased to 6 hours (*see Section 4.2*).

Hepatic insufficiency: Paracetamol has been studied in patients with hepatic impairment. In one study, paracetamol was given at 4 g daily for 5 days in six patients with chronic stable liver failure. Paracetamol concentrations determined midway of the third and fourth dose at 1 g/day varied between 4.5µg/ml and 26.7µg/ml, which are well below the toxic levels. No significant paracetamol accumulation was observed and there was no change in the clinical status or laboratory values of the patients. Mean elimination half-life was 3 to 4 hours which did not significantly differ from that reported in healthy individuals. In the same study, 20 additional subjects with chronic stable liver failure were randomized to a double-period cross-over study and received a dose of 4 g daily for 13 days. There has been an increase in liver function tests (LFTs) in one subject, but no abnormality has been observed in two consecutive applications after this episode has been resolved. It was concluded that these LFTs were not drug-related and that the use of paracetamol at therapeutic doses in patients with chronic stable hepatic insufficiency is not contraindicated.

Several clinical studies have shown a slightly impaired metabolization of paracetamol in patients with hepatic insufficiency including alcoholic cirrhosis. This was demonstrated by the increase in plasma concentrations of paracetamol and the prolonged elimination half-life. In these reports, the increase in plasma half-life of paracetamol is associated with a decrease in the synthetic capacity of the liver. As a result, paracetamol should be used with caution in patients with hepatic insufficiency and is contraindicated in the presence of active disease, especially alcoholic cirrhosis, caused by CYP2E1 induction.

Pediatric population: The pharmacokinetic parameters of paracetamol in infants and children 0-1 year-old are similar to those observed in adults, with plasma half-lives being 1.5-2 hours

shorter than adults. The plasma half-life in the newborn is about 3.5 hours longer than that of infants 0-1 year-old.
Less glucuronides and more sulfate conjugates are eliminated in neonates, infants 0-1 year-old, and children up to 10 year-old than in the adult. Total excretion of paracetamol and its metabolites is identical in all ages.
Elderly: The pharmacokinetics and the metabolism of paracetamol are not modified in elderly subjects. No dose adjustment is required in this population.

5.3 Preclinical safety data

Carcinogenicity, mutagenicity, teratogenicity

The effect of paracetamol in the diet of rats and mice was studied for 2 years at 0, 600, 3000 and 6000 PPM. Paracetamol was non-carcinogenic in male rats as well as male and female mice. Carcinogenic activity has been suspected in female rats due to an increase in the incidence of mononuclear cell leukemia.

A comparative review of literature on genotoxicity and carcinogenicity of paracetamol, has shown that the genotoxic effects of paracetamol occurred only at doses above the recommended range, and resulted in severe liver and bone marrow toxicity. At therapeutic doses of paracetamol, the genotoxicity threshold has not been reached.

Animal toxicity

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC. Studies on local tolerance of POLAMINOFEN in rats and rabbits showed good tolerability.

Absence of delayed contact hypersensitivity has been tested in guinea pigs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Cysteine hydrochloride monohydrate
Disodium phosphate dihydrate
Sodium hydroxide
Water for injection

6.2 Incompatibilities

POLAMINOFEN must not be mixed with other medicinal products (*see Section 4.5*).

6.3 Shelf life

24 months

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Use within one hour after dilution with 0.9% sodium chloride and 5% dextrose solutions.

The maximum usability of unpacked or diluted solutions of POLAMINOFEN is not longer than 1 hour including the period of infusion.

6.4 Special precautions for storage

Store at room temperatures below 25°C and in original container.

Do not refrigerate or freeze.

Keep in the bag in aluminum outer pack. Used immediately after opening the outer packaging.

6.5 Nature and contents of container

POLAMINOFEN 10 mg/ml Solution for IV Infusion is available in non-set form in 100 ml PP bags inside a transparent outer bag.

Pack size: Single bag and 12 bags per carton.

6.6 Special precautions for disposal and other handling

Before administration, the product should be visually inspected for any particulate matter and discoloration. For single use only. Any unused solution should be discarded.

Due to sterilization, moisture can occur between the bag and the outer packaging. This does not affect the quality of the solution.

Do not dispose expired or unused medicines via the household waste! Send them to a waste collection system designated by the Ministry of Environment and Urbanization.

Instructions for Use

Check the solution before use.

The solution is administered by intravenous infusion through sterile and non-pyrogenic sets.

Use only products that are clear, free from particles and with intact package integrity.

Administer shortly after insertion of the infusion set.

Do not connect other solutions for infusion in series in order to avoid air embolism due to possible residual air contained in the bag.

Use an aseptic method to set up the infusion and administer the solution. The delivery kit should be primed with the solution in order to prevent air entering the system.

Additive medications can be added before and during the infusion, in aseptic conditions using a needle at the injection tip. Verify isotonicity of the final product prior to parenteral administration.

Thorough mixing of any additive is mandatory before administered to the patient. Solutions containing additive medicines should be used immediately and not stored for later use.

Adding other medication or using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In case of adverse reaction, infusion must be stopped immediately.

Do not store partially used solutions.

Do not reconnect partially used bags to any systems for administration to patients.

Opening:

1. Check the outer package for firmness and tightness, and discard if damaged.
2. Tear to open the protective outer pack.
3. Check the inner bag inside the protective pack for firmness by squeezing. Check the solution inside the bag for clarity and absence of foreign matter.

Preparation for administration:

1. Suspend the bag.
2. Remove the protective cap on the delivery tip.
3. Tightly press the spike of the administration kit onto the delivery tip.
4. Strictly observe the kit's usage instructions when administering the solution to the patient.

Addition of additive medication:

Caution: As with all parenteral solutions, additives to be added to the solution must be compatible with the product. In case of any additives, compatibility must be checked during the final mix before the solution is administered to the patient.

Adding medication prior to administration

1. Disinfect the drug delivery tip.
2. Spike the medication to be added into the bag via the syringe with 19-22 gauge needle.
3. Mix solution and medication thoroughly. To mix with concentrated medicines such as potassium chloride, gently tap on the delivery tip of the bag while in upright position

Caution: Bags spiked with medication should be discarded.

Adding medication during administration

1. Close clamp on the set.
2. Disinfect the drug delivery tip.
3. Administer the drug to be added via the drug delivery tip fitted to a syringe with 19-22 gauge needle.
4. Remove container from IV pole and turn to an upright position.
5. Mix the solution and medication by tapping gently on the delivery tip of the bag and syringe inlet while in this position.
6. Return the bag to its former position, open the clamp and continue administration.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

2016/625

9. FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first Authorization: 05.09.2016

Renewal of the Authorization:

10. DATE OF REVISION OF THE TEXT

11.07.2019