

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mannitol Intravenous Infusion BP 20% w/v Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mannitol 200 g/l

Each ml contains 200 mg Mannitol

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion.

Clear, colourless solution, free from visible particles.

Osmolarity: 1098 mOsm/l (approx)

pH: 4.5 -7.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mannitol 20% Solution for infusion is indicated for use as an osmotic diuretic in the following situations:

1. Promotion of diuresis in the prevention and/or treatment of the oliguric phase of acute renal failure before irreversible renal failure becomes established.
2. Reduction of intracranial pressure and cerebral oedema, when blood-barrier is intact.
3. Reduction of elevated intraocular pressure when it cannot be lowered by other means.
4. Promotion of elimination of renally excreted toxic substances in poisoning.

4.2 Posology and method of administration

Posology:

The choice of the specific mannitol concentration, dosage and rate of administration depends on the age, weight, clinical and biological condition of the patient and concomitant therapy.

Adults and adolescents

Acute renal failure

The general dose range is 50 to 200 g mannitol in a 24 hour period (250 to 1000ml/day), with a dosage limit of 50g mannitol (250ml) on any one occasion. In most instances adequate response will be achieved at a dosage of 50g to 100g mannitol/day (250 to 500 ml/day) .

The normal infusion rate is 30 to 50 ml/hour.

Only in emergency situations, the maximum infusion rate can be as high as 200 mg/kg infused over 5 minutes (see also test dose). After 5 minutes, the infusion rate should be readjusted to maintain a urine flow of at least 30-50 ml per hour, with a maximum dose of 200 g/24h.

An infusion of 50 to 100gm of Mannitol may be given during cardiovascular and other types of surgery as an aid in preventing acute renal failure. The concentration and volume to be administered will depend upon the fluid requirement of the patient.

- Use in patients with oliguria or renal impairment

Patients with marked oliguria or suspected inadequate renal function should first receive a test dose of approximately 1 ml/kg body weight (bw) (200 mg mannitol/kg bw) over a period of 3 to 5 minutes. For example, in an adult patient with a body weight of 70 kg: approximately 75 mL of a 20% solution or 100 mL of a 15% solution. The response to the test dose is considered adequate if at least 30-50 ml/hour of urine is excreted for 2-3 hours. If an adequate response is not attained, a further test dose may be given. If an adequate response to the second test dose is not attained, treatment with mannitol should be discontinued and the patient reassessed as established renal failure may be present.

Reduction of intracranial pressure, cerebral volume and intraocular pressure

The usual dose is 1.5 to 2 g/kg bw (7.5 to 10 ml/kg bw), infused over 30 to 60 minutes. When used preoperatively, the dose should be administered 1 to 1.5 hours before surgery to obtain the maximum effect.

Promotion of elimination of renally excreted toxic substances in poisoning

In induction of forced diuresis in the adjunctive treatment of severe drug intoxications, the dose of mannitol should be adjusted to maintain urinary output of at least 100ml/hour and positive fluid balance of 1-2 litres. An initial loading dose of approximately 125 ml may be given.

Paediatric Population:

In renal insufficiency, the test dose should be 1 ml/kg bw (200 mg mannitol/kg bw) over 3-5 minutes. The treatment dose ranges from 0.5 to 1.5 g/kg bw (2.5 ml to 7.5 ml/kg bw). This dose may be repeated once or twice, after an interval of 4 to 8 hours, if necessary.

For increased intracranial and intraocular pressure, this dose may be given over 30 to 60 minutes as for adults.

Elderly population:

As for adults, the dosage depends on the weight, clinical and biological condition of the patient and concomitant therapy. The general dose range is the same as for adults 50 to 200 g mannitol in a 24 hour period (250 to 1000 ml/day), with a dosage limit of 50 g mannitol (250 ml) on any one occasion. Since incipient renal insufficiency may be present, caution should be used when reviewing patient's status prior to dose selection.

Method of Administration

The solution is for intravenous administration only through a sterile and non-pyrogenic administration set which includes a final in-line filter because of the potential for mannitol crystals to form and using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.

Do not remove unit from overwrap until ready for use. The inner bag maintains the sterility of the product.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Use only if the solution is clear, without visible particles and the seal is intact. Confirm the integrity of the bag. Use only if the container is undamaged. Administer immediately following insertion of the infusion set.

Hyperosmolar mannitol solutions may cause vein damage. Check product's osmolarity before administration. This hypertonic solution should be administered via a large peripheral or preferably a central vein. Rapid infusion in peripheral veins may be harmful.

Mannitol solutions may crystallize when exposed to low temperature. At higher concentrations, the solutions have a greater tendency to crystallize. Inspect for crystals prior to administration.

If crystals are visible, re-dissolve by warming the solution up to 70°C, with agitation. Solutions should not be heated in water or in a microwave oven due to the potential for product contamination or damage. Allow the solution to cool to room or body temperature before re-inspection for crystals and use. Please see also sections 4.4 and 6.6.

For information on incompatibilities and preparation of the product and additives, please see sections 6.2 and 6.6.

4.3 Contraindications

Mannitol 20% Solution for Infusion is contra-indicated in patients presenting with:

- Pre-existing plasma hyperosmolarity
- Severe dehydration
- Well established anuria
- Severe heart failure
- Severe pulmonary congestion or pulmonary oedema
- Active intracranial bleeding, except during craniotomy
- Disturbance of the blood-brain barrier
- Hypersensitivity to mannitol
- Failure to respond to test dosing – see section 4.2
- Progressive renal damage or dysfunction after institution of mannitol therapy, including increasing oliguria and azotemia

4.4 Special warnings and precautions for use

WARNINGS

• Hypersensitivity

Anaphylactic/anaphylactoid reactions, including anaphylaxis, as well as other hypersensitivity/infusion reactions have been reported with mannitol. Fatal outcome has been reported. (See section 4.8)

The infusion must be stopped immediately if any signs or symptoms of a suspected hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Mannitol occurs in nature (e.g., in some fruits and vegetables) and is widely used as excipient in drugs and cosmetics. Therefore, patients may be sensitized without having received intravenous treatment with mannitol.

• CNS toxicity

CNS toxicity manifested by, e.g. confusion, lethargy, coma has been reported in patients treated with mannitol, in particular in the presence of impaired renal function. Fatal outcomes have been reported.

CNS toxicity may result from:

- High serum mannitol concentrations
- Serum hyperosmolarity resulting in intracellular dehydration within the CNS
- Hyponatremia or other disturbances of electrolyte and acid/base balance secondary to mannitol administration.

At high concentrations, mannitol may cross the blood brain barrier and interfere with the ability of the brain to maintain the pH of the cerebrospinal fluid especially in the presence of acidosis.

In patients with preexisting compromised blood brain barrier, the risk of increasing cerebral edema (general or focal) associated with repeated or continued use of mannitol must be individually weighed against the expected benefits.

A rebound increase of intracranial pressure may occur several hours after the use of mannitol. Patients with compromised blood brain barrier are at increased risk.

• Risk of renal complications

Reversible, acute oligoanuric renal failure, has occurred in patients with normal pretreatment renal function who received large intravenous doses of mannitol.

Although the osmotic nephrosis associated with mannitol administration is in principle reversible, osmotic nephrosis in general is known to potentially proceed to chronic or even end-stage renal failure.

Patients with pre-existing renal disease, or those receiving potentially nephrotoxic drugs, are at increased risk of renal failure following administration of mannitol.

Mannitol should be administered with caution to patients with impaired renal function.

See also Dosage and administration

If the urine output declines during mannitol infusion, the patient's clinical status should be closely reviewed for developing renal impairment, and the mannitol infusion suspended, if necessary.

- Risk of hypervolemia

Evaluate cardiovascular status of the patient prior to mannitol administration.

High doses and/or high rates of infusion as well as accumulation of mannitol (due to insufficient renal excretion of mannitol), may result in hypervolemia, overexpansion of the extracellular fluid, which may lead to or exacerbate existing congestive heart failure.

If the patient's cardiac or pulmonary function deteriorates, treatment should be discontinued.

- Risk of water and electrolyte imbalances, hyperosmolarity

Mannitol-induced osmotic diuresis may cause or worsen dehydration/hypovolemia and hemoconcentration. Administration of mannitol may also cause hyperosmolarity.

In addition, depending on dosage and duration of administration, electrolyte and acid/base imbalances may result from transcellular shifts of water and electrolytes, osmotic diuresis and/or other mechanisms. Such imbalances may be severe and potentially fatal.

Imbalances that may result from mannitol treatment include:

- Hyponatremia, dehydration and hemoconcentration (resulting from excessive water loss)
- Hyponatremia (resulting from increased sodium excretion during mannitol-induced osmotic diuresis or from the shift of intracellular fluid into extracellular spaces)

Hyponatremia can lead to headache, nausea, seizures, lethargy, coma, cerebral edema, and death. Acute symptomatic hyponatremic encephalopathy is considered a medical emergency.

The risk for developing hyponatremia is increased, for example,

- in children
- in elderly patients
- in women
- postoperatively
- in persons with psychogenic polydipsia.

The risk for developing encephalopathy as a complication of hyponatremia is increased, for example,

- in paediatric patients (≤ 16 years of age)
- in women (in particular, premenopausal women)
- in patients with hypoxemia
- in patients with underlying central nervous system disease.

- Hypokalemia
- Hyperkalemia

- Other electrolytes imbalances
- Metabolic acidosis
- Metabolic alkalosis

By sustaining diuresis, mannitol administration may obscure and intensify inadequate hydration or hypovolemia.

- Infusion reactions

Infusion site reactions have occurred with the use of mannitol. They include signs and symptoms of infusion site irritation and inflammation, as well as severe reactions (compartment syndrome and bullous eruptions) when associated with extravasation.

See Post-marketing Adverse Reactions section

Mannitol should be administered with caution to patients with severely impaired renal function. A test dose should be employed and therapy with mannitol continued only if an adequate urine flow is achieved (see Section 4.2).

Patients with pre-existing renal disease, or those receiving potentially nephrotoxic medicinal products, are at increased risk of renal failure following administration of mannitol. Serum osmolal gap and renal function should be closely monitored and appropriate action initiated should signs of worsening renal function appear.

In patients with shock and renal dysfunction, mannitol should not be administered until volume (fluid; blood) and electrolytes have been replaced.

PRECAUTIONS

- Volume and electrolyte replacement before use

Mannitol should not be administered in patients with hypovolemic shock or renal dysfunction until volume and electrolytes have been restored.

- Monitoring

To identify excessive fluid and electrolyte shifts and for early detection of renal, cardiac and other complications, it is essential to monitor

- serum osmolality,
- serum electrolytes and acid base balance,
- for signs of dehydration or hypervolemia and
- renal, cardiac and pulmonary function.

- Incompatibility with blood

Mannitol should not be given concomitantly with blood because it may cause agglutination and crenation of blood cells.

- Crystallization

When exposed to low temperatures, solutions of mannitol may crystallize. Inspect for crystals prior to administration. If crystals are visible, redissolve by warming the solution up to 70°C, with agitation.

See Dosage and Method of Administration

- Laboratory test interferences

Mannitol can cause false low results in some tests systems for inorganic phosphorus blood concentrations.

Mannitol produces false positive results in tests for blood ethylene glycol concentrations in which mannitol is initially oxidized to an aldehyde.

- Paediatric use

Safety and effectiveness in the paediatric population have not been established in clinical studies performed by Baxter Healthcare.

- Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

- Risk of Air Embolism

- Do not connect flexible plastic containers in series in order to avoid air embolism due to possible residual air contained in the primary container.
- Pressurizing intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.
- Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

The acid base balance, renal function and serum osmolality must be monitored carefully when mannitol is used.

Should patient serum osmolality increase during treatment, the effects of mannitol on diuresis and reduction of intracranial and intraocular pressure may be impaired.

Patients receiving mannitol should be monitored for any deterioration in renal, cardiac or pulmonary function and treatment discontinued in the case of adverse events.

The cardiovascular status of the patient should be carefully evaluated before rapidly administering Mannitol 20% Solution for Infusion since sudden expansion of the extracellular fluid may lead to sudden congestive heart failure.

Shift of sodium-free intracellular fluid into the extra cellular compartment following mannitol infusion may lower serum sodium concentration and aggravate pre-existing hyponatraemia. Sodium may be lost in the urine. Mannitol may obscure and intensify inadequate hydration and hypovolaemia.

Urinary output, fluid balance, central venous pressure and electrolyte balance (in particular serum sodium and potassium levels) should be carefully monitored.

Accumulation of mannitol may result if urine output continues to decline during administration and this may intensify existing or latent congestive heart failure.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

In cooler temperatures mannitol may form crystals. Storing it at a temperature of 20° to 30° will minimize the deposition of crystals. Redissolve any crystallised mannitol by moderately warming the product in a water bath, gently agitating the solution periodically.

ENSURE THAT THE SOLUTION IS COOLED TO 37° C BEFORE INFUSION.

Adding other medications or using an incorrect administration technique may cause febrile reactions due to possible introduction of pyrogens. In case of an adverse reaction, infusion must be stopped immediately. For information on incompatibilities and preparation of the product and additives, please see sections 6.2 and 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Effect Potentialisation

Concurrent use of other diuretics may potentiate the effects of mannitol and dose adjustments may be required.

Effect Inhibition

Mannitol promotes urine flow, which will mainly affect drugs that are renally reabsorbed to a large extent - thereby increasing their clearance and reducing their exposure.

Mannitol increases urinary excretion of lithium and therefore concomitant use of mannitol may impair the response to lithium.

Nephrotoxicity of drugs due to fluid imbalance related to mannitol

Although an interaction in humans is unlikely, patients receiving concomitant cyclosporine and aminoglycoside should be closely monitored for signs of nephrotoxicity.

Neurotoxic agents

Concomitant use of neurotoxic agents (e.g. aminoglycoside) and mannitol may potentiate the toxicity of neurotoxic agents. (See also section 4.4).

Agents affected by electrolyte imbalances

The development of electrolyte imbalances (e.g., hyperkalaemia, hypokalaemia) associated with mannitol administration may alter the effects of agents that are sensitive to such imbalances (e.g., digoxin, agents that may cause QT prolongation, neuromuscular blocking agents).

Other potential interactions are with, tubocurarine and depolarising neuromuscular blocking drugs (enhancement of their effects by mannitol), oral anticoagulants (mannitol may reduce their effects by increasing the concentration of clotting factors secondary to dehydration) and digoxin (if hypokalaemia follows mannitol treatment there is a risk of digoxin toxicity).

4.6 Fertility, pregnancy and lactation

There are no relevant published data from the use of mannitol in pregnant women.

There are no relevant published data from animal studies with respect to mannitol's effect on pregnancy and/or embryo/foetal development and/or parturition and/or postnatal development.

Mannitol should not be used during pregnancy unless clearly needed.

There is no information on excretion of mannitol in breast milk.

Mannitol should not be used during lactation unless clearly necessary.

4.7 Effects on ability to drive and use machines

There is no information on the effects of mannitol on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable effects

The following adverse reactions have been reported in post-marketing experience. The frequency of the adverse drug reactions listed in this section cannot be estimated from the available data.

MedDRA System Organ Class	Adverse reaction (MedDRA Preferred Term)	Frequency
Immune system disorders	Allergic reaction	Not known
	Anaphylactic reaction-including-anaphylactic shock *	
Metabolism and nutrition disorders	Fluid and electrolytes imbalance**	Not known
	Dehydration	
	Oedema	
	Metabolic acidosis	
Nervous system disorders	Headache	
	Dizziness	
	Rebound intracranial pressure increase	
	CNS toxicity manifested by	
	Convulsions	
	Coma	
	Confusion	
	Lethargy	
Eye disorders	Blurred vision	Not known
Cardiac disorders	Cardiac arrhythmia	Not known
	Congestive heart failure	
	Palpitations	
Vascular disorders	Hypotension	Not known
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema	Not known
	Rhinitis	
Gastrointestinal disorders	Mouth dry	Not known
Skin and subcutaneous tissue disorders	Skin necrosis	Not known
	Urticaria	
Musculoskeletal and connective tissue disorders	Cramps	Not known
Renal and urinary disorders	Excessive diuresis	Not known
	Nephrosis osmotic	
	Urinary retention	
	Acute renal failure	
	Azotemia	
	Anuria	
	Haematuria	
	Oliguria	
	Polyuria	
General disorders and administration site conditions	Chills	Not known
	Chest pain (angina-like chest pain)	
	Fever	

	Asthenia	
	Malaise	
	Infusion site reactions including infusion thrombophlebitis	
	infusion site inflammation	
	infusion site pain	
	infusion site rash	
	infusion site erythema	
	infusion site pruritus	
	Compartment syndrome (associated with extravasation and swelling at the injection site)	

*It can be manifested with skin, gastrointestinal, and severe circulatory (hypotension), and respiratory manifestations (e.g. dyspnea). Other hypersensitivity/infusion reactions, include hypertension, pyrexia, chills, sweating, cough, musculoskeletal stiffness and myalgia, urticaria/rash, pruritus, generalized pain, discomfort, nausea, vomiting, and headache.

** including hypervoalaemia, peripheral oedema, dehydration, hyponatraemia, hypernatraemia, hyperkalaemia, hypokalaemia.

Other adverse reactions
Severe anaphylaxis with cardiac arrest, and fatal outcome.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

In case of suspected overdose, treatment with mannitol should be stopped immediately.

Prolonged administration or rapid infusion of large volumes of hyperosmotic solutions may result in circulatory overload and acidosis. Headache, nausea and shivering without temperature change may represent initial signs/symptoms. Confusion, lethargy, convulsions, stupor and coma may follow.

Management is symptomatic and supportive, with monitoring of fluid and electrolyte balance. Mannitol is dialyzable. Haemodialysis may be helpful.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: “Solutions producing osmotic diuresis”, ATC cose: “B05BC01”

Mannitol, a carbohydrate, is confined to the extracellular compartment. It has an osmotic effect, which causes fluid to pass from the intracellular to the extracellular compartment.

Mannitol is freely filterable at the kidney glomerulus and less than 10% is reabsorbed back from the kidney tubule. Confined to the kidney tubules, mannitol exerts an osmotic effect, which prevents fluid reabsorption from the glomerular filtrate and produces diuresis. It thereby promotes urine flow in oliguria/anuria or in situations where the patient is at risk of onset of acute renal failure. Mannitol also increases electrolyte excretion, especially sodium, potassium and chloride. Excretion of renally excreted toxic substances such as aspirin and barbiturates is also increased.

Mannitol does not penetrate the blood-brain barrier under usual circumstances. Confined to the plasma, mannitol exerts an osmotic pressure, causing fluid to leave the brain tissue, and brain volume and intracranial pressure to be reduced.

Mannitol does not penetrate the eye. Mannitol promotes excretion of aqueous humour and thereby reduces intraocular pressure.

5.2 Pharmacokinetic properties

When administered intravenously, mannitol is eliminated largely unmetabolised through the glomeruli. It is freely filtered by the glomeruli, with less than 10% tubular reabsorption and is not secreted by tubular cells. The elimination half life in adults is approximately 2 hours, longer where renal failure is present. 80% of an intravenous dose is excreted unchanged within 3 hours.

5.3 Preclinical safety data

The preclinical safety assessment of mannitol 20% in animals is not relevant as mannitol is a substance with well-established use in patients and is covered by appropriate pharmacopoeial references.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide (for pH adjustment)
Water for Injection

6.2 Incompatibilities

Mannitol 20% Solution for Infusion should not be administered simultaneously with, before, or after administration of blood through the same infusion equipment, due to risk of pseudoagglutination. See section 4.4.

Incompatibility of the medicinal product to be added with the solution in the Viaflex container must be assessed before addition.

The Instructions for Use of the medicinal product to be added must be consulted.

Before adding a medicinal product, verify it is soluble and stable in water at the pH of the mannitol solution (4.5 to 7.0).

As a guide, cefepime, imipenem, cilastin and filgrastim are incompatible with mannitol solutions, but this list is not exhaustive. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

The addition of potassium or sodium chloride to Mannitol 20% may cause precipitation of mannitol.

6.3 Shelf life

Unopened: 2 years.
Once opened, use immediately.

6.4 Special precautions for storage

Do not store above 30°C.
Do not refrigerate.

6.5 Nature and contents of container

The product is a clear, colourless, aqueous, solution supplied in single dose 500ml or 1000ml collapsible PVC Vialflex bags.

Each container is held within a plastic overpouch.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Use only if the solution is clear, without visible particles and if the container is undamaged. Administer immediately following insertion of the infusion set.

Do not remove unit from overwrap until ready for use. The inner bag maintains the sterility of the product.

Do not use plastic containers in series connections. Such use could result in embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

Medicinal products may be introduced before infusion or during infusion through the injection site.

Mannitol solutions may crystallize when exposed to low temperature. Inspect for crystals prior to administration. If crystals are visible, re-dissolve by warming the solution up to a maximum of 70°C, with agitation. Solutions should not be heated in water or in a microwave oven due to the potential for product contamination or damage. Allow the solution to cool to room or body temperature before reinspection for crystals and use. Discard after single use.

Discard any unused portion.

Do not reconnect partially used bags.

To open

Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution, as sterility may be impaired.

Preparation for administration

1. Suspend container from eyelet support.
2. Remove blue protector from outlet port.
3. Use an aseptic method to set up the infusion.
4. Attach administration set. Refer to complete directions accompanying set.

Techniques for injection of additive medicinal products

Warning: Additives may be incompatible.

To add medicinal products before administration

1. Disinfect medication port.
2. Using syringe with 20 to 22 gauge needle, puncture resealable medication port and inject.
3. Mix solution and medication thoroughly. For high-density medication such as potassium chloride, tap the ports gently while ports are upright and mix.

To add medicinal products during administration

1. Close clamp on the set.
2. Disinfect medication port
3. Using syringe with 20 to 22 gauge needle, puncture resealable medication port and inject.

4. Remove container from intravenous pole and/or turn to an upright position.
5. Evacuate both ports by tapping gently while the container is in an upright position.
6. Mix solution and medication thoroughly.
7. Return container to in use position, re-open the clamp and continue administration.

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.
Caxton Way
Thetford
Norfolk
IP24 3SE
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0167/037/009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 June 1984
Date of last renewal: 29 June 2004

10 DATE OF REVISION OF THE TEXT

March 2016