Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cefotaxime Netpharmalab 1g Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cefotaxime sodium equivalent to 1 g cefotaxime base.

Each gram of cefotaxime contains approximately 48 mg (2.09 mmol) of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

A white to pale yellow-white crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefotaxime Netpharmalab is active in vitro against Gram-negative organisms sensitive or resistant to first or second generation cephalosporins. It is similar to other cephalosporins in activity against Gram-positive organisms.

Cefotaxime Netpharmalab is indicated in the treatment of the following infections either before the infecting organism has been identified or when caused by bacteria of established sensitivity (see sections 4.4 and 5.1).

- Acute and chronic bronchitis,
- Infected bronchiectasis,
- Lung abscess
- Post-operative chest infections.
- Nosocomial pneumonia
- Complicated urinary tract infections
- Complicated skin and soft tissue infections.
- Bone and Joint Infections such as osteomyelitis, septic arthritis.
- Obstetric and Gynaecological Infections such as pelvic inflammatory disease.
- Gonorrhoea particularly when penicillin has failed or is unsuitable.
- Bacterial meningitis

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Consideration should be given to official guidance on the appropriate use and prescription of antibacterial agents.

4.2 Posology and method of administration

Posology

Cefotaxime Netpharmalab may be administered intravenously or by slow injection or infusion or intramuscularly. The dosage, route and frequency of administration should be determined by the severity of infection, the sensitivity of causative organism and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

Adults and adolescents (12 to 18 years)

The recommended dosage for mild to moderate infections is 1g 12 hourly. However, dosage may be varied according to the severity of the infection, sensitivity of causative organisms and condition of the patient. Therapy may be initiated before the results of sensitivity tests are known.

In severe infections dosage may be increased up to 12g daily given in 3 or 4 divided doses. For infections caused by sensitive Psuedomonas spp. daily doses of greater than 6 g will usually be required.

Dosage in Gonorrhea: A single injection of 1g may be administered intramuscularly or intravenously.

Paediatric population

Infants, toddlers (28 days to 23 months) and children (2 to 11 years)
The usual dosage range is 50-150mg/kg/day in 2 to 4 divided doses. However, in very severe infections doses of up to 200mg/kg/day may be required.

Neonates
The recommended dosage is 50mg/kg/day in 2 to 4 divided doses. In severe infections 150-200mg/kg/day, in divided doses, have been given.
The following table may serve as a guide to dosages.

Age	Daily dose of cefotaxime
0-7 days	50mg/kg/day every 12 hours IV
8 days-1 month	50mg/kg/day every 8 hours IV

Dosage in Renal Impairment

Because of extra-renal elimination, it is only necessary to reduce the dosage of Cefotaxime Netpharmalab in severe renal failure (GFR <5ml/min = serum creatinine approximately 751 micromol/1). After an initial loading dose of 1g, daily dose should be halved without change in the frequency of dosing, i.e. 1g in 12 hourly becomes 0.5g 12 hourly, 1g 8 hourly becomes 0.5g 8 hourly, 2g 8 hourly becomes 1g 8 hourly etc. As in all other patients, dosage may require further adjustment according to the course of the infection and the general condition of the patient.

Method of administration

Intravenous and Intramuscular administration:

Intravenous administration (Injection or infusion):

Reconstitute Cefotaxime Netpharmalab with Water for Injection as given in the Dilution Table. Shake well until dissolved and then withdraw the entire contents of the vial into the syringe and use immediately.

Dilution Table:

Víal Size	Diluent to be added
1 g	4 ml

Cefotaxime Netpharmalab may be administered by intravenous infusion. 1g (1 vial) is dissolved in 40-100ml of Water for Injection or in the infusion fluids listed under Pharmaceutical Particulars in Section 6.6 Instructions for use/handling. The prepared infusion may be administered over 20-60 minutes. To produce an infusion using vials with an infusion connector, remove the safety cap and directly connect the infusion bag. The needle in the closure will automatically pierce the vial stopper. Pressing the infusion bag will transfer solvent into the vial. Reconstitute by shaking the vial and finally, transfer the reconstituted solution back to the infusion bag ready for use.

For intermittent I.V. injections, the solution must be injected over a period of 3 to 5 minutes. During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter. Cefotaxime and aminoglycosides should not be mixed in the same syringe or infusion fluid.

Intramuscular administration

In case of intramuscular administration, reconstitute Cefotaxime Netpharmalab with Water for Injection or as per the Dilution Table below.

	Volume of diluent	Nature of diluent
Cefotaxime Netpharmalab 1 g	4 ml	Water for injection

4.3 Contraindications

Hypersensitivity to cephalosporins.

Hypersensitivity to cefotaxime or to any of the excipients listed in section 6.1.

Allergic cross reactions can exist between penicillins and cephalosporins (see section 4.4 Special Warnings and Precautions for Use).

4.4 Special warnings and precautions for use

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If super infection occurs during therapy, appropriate measures should be taken (see Section 4.8).

- Anaphylactic reactions

Serious, including fatal hypersensitivity reactions have been reported in patients receiving cefotaxime (see sections 4.3 and 4.8). If a hypersensitivity reaction occurs, treatment must be stopped.

The use of cefotaxime is strictly contra -indicated in subjects with a previous history of immediate type hypersensitivity to cephalosporins.

Since cross allergy exists between penicillins and cephalosporins, use of the latter should be under taken with extreme caution in penicillin sensitive subjects.

- Serious bullous reactions

Cases of serious bullous skin reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with cefotaxime (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

- Clostridium difficile associated disease (e.g. pseudomembranous colitis)

Diarrhea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks following treatment, may be symptomatic of Clostridium difficile associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudo-membranous colitis.

The diagnosis of this rare but possibly fatal condition can be confirmed by endoscopy and/or histology. It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of cefotaxime.

If a diagnosis of pseudomembranous colitis is suspected, cefotaxime should be stopped immediately and appropriate specific antibiotic therapy should be started without delay. Clostridium difficile associated disease can be favoured by faecal stasis. Medicinal products that inhibit peristalsis should not be given

- Blood disorders

Leukopenia, neutropenia and, more rarely, bone marrow failure, pancytopenia or agranulocytosis may develop during treatment with cefotaxime. For treatment courses lasting longer than 7-10 days, the blood white cell count should be monitored and treatment stopped in the event of neutropenia. Some cases of eosinophilia and thrombocytopenia, rapidly reversible on stopping treatment, have been reported. Cases of haemolyticanemia have also been reported. (see section 4.8)

- Patients with renal insufficiency

The dosage should be modified according to the creatinine clearance calculated. Caution should be exercised if cefotaxime is administered together with aminoglycosides or other nephrotoxic drugs (see section 4.5). Renal function must be monitored in these patients, the elderly, and those with preexisting renal impairment.

- Neurotoxicity

High doses of beta-lactam antibiotics, including cefotaxime, particularly in patients with renal insufficiency, may result in encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8).

Patients should be advised to contact their doctor immediately prior to continuing treatment if such reactions occur.

- Precautions for administration

During post-marketing surveillance, potentially life-threatening arrhythmia has been reported in a very few patients who received rapid intravenous administration of cefotaxime through a central venous catheter. The recommended time for injection or infusion should be followed (see section 4.2).

- Effects on Laboratory Tests

As with other cephalosporins a positive Coombs' test has been found in some patients treated with cefotaxime. This phenomenon can interfere with the cross-matching of blood. Urinary glucose testing with non-specific reducing agents may yield false-positive results. This phenomenon is not seen when a glucose-oxydase specific method is used.

- Sodium intake

The sodium content of cefotaxime sodium (48.2 mg/g) should be taken into account by patients on a sodium controlled diet.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid interferes with the renal tubular transfer of cephalosporins, thereby delaying their excretion and increasing their plasma concentrations.

As with other cephalosporins, cefotaxime may potentiate the nephrotoxic effects of nephrotoxic drugs such as aminoglycosides or potent diuretics (e.g. furosemide). Renal function must be monitored (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of cefotaxime has not been established in human pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity

There are, however, no adequate and well controlled studies in pregnant women. Cefotaxime crosses the placental barrier. Therefore, cefotaxime should not be used during pregnancy unless the anticipated benefit outweighs any potential risk.

Breast-feeding

Cefotaxime passes into human breast milk.

Effects on the physiological intestinal flora of the breast-fed infant leading to diarrhoea, colonization by yeast-like fungi, and sensitisation of the infant cannot be excluded. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired. In such cases patients should refrain from driving cars and using machines. High doses of cefotaxime, particularly in patients with renal insufficiency, may cause encephalopathy (e.g. impairment of consciousness, abnormal movements and convulsions) (see section 4.8). Patients should be advised not to drive or operate machinery if any such symptoms occur.

4.8 Undesirable effects

System organ class	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)	Not known (cannot be estimated form available data)
Infections and infestations						Superinfection (see section 4.9)
Blood and the lymphatic system disorders			Leukopenia Eosinophilia Thrombocytopenia			Bone marrow failure Pancytopenia Neutropenia Agranulocytosis (see section 4.4) Haemolytic anaemia
Immune system disorders			Jarisch-Herxheimer reaction			Anaphylactic reactions Angioedema Bronchospasm Anaphylactic shock
Nervous system disorders			Convulsions (see section 4.4)			Headache Dizziness Encephalopathy (e.g. impairment of consciousness, abnormal movements) (see section 4.4)
Cardiac disorders						Arrhythmia following rapid bolus infusion through central

						venous catheter
Gastrointestinal disorders			Diarrhea			Nausea Vomiting Abdominal pain Pseudomembranous colitis (see section 4.4)
Hepato-bilary disorders			Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin			Hepatitis* (sometimes with jaundice)
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria			Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis (see section 4.4) Acute generalised exanthematous pustulosis (AGEP)
Renal and Urinary disorders			Decrease in renal function/increase of creatinine (particularly when coprescribed with aminoglycosides)			Acute renal failure (See Section 4.4) Interstitial nephritis
General disorders and administration site conditions	For IM formulations: Pain at the Injection site		Fever Inflammatory reactions at the injection site, including phlebitis/ thrombophlebitis			

*postmarketing experience

Jarisch-Herxheimer reaction

For the treatment of borreliosis, a Jarisch-Herxheimer reaction may develop during the first days of treatment.
The occurrence of one or more of the following symptoms has been reported after several week's treatment of borreliosis: skin rash, itching, fever, leucopenia, increase in liver enzymes, difficulty of breathing, joint discomfort.

Hepatobiliary disorders

Increase in liver enzymes (ALAT, ASAT, LDH, gamma-GT and/or alkaline phosphatase) and/or bilirubin have been reported. These laboratory abnormalities may rarely exceed twice the upper limit of the normal range and elicit a pattern of liver injury, usually cholestatic and most often asymptomatic.

Superinfection

As with other antibiotics, the use of cefotaxime, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If super infection occurs during therapy, appropriate measures should be taken.

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

Symptoms of overdose may largely correspond to the profile of side effects.
There is a risk of reversible encephalopathy in cases of administration of high doses of b-lactam antibiotics including cefotaxime.

In case of overdose, cefotaxime must be discontinued, and supportive treatment initiated, which includes measures to accelerate elimination, and symptomatic treatment of adverse reactions (e.g. convulsions).
No specific antidote exists. Serum levels of cefotaxime can be reduced by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 3rd generation cephalosporin antibiotics, ATC code: J01DD01

Mechanism of action
The bactericidal activity of cefotaxime results from the inhibition of bacterial cell wall synthesis (during the period of growth) caused by an inhibition of penicillin-binding proteins (PBPs) like transpeptidases.

Mechanism of resistance
A resistance to cefotaxime may be caused by following mechanisms:

- Inactivation by beta-lactamases. Cefotaxime can be hydrolysed by certain beta-lactamases, especially by extended-spectrum beta-lactamases (ESBLs) which can be found in strains of Escherichia coli or Klebsiella pneumoniae, or by chromosomal encoded inducible or constitutive beta-lactamases of the AmpC type which can be detected in Enterobacter cloacae. Therefore infections caused by pathogens with inducible, chromosomal encoded AmpC-beta-lactamases should not be treated with cefotaxime even in case of proven in-vitro-susceptibility because of the risk of the selection of mutants with constitutive, derepressed AmpC-beta-lactamases-expression.

- Reduced affinity of PBPs to cefotaxime. The acquired resistance of Pneumococci and other Streptococci is caused by modifications of already existing PBPs as a consequence of a mutation process. In contrast to this concerning the methicillin-(oxacillin-) resistant Staphylococcus, the creation of an additional PBP with reduced affinity to cefotaxime is responsible for resistance.

- Inadequate penetration of cefotaxime through the outer cell membrane of gram-negative bacteria so that the inhibition of the PBPs is insufficient.

- The presence of transport mechanism (efflux pumps) being able to actively transport cefotaxime out of the cell. A complete cross resistance of cefotaxime occurs with ceftriaxone and partially with other penicillins and cephalosporins.

Breakpoints

The following minimal inhibitory concentrations were defined for sensitive and resistant germs:
EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints (2016-01-1):

Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤ 1mg /ml	>2 mg/ml
Pseudomonas spp.	-	-
Acinetobactes spp.	-	-
Staphylococcus spp.	Note[1]	Note[1]
Enterococcus spp.	-	-
Streptococcus groups A, B, C and G	Note[2]	Note[2]
Streptococcus pneumoniae	≤ 0.5 mg /ml	> 2 mg/ml
Viridans group streptococci	≤ 0.5 mg /ml	> 0.5 mg/ml
Haemophilus influenzae	≤ 0.125 mg /ml	> 0.125 mg/ml
Moraxella catarrhalis	≤ 1mg /ml	>2 mg/ml
Neisseria gonorrhoeae	≤ 0.125 mg /ml	> 0.125 mg/ml
Neisseria meningitidis	≤ 0.125 mg /ml	> 0.125 mg/ml
Gram positive anaerobes	-	-
Gram negative anaerobes	-	-
Pasteurella multocida	≤ 0.03 mg /ml	> 0.03 mg/ml
PK/PD non species related	≤ 1mg /ml	>2 mg/ml

Note[1]: Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility except for cefixime, ceftazidime, ceftibuten and ceftolozone-tazobactam, which do not have breakpoints and should not be used for staphylococcal infections.
Note[2]: The susceptibility of streptococcus groups A, B, C and G to cephalosporins is inferred from the benzylpenicillin.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. If the efficacy of cefotaxime is questionable due to the local prevalence of resistance, expert opinion should be sought regarding the choice of therapy. In particular in the case of severe infections or failure of therapy, a microbiological diagnosis including a verification of the germ and its susceptibility should be aspired.

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms *Staphylococcus aureus,* methicillin-susceptible *Streptococcus agalactiae* *Streptococcuspneumoniae* (including penicillin-resistant strains) *Streptococcus pyogenes*
Aerobic Gram-negative micro-organisms *Borrelia burgdorferi* *Haemophilus influenza* *Moraxella catarrhalis* *Neisseria gonorrhoeae* *Neisseria meningitidis* *Proteus mirabilis*[3]
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms *Staphylococcus aureus* *Staphylococcus epidermidis*[1] *Staphylococcus haemolyticus* [1] *Staphylococcus hominis*[1]

Aerobic Gram-negative micro-organisms *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia Coli*[3] *Kleibsella oxytoca*[3] *Kleibsella pneumoniae*[2,3] *Morganella morganii* *Proteus vulgaris* *Serratia marcescens*
Anaerobes *Bacteroides fragilis*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Enterococcus spp.* *Listeria monocytogenes* *Staphylococcus aureus* (methicillin-resistant)
Aerobic Gram-negative micro-organisms *Acinetobacter baumannii* *Pseudomonas aeruginosa* *Stenotrophomonas maltophila*
Anaerobes *Clostridium difficile*
Other microorganisms *Chlamydia spp.* *Chlamydophila spp.* *Legionella pneumophila* *Mycoplasma spp.* *Treponema pallidum*
[1] In at least one region the resistance rate is > 50%. [2] In intensive Care Units the resistance rate is 10%. [3] Extended Spectrum Beta-Lactamase (ESBL) producing strains are always resistant.

5.2 Pharmacokinetic properties

Pharmacokinetics: After a 1000mg intravenous bolus, mean peak plasma concentrations of cefotaxime usually range between 81 and 102µg/ml. Doses of 500mg and 2000mg produce plasma concentrations of 38 and 200µg/ml, respectively. There is no accumulation following administration of 1000mg intravenously or 500 mg intramuscularly for 10 or 14 days.

The apparent volume of distribution at steady-state of cefotaxime is 21.6L/1.73m^2 after 1g intravenous 30 minute infusion.

Concentrations of cefotaxime (usually determined by non-selective assay) have been studied in a wide range of human body tissues and fluids. Cerebrospinal fluid concentrations are low when the meninges are not inflamed, but are between 3 and 30µg/ml in children with meningitis.

Cefotaxime usually passes the blood-brain barrier in levels above the MIC of common sensitive pathogens when the meninges are inflamed. Concentrations (0.2-5.4 µg/ml), inhibitory for most Gram-negative bacteria, are attained in purulent sputum, bronchial secretions and pleural fluid after doses of 1 or 2g. Concentrations likely to be effective against most sensitive organisms are similarly attained in female reproductive organs, otitis media effusions, prostatic tissue, interstitial fluid, renal tissue, peritoneal fluid and gall bladder wall, after usual therapeutic doses. High concentrations of cefotaxime and desacetyl-cefotaxime are attained in bile.

Cefotaxime is partially metabolised prior to excretion. The principle metabolite is the microbiologically active product, desacetyl-cefotaxime. Most of a dose of cefotaxime is excreted in the urine about 60% as unchanged drug and a further 24% as desacetyl-cefotaxime. Plasma clearance is reported to be between 260 and 390ml/minute and renal clearance 145 to 217ml/minute.

After intravenous administration of cefotaxime to healthy adults, the elimination half-life of the parent compound is 0.9 to 1.14 hours and that of the desacetyl metabolite, about 1.3 hours.

In neonates the pharmacokinetics are influenced by gestational and chronological age, the half-life being prolonged in premature and low birth weight neonates of the same age.

In severe renal dysfunction the elimination half-life of cefotaxime itself is increased minimally to about 2.5 hours, whereas that of desacetyl-cefotaxime is increased to about 10 hours. Total urinary recovery of cefotaxime and its principal metabolite decreases with reduction in renal function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Prolonged use of an anti-infective may result in the development of superinfection due to organisms resistant to that anti-infective.
Cefotaxime Netpharmalab should not be mixed with solutions containing sodium bicarbonate, also aminoglycosides are incompatible with cephalosporins in parenteral mixtures.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 2 years.

For the reconstituted solution: chemical and physical in-use stability has been demonstrated for 12 hours at 2-8ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 12 hours at 2 to 8ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: do not store above 25°C. Store in the outer carton in order to protect from light.

For storage times following reconstitution, see section 6.3.

6.5 Nature and contents of container

Cefotaxime Netpharmalab is supplied in clear type I glass vials, with a capacity of 15ml, stoppered with greyrubber stoppers and sealed with an aluminum over-cap.

Available in packs of 1 and 10 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. Discard any unused contents.

When dissolved in Water for Injections, a straw-coloured solution is formed which is suitable for intravenous or intramuscular injection.

Reconstituted Solution: Whilst it is preferable to use only freshly prepared solutions for both intravenous and intramuscular injection, Cefotaxime Netpharmalab is compatible with several commonly used intravenous infusion fluids and will retain satisfactory potency for up to 12 hours refrigerated (2-8 °C) in the following:

Water for Injections.
0.9% Sodium Chloride Injection.
5% Dextrose Injection.
5% dextrose and 0.9% sodium chloride injection.
Compound Sodium Lactate Injection (Ringer-lactate Injection).

Some increase in colour of prepared solutions may occur on storage.

However, provided the recommended storage conditions are observed, this does not indicate change in potency or safety.

7 MARKETING AUTHORISATION HOLDER

Netpharmalab Consulting Services S. L.
Edificio Net-Pharma
Carretera Fuencarral, 22
28108 Alcobendas (Madrid)
Spain

8 MARKETING AUTHORISATION NUMBER

PA22665/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th April 2018
Date of last renewal: 12th February 2022

10 DATE OF REVISION OF THE TEXT

November 2022