Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin Villerton 300 mg solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains clindamycin phosphate equivalent to 6 mg of clindamycin.
Each bag of 50 ml solution contains 300 mg clindamycin.

Excipients with known effect
Each bag of 50 ml contains 5.674 mg sodium (0.247 mmol) and 2.5 g of glucose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

The medicinal product is a clear and colourless solution.

pH = 5.5 – 7.0

Osmolality: 268 to 308 mOsmol/Kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clindamycin is indicated for the treatment of the following severe infections caused by susceptible microorganisms (see section 5.1) in adults and adolescents older than 12 years:
- Staphylococcal bone and joint infections such as osteomyelitis and septic arthritis.
- Chronic sinusitis caused by anaerobic microorganisms.
- Infections of the lower respiratory tract such as:
  -aspiration pneumonia, pulmonary abscess, necrotising pneumonia, and empyema. In case of suspected polymicrobial pulmonary infections, an agent with adequate activity against Gram-negative bacteria should also be given in combination to cover possible Gram-negative bacteria.
- Complicated intra-abdominal infections such as peritonitis and abdominal abscess where the treatment of choice is clindamycin associated with an antibiotic with good activity against aerobic Gram-negative bacteria.
- Pelvic and female genital infections such as PID, endometritis, perivaginal infections, tubo-ovarian abscesses, salpingitis, pelvic cellulitis when simultaneously another antibiotic with good activity against aerobic Gram-negative bacteria is administered.

- Skin and soft tissue infections.

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

4.2 Posology and method of administration

Posology
Clindamycin solution for infusion is an injectable solution that does not require further dilution.

Adults and adolescents older than 12 years
- for the treatment of severe infections (such as intra-abdominal infections, female pelvic infections or other severe infections): 1800 – 2700 mg/day of clindamycin administered in two or three equal doses, generally in combination with an antibiotic with good activity against aerobic Gram-negative bacteria.
- for the treatment of less complicated infections:

1200 – 1800 mg/day of clindamycin administered in two, three or four equal doses.

Normally the maximum daily dose for adults and adolescents older than 12 years is 2700 mg clindamycin in 2 or 3 equal doses. In life-threatening infections doses up to 4800 mg/day have been given.

Children over 1 month of age up to 12 years
Clindamycin Villerton has been developed as a ready-to-use solution for infusion in 50 ml bags and is not suitable for use in children. Therefore, for the paediatric population posology, the use of clindamycin 150 mg/ml solution for injection in ampoules is recommended.

Elderly patients
The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate are not altered by increased age. Analysis of data from clinical studies has not revealed any age-related increase in toxicity. Dosage requirements in elderly patients should not be influenced, therefore, by age alone. See section 4.4 for other factors which should be taken into consideration.

Patients with hepatic impairment
In patients with liver disease of moderate to a severe degree, the elimination half-life of clindamycin is prolonged. A reduction in dosage is generally not necessary if Clindamycin Villerton is administered every 8 hours. However, the plasma concentration of clindamycin should be monitored in patients with severe hepatic insufficiency. Depending on the results, this measure can make a reduction in dosage or an increase in the dose intervals necessary.

Patients with renal impairment
In the presence of kidney diseases, the elimination half-life is prolonged; however, a dosage reduction is not necessary for the event of mild to moderate impairment of renal function. Nevertheless, the plasma concentration should be monitored in patients with severe renal insufficiency or anuria. Depending on the results, this measure can make a reduction in dosage or an increase in the dosing interval of 8 or even 12 hours necessary.

Dosage in the event of haemodialysis
Clindamycin cannot be removed by haemodialysis. Therefore, no additional dose is necessary before or after haemodialysis.

Treatment for infections caused by beta-haemolytic streptococci
Treatment for infections caused by beta-haemolytic streptococci should be continued for at least 10 days to guard against subsequent rheumatic fever or glomerulonephritis.

Method of administration
Intravenous infusion.
Clindamycin Villerton is administered by intravenous infusion (IV) and should be infused over at least 10-60 minutes. The concentration of clindamycin solution for infusion is equal to 6 mg/ml or 12 mg/ml.

The medicinal product is to be visually inspected prior to use. Do not use Clindamycin Villerton if you notice any particles or strong coloration of the solution.
Only clear solutions free of visible particles should be used.

4.3 Contraindications

Hypersensitivity to clindamycin, lincomycin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Clindamycin should only be used in the treatment of serious or life-threatening infections. When considering the use of Clindamycin Villerton, the practitioner should bear in mind the type of infection and the potential hazard of the diarrhoea which may develop, since cases of colitis have been reported during, or even two or three weeks following, the administration of Clindamycin Villerton. The disease is likely to follow a more severe course in older patients or patients who are debilitated.

Severe hypersensitivity reactions including severe skin reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN, Lyell's syndrome) and acute generalized exanthematous pustulosis (AGEP) have been reported in patients receiving clindamycin therapy. If a hypersensitivity or severe

skin reaction occurs, treatment with clindamycin should be discontinued and appropriate therapy should be initiated (see sections 4.3 and 4.8).

Caution should be exercised in patients with:
- impaired hepatic and renal function (see section 4.2),
- disturbances in neuromuscular transmission (myasthenia gravis, Parkinson's disease, etc.) as well as a history of gastrointestinal disorders (e.g. earlier inflammations of the colon),
- atopic diseases.

Severe allergic reactions can occur even after the first application. In this event, treatment with Clindamycin Villerton must be discontinued immediately and the standard emergency measures should be implemented.

In long-term therapy (treatment for more than 10 days), the haemogram as well as hepatic and renal function should be monitored at regular intervals.

Acute kidney injury, including acute renal failure, has been reported infrequently. In patients suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs, monitoring of renal function should be considered (see section 4.8).

Long-term and repeated application of Clindamycin Villerton can lead to a super-infection and/or colonization with resistant pathogens or yeast on the skin and mucous membranes.

Under certain circumstances, clindamycin therapy may be an alternative form of treatment in patients with a penicillin allergy (penicillin hypersensitivity). There have been no reports of a cross-allergy between clindamycin and penicillin and, based on the structural differences between the substances, this is not to be expected. However, in individual cases, information does exist on anaphylaxis (hypersensitivity) towards clindamycin in persons with an already existing penicillin allergy. This should be taken into consideration in a course of clindamycin treatment in patients with a penicillin allergy.

Colitis: The development of *Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin. It ranges from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*.

Clostridium difficile produces toxins A and B which contribute to the development of CDAD and is a primary cause of 'antibiotic-associated colitis'.

Hypervirulent strains of *Clostridium difficile* are associated with increased morbidity and mortality since such infections may be resistant to antibiotic therapy and may require colectomy.

It is important to consider the diagnosis of CDAD in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

In this case, a careful anamnesis has to be performed since a CDAD can occur up to two months after antibiotic therapy.

If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including clindamycin, should be discontinued and adequate therapeutic measures should be initiated immediately.

Medicinal products inhibiting peristalsis are contraindicated in this situation.

Clindamycin Villerton should not be used in case of acute infections of the respiratory tract if these are caused by viruses.

Clindamycin Villerton is not suitable for the treatment of meningitis, as the concentration of antibiotic obtained in the cerebrospinal fluid is insufficient.

Paediatric population
Safety and appropriate dosage of clindamycin in infants less than one-month old have not been established. Due to the formulation of Clindamycin Villerton Invest, dosing is not recommended for children younger than 12 years.

Important information about some excipients:
This medicine contains 2.5 g of glucose per bag. This should be taken into account in patients with diabetes mellitus.

This medicine contains less than 1 mmol (23 mg) sodium per 50 ml bag volume, that is to say essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently monitored in patients treated with vitamin K antagonists.

There is cross-resistance of pathogens towards clindamycin and lincomycin.

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. It should be used with caution, therefore in patients receiving such agents.

Clindamycin is metabolized predominantly by CYP3A4, and to a lesser extent, by CYP3A5, to the major metabolite clindamycin sulfoxide and minor metabolite N-desmethylclindamycin. Therefore, inhibitors of CYP3A4 and CYP3A5 may increase plasma concentrations of clindamycin. Some examples of strong CYP3A4 inhibitors are itraconazole, voriconazole, clarithromycin, telitromycin, ritonavir and cobicistat. Caution is recommended if clindamycin is used together with strong CYP3A4 inhibitors. Inducers of these enzymes may increase clearance of clindamycin, resulting in decreased plasma concentrations. In a prospective study with orally administered clindamycin, trough concentrations of clindamycin were decreased by 80% if given concomitantly with rifampicin, a strong inducer of CYP3A4. Patients should be observed for reduced treatment efficacy if clindamycin is used together with strong CYP3A4 inducers such as rifampicin, St John's wort (*Hypericum perforatum*), carbamazepine, phenytoin or phenobarbital.

In vitro studies indicate that clindamycin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6. Therefore, clinically important interactions between clindamycin and co-administered drugs metabolized by these CYP enzymes are unlikely. Based on *in vitro*-data orally administered clindamycin may inhibit intestinal CYP3A4, but clinically relevant effects of parenterally administered clindamycin on concomitantly administered medicinal products metabolized by CYP3A4 are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy
Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

A large study in pregnant women, in which approximately 650 neonates exposed in the first trimester of pregnancy were examined, showed no increase in malformation rates. However, there are inadequate data regarding the safety of clindamycin in pregnancy.

Clindamycin crosses the placenta. It is assumed that a concentration with therapeutic effect can be reached in the fetus. When administered during pregnancy, the benefits and risks must be carefully considered.

Breast-feeding
Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from <0.50 to 3.8 microg/ml. Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. Systemically administered clindamycin is not recommended during breast-feeding, and a decision should be made whether to discontinue breast-feeding or to select an alternative treatment option. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin.

Fertility
Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability. There are no data on the influence of clindamycin on human fertility.

4.7 Effects on ability to drive and use machines

Clindamycin has mild to moderate influence on the ability to drive and use machines. However, the occurrence of certain undesirable effects (like dizziness, sleepiness, and headaches) can impair the ability to drive and use machines and the ability to react.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency.
The frequency grouping is defined using the following convention:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); and Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 from the available data)**
Infections and infestations		antibiotic-associated pseudo-membranous colitis#				*clostridium difficile* colitis, vaginal infection
Blood and lymphatic system disorders		agranulocytosis, leukopenia, neutropenia, thrombocytopenia, eosinophilia				
Immune system disorders				drug fever	anaphylactic reaction#	anaphylactoid reaction, anaphylactic shock, hypersensitivity
Nervous system disorders			dysgeusia, neuromuscular blocking effect			headache, sleepiness, dizziness
Cardiac disorders			cardiorespiratory arrest §			
Vascular disorders		thrombophlebitis	Hypotension §			
Gastrointestinal disorders	diarrhoea, abdominal pain, vomiting nausea					
Hepatobiliary disorders					transient hepatitis with cholestatic jaundice	jaundice

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 from the available data)**
Skin and subcutaneous tissue disorders		maculo-papular exanthema,			toxic epidermal necrolysis	rash and formation of blisters	drug reaction with eosinophilia and systemic symptoms

		morbilliform exanthema, urticaria			(TEN), Stevens -Johnson syndrome (SJS), Lyell syndrome, angioedema, exfoliative dermatitis, bullous dermatitis, erythema multiforme, pruritus, vaginitis	(hypersens itivity reaction)	(DRESS), acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders						polyarthritis	
General disorders and administration site conditions			pain, injection site abscess				injection site irritation
Investigations		liver function test abnormal					
Renal and urinary disorders							Acute kidney injury#

See section 4.4.
* Side effects identified from post-marketing experience
§ Rare instances have been reported following too rapid intravenous administration (see section 4.4).

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

No overdose symptoms have yet been observed. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. There is no known specific antidote. Clindamycin Villerton is administered via the IV route therefore gastric lavage is not useful.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; macrolides, lincosamides and streptogramins; lincosamides, ATC code: J01FF01

Mechanism of action
Clindamycin binds to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibits protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

Pharmacodynamic effects

The efficacy is basically dependent on the time period in which the agent level is above the minimum inhibitory concentration (MIC) of the pathogen.

Mechanism of resistance
Resistance to clindamycin can be due to the following mechanisms:

Resistance to staphylococci and streptococci is often based on methyl groups increasingly binding to the 23S rRNA (so-called constitutive MLSB-resistance), whereby the binding affinity of clindamycin to the ribosome is highly reduced.
The majority of methicillin-resistant *S. aureus* (MRSA) shows the constitutive MLSB type of resistance and is therefore resistant to clindamycin. Infections caused by macrolide-resistant staphylococci should not be treated with clindamycin, also when in-vitro susceptibility was proven, because therapy may lead to a selection of mutants with constitutive MLSB resistance.

Strains with constitutive MLSB resistance show complete cross-resistance of clindamycin with lincomycin, macrolides (e.g. azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin) as well as streptogramin B.

Breakpoints

The following minimum inhibitory concentrations for susceptible and resistant germs were defined:

EUCAST Breakpoint (Version 8.1, valid from 2018-05-15)

Breakpoints

Pathogen	**Susceptible (S) ≤ mg/L**	**Resistant (R) > mg/L**
Staphylococcus spp[1]	0.25	0.5
Streptococcus groups A,B,C and G[1, 2]	0.5	0.5
Streptococcus pneumoniae[3]	0.5	0.5
Viridans group *streptococci*[3]	0.5	0.5
Gram-negative anaerobes	4	4
Gram-positive anaerobes	4	4
Corynebacterium spp.	0.5	0.5

[1] Inducible clindamycin resistance can be detected by antagonism of clindamycin activity by a macrolide agent. If not detected, then report as susceptible. If detected, then report as resistant and consider adding this comment to the report: "Clindamycin may be still used for a short-term therapy of less serious skin and soft tissue infections as constitutive resistance is unlikely to develop during such therapy".
[2] The clinical importance of inducible clindamycin resistance in combination treatment of severe S. pyogenes infections is not known.
[3] Inducible clindamycin resistance can be detected by antagonism of clindamycin activity by macrolide agent. If not detected, then report as susceptible. If detected, then report as resistant.

Prevalence of acquired resistance
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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Particularly in severe infections or therapy failure microbiological diagnosis with verification of the pathogen and its susceptibility to clindamycin is recommended.
Prevalence of acquired resistance in Europe on the basis of the last 5 year's data from national German resistance surveillance projects and studies (Z.A.R.S. January 2017).

Common susceptible species
Aerobic gram-positive microorganisms
Actinomyces israelii°
Staphylococcus aureus (Methicillin-sensitive)
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococci of the viridans-group^ °
Anaerobic microorganisms
Bacteroides spp.° (excl. B. fragilis) *Clostridium perfringens* °

Fusobacterium spp.° *Peptoniphilus* spp.°
Peptostreptococcus spp.°
Prevotella spp.°
Propionibacterium spp. °
Veillonella spp.°
Other microorganisms
Chlamydia trachomatis°
Chlamydophila pneumoniae°
Gardnerella vaginalis°
Mycoplasma hominis°

Species for which acquired resistance may be a problem
Aerobic gram-positive microorganisms
Staphylococcus aureus
Staphylococcus aureus (Methicillin-resistant)[+]
Staphylococcus epidermidis[+]
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus agalactiae
Aerobic gram-negative microorganisms
Moraxella catarrhalis[$]
Anaerobic microorganisms
Bacteroides fragilis

Inherently resistant organisms
Aerobic gram-positive microorganisms
Enterococcus spp.
Listeria monocytogenes
Aerobic gram-negative microorganisms
Escherichia coli
Haemophilus influenzae
Klebsiella spp.
Pseudomonas aeruginosa
Anaerobic microorganisms
Clostridium difficile
Other microorganisms
Mycoplasma pneumoniae
Ureaplasma urealyticum

◦ No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.
[$] Inherent susceptibility of most of the isolates shows intermediate resistance.
[+] At least on region shows resistance rates higher than 50 %.
[^] Collective name for a heterogeneous group of streptococci species. Resistance rate may vary according to the streptococci species present.

5.2 Pharmacokinetic properties

Absorption
A difference only has to be made between the clindamycin derivatives used up until the time of absorption and splitting of the esters. Afterward, clindamycin exists in the body as a free base (active form). The esters should be considered as being prodrugs.

Clindamycin phosphate is a water-soluble ester for parenteral application. Following intravenous application of 300 mg, the mean serum concentration after one hour is approximately 4 to 6 microg/ml.

Distribution
The degree of binding of clindamycin to plasma proteins is concentration-dependent and lies within the therapeutic range between 40 and 94 %.

Clindamycin readily distributes into the tissues, passes through the placental barrier and distributes into breast milk. Even if the meninges are inflamed, diffusion into the subarachnoid space is inadequate.

High concentrations are achieved in bone tissue, synovial fluid, pleural fluid, expectorations, and pus.

The following concurrent serum concentrations of the active substance are reported: in bone tissue 40% (20-75%), in synovial fluid 50%, in peritoneal fluid 50%, in pleural fluid 50-90%, in expectorations 30-75% and in pus 30%.

Biotransformation
Clindamycin is metabolized primarily in the liver.

In vitro studies in human liver and intestinal microsomes indicated that clindamycin is predominantly oxidized by CYP3A4, with a minor contribution from CYP3A5, to form clindamycin sulfoxide and a minor metabolite, N-desmethylclindamycin.

The serum half-life of clindamycin is approx. 3 hours in adults and approx. 2 hours in children. In the presence of renal insufficiency and moderate to severe hepatic insufficiency, the half-life is prolonged.

Some metabolites are microbiologically active (N-demethyl and sulphoxide). Medicinal products that act as enzyme inducers in the liver shorten the mean retention time of clindamycin in the body.

Elimination
Clindamycin is eliminated via the faeces at 2/3 and via the urine at 1/3 of the dose. Less than 10% of the dose is excreted unchanged in the urine.

Clindamycin cannot be dialyzed.

5.3 Preclinical safety data

Symptoms of intoxication are decreased activity of the animals and convulsions.

After repeated doses (i.m.) of clindamycin to dogs an increase of the AST and ALT was reported and also a slight increase of the liver-weight without morphologic changes were documented. Long-term administration of clindamycin to dogs induced damage to the gastric mucosa and to the gall bladder.

Local reactions at the injection site (inflammations, haemorrhages and tissue damage) were observed following intramuscular and subcutaneous administration, however, the concentration of the solution administered far exceeded the maximum therapeutic concentration.

Mutagenicity and tumorigenic potential
In-vitro and in-vivo studies did not reveal any mutagenic potential of clindamycin. No long-term animal studies investigating the tumorigenic potential of clindamycin have been conducted.

Reproduction toxicity
Studies on clindamycin in rats and mice provided no evidence to indicate any fertility impairment or embryo/fetotoxic properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose monohydrate
Disodium edetate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibilities studies, this medicinal product must not be mixed with other medicinal products.

Incompatibility has been reported with:
Ampicillin sodium, aminophylline, barbiturates, calcium gluconate, ceftriaxone sodium, ciprofloxacin, diphenylhydantoin, idarubicin hydrochloride, magnesium sulphate, phenytoin sodium and ranitidine hydrochloride.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

100 mL transparent polyolefin bag equipped with two polyolefin tubing ports and a twist off port (composed of Polyolefinic materials), containing 50 ml of sterile solution.

Pack sizes:
10 bags in foil overpouches
24 bags in foil overpouches

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

To be used immediately after the bag is opened.
Discard any unused solution immediately after initial use.

7 MARKETING AUTHORISATION HOLDER

Villerton Invest S.A.
14, Rue Edward Steichen
2540
Luxembourg

8 MARKETING AUTHORISATION NUMBER

PA1960/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th July 2019

10 DATE OF REVISION OF THE TEXT

August 2022