SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Benzylpenicillin benzathine for injection2.4 Million I.U

2. Qualitative and quantitative composition

1 vial of powder for suspension for injection contains 2.4 Million I.U., equivalent to approximately 1836 mg benzylpenicillin benzathine, or approximately 1440 mg benzylpenicillin.

Excipients with known effect:

Lecithin

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for suspension for injection.

White crystalline powder.

4. Clinical particulars

4.1 Therapeutic indications

Benzylpenicillin benzathine is indicated in adults, adolescents, children and neonates for the treatment and prophylaxis of the following infections (see section 5.1):

For the treatment of:

- erysipelas
- syphilis: early syphilis (primary and secondary)
- latent syphilis (except for neurosyphilis and presence of pathological CSF findings)
- yaws
- pinta

For the prophylaxis of:

- rheumatic fever (chorea, rheumatic carditis)
- poststreptococcal glomerulonephritis
- erysipelas

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

4.2 Posology and method of administration

Posology

The dosing recommendations depend on the severity and the type of infection, the age and the hepato-renal function of patients.

Dosage and duration of treatment

1. General therapy:

- Adults and adolescents:	1.2 Million I.U.
- Children (> 30 kg body weight):	1.2 Million I.U.
- Children (< 30 kg body weight):	0.6 Million I.U.
Duration of treatment:	Single dose

Note: In streptococcal diseases, a 10-day minimum course of treatment should be observed to avoid secondary diseases. This is generally ensured with a single injection of 0.6 Million I.U., 1.2 Million I.U. or 2.4 Million I.U..

2. Treatment of syphilis:

2.1. Primary and secondary stage

- Adults and adolescents:	2.4 Million I.U.
- Children:	50,000 IU per kg body weight; however not more than 2.4 Million I.U.
Duration of treatment:	Single dose (If clinical symptoms recur or laboratory findings remain strongly positive, treatment should be repeated.)

2.2. Late-stage syphilis (latent seropositive syphilis)

- Adults and adolescents:	2.4 Million I.U.
- Children:	50,000 IU per kg body weight per week; however not more than 2.4 Million I.U.
Duration of treatment:	Once weekly for 3 weeks

2.3. Treatment of congenital syphilis (without neurological involvement)

- Neonates and infants:	50,000 IU per kg body weight
Duration of treatment:	Single dose

3. Treatment of yaws and pinta:

- Adults and adolescents:	1.2 Million I.U.
- Children (> 30 kg body weight):	1.2 Million I.U.

- Children (< 30 kg body weight): Duration of treatment:	0.6 Million I.U. Single dose

4. Prophylaxis of rheumatic fever, poststreptococcal glomerulonephritis and erysipelas:

- Adults and adolescents:	1.2 Million I.U.
- Children (> 30 kg body weight):	1.2 Million I.U.
- Children (< 30 kg body weight):	0.6 Million I.U.
Duration of treatment:	
a) without cardiac involvement:	at least 5 years (or up to 21 years of age) every 3-4 weeks
b) transient cardiac involvement:	at least 10 years (or up to 21 years of age) every 3-4 weeks
c) persistent cardiac involvement:	at least 10 years (or up to 40 years of age) every 3-4 weeks; life-long prophylaxis is sometimes necessary

Special patient groups

Patients with impaired renal function

Table 1 - Recommended dose adjustments in patients with impaired renal function.

Dosage for adults, adolescents and children based on creatine clearance			
Creatinine clearance in ml/min	≥ 60	59 – 15	< 15
Proportion of the normal daily dose (%)	100	75	20 – 50 (1 – 3 Million I.U. per day maximum.)
Dosage interval	1 single administration	1 single administration	in 2 – 3 single administrations

Haemodialysis patients

Benzylpenicillin benzathine can be removed by haemodialysis. There are no data available on the influence of dialysis on the plasma levels of benzylpenicillin. The

decision to treat patients on dialysis with Benzylpenicillin benzathine 1.2 Million I.U. and 2.4 Million I.U. powder for suspension for injection needs therefore to be taken on a case by case basis.

Patients with impaired hepatic function

In very severe cases of impaired hepatic and renal function, there may be a delay in the degradation and excretion of penicillin.

Method of administration

The preparation is **strictly for intramuscular injection**(see section 4.4).

The injection must not be administered into tissue with reduced perfusion (see section 4.4).

Benzylpenicillin benzathine 1.2 Million I.U. and 2.4 Million I.U. powder for suspension for injection should be administered by deep intramuscular injection into the upper, outer quadrant of the gluteus maximus or Hochstetter's ventrogluteal field, with the needle pointing towards the iliac crest or according to von Hochstetter's method. The puncture should be as vertical to the skin surface as possible and the injection as far away from major vessels as possible. In all events, aspiration must be performed prior to the injection. If aspiration of blood or pain occurs during the injection, it must be discontinued.

In children, the mid-lateral thigh muscles (quadriceps femoris) are recommended as an injection site. The deltoid muscle is only suitable if it is well formed; in this case, attention must be paid to the radial nerve.

In infants and young children, the peripheral area of the upper outer quadrant of the gluteal region should be used as the area for injection only in exceptional cases (e.g. widespread burns), in order to avoid sciatic nerve lesions.

In general, a needle of a diameter of at least 700µm (needle gauge: 22, 21 or 20) for intramuscular injection is preferred.

For depot preparations, a total volume of 5ml per injection site is stated as the tolerance limit. Thus, no more than 5ml of the ready-to-inject suspension should be administered at any one time into one site. Benzylpenicillin benzathine 1.2 Million I.U. powder for suspension reconstituted with at least 3.5ml of diluent may therefore be injected into a single injection site where clinically appropriate and provided no more than 4ml of diluent is used in the case of 1.2 Million I.U. vials. In the case of Benzylpenicillin benzathine 2.4 Million I.U. powder for suspension for injection reconstituted with at least 5ml of diluent, the final reconstituted volume of approximately 7ml should be divided and administered across two injection sites.

The injection should be given as slowly as possible and only with the application of low pressure. “Rubbing” after the injection should be avoided.

Severe local reactions may occur during intramuscular administration, especially in young children. If possible, taking into account the therapeutic indications and schedule regimens and weighing the benefit-risk ratio, alternative treatments such as intravenous therapy with a suitable penicillin product should be considered (see also section 4.4).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporin, carbapenem or monobactam).

- When lidocaine solution is used as a solvent, contraindications to lidocaine must be excluded before intramuscular injection of benzylpenicillin benzathine (see section 4.4 and section 6.6).

4.4 Special warnings and precautions for use

Benzylpenicillin benzathine should not be used in tissues with reduced perfusion.

Before initiating therapy with benzylpenicillin benzathine, a careful investigation should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity (analphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, benzylpenicillin benzathine must be discontinued and appropriate therapy instituted.

Prior to treatment, a hypersensitivity test should be performed if possible. The patient should be made aware of the possible occurrence of allergic symptoms and of the need to report them.

Caution should be exercised in patients with the following conditions:

- allergic diathesis or bronchial asthma (there is an increased risk of a hypersensitivity reaction):

- renal insufficiency (for dose adjustment, see section 4.2);

- impaired hepatic function (see section 4.2).

Based on a general principle, particularly in some exposed patients, medical observation should if possible be ensured for at last half an hour after the administration of this antibiotic, as severe immediate allergic reactions may occur even after the first administration.

Beta-lactams are associated with a risk of encephalopathy (confusion, altered levels of consciousness, epilepsy or movement abnormalities), particularly in cases of over-dose or impaired renal function.

When treating syphilis, a Jarisch-Herxheimer reaction may occur as a result of the bactericidal action of penicillin on pathogens. Within 2 to 12 hours after administration headaches, fever, sweating, shivering, myalgia, arthralgia, nausea, tachycardia, increased blood pressure followed by hypotension may occur. These symptoms resolve after 10 to 12 hours. Patients should be informed that this is a usual, transient sequela of antibiotic therapy. Appropriate therapy should be instituted to suppress or attenuate a Jarisch-Herxheimer reaction (see section 4.8).

With long-term treatment (more than a single dose), periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is recommended.

Prolonged use of benzylpenicillin benzathine may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for superinfections.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including benzylpenicillin benzathine and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, benzylpenicillin benzathine should be discontinued, a physician be consulted, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

If neurological involvement cannot be excluded in patients with congenital syphilis, forms of penicillin that reach a higher level in cerebrospinal fluid should be used.

In diseases such as severe pneumonia, empyema, sepsis, meningitis or peritonitis, which require higher serum penicillin levels, alternative treatment such as the water-soluble alkali salt of benzylpenicillin should be considered.

Notes on administering benzylpenicillin benzathine

Painful induration may occur in the event of accidental subcutaneous administration. Ice packs help in such cases.

In the event of inadvertent intravascular injection, Hoigné syndrome may occur (symptoms of shock with mortal fear, confusion, hallucinations, possibly cyanosis, tachycardia and motor disorders, although no circulatory collapse), caused by microemboli of the suspension. The symptoms regress within an hour. If progression is severe, parenteral administration of sedatives is indicated.

In the event of inadvertent intra-arterial injection, particularly in children, serious complications may occur, such as vascular occlusion, thrombosis and gangrene. Initial signs are pale patches in the skin area of the gluteal region. As a result of high

injection pressure, retrograde entry of the injected liquid into the common iliac artery, aorta or spinal arteries may occur.

Repeated injections into a limited area of the muscle tissue, which are associated with long term therapy with depot-penicillins (e.g. in the treatment of syphilis) may induce tissue damage and increased local vascularization. Subsequent injections increase the possibility of penetration of injection substance into the blood, either by direct injection into a blood vessel or caused by the injection pressure itself, or by "rubbing" of the depot. During long term therapy it is therefore recommended to administer each injection a large distance from the preceding injection.

Effect on diagnostic laboratory procedures:

- A positive direct Coombs' test often develops (≥ 1% to < 10%) in patients receiving 10 million IU (equivalent to 6 g) benzylpenicillin or more per day. After discontinuation of the penicillin, the direct antiglobulin test may remain positive for 6 to 8 weeks (see section 4.8).

- Determination of urinary protein using precipitation techniques (sulphosalicylic acid, trichloroacetic acid), the Folin-Ciocalteu-Lowry method or the biuret method may lead to false positive results. Urinary protein should therefore be determined by other methods.

- Urinary amino acid determination using the ninhydrin method may likewise lead to false-positive results.

- Penicillins bind to albumin. In electrophoresis methods to determine albumin, pseudobisalbuminaemia may therefore be simulated.

- During therapy with benzylpenicillin benzathine, non-enzymatic urinary glucose detection and urobilinogen detection may exhibit a false positive.

- When determining 17-ketosteroids (using the Zimmermann reaction) in the urine, increased values may occur during therapy with benzylpenicillin benzathine.

Excipients

Benzylpenicillin benzathine 1.2 Million I.U. and 2.4 Million I.U. powder for suspension for injection contains phospholipids from the soya lecithin. If you are allergic to peanut or soya, do not use this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per vial of 1.2 Million I.U. and 2.4 Million I.U., i.e. essentially 'sodium-free'.

Delayed excretion of povidone should be taken into consideration in patients with renal impairment. As this medicinal product contains povidone, it cannot be ruled out that frequent or prolonged use may very rarely lead to the accumulation of povidone in the reticuloendothelial system (RES), or to local deposits and the formation of foreign body granulomas which may be confused with tumours.

Use of lidocaine

When lidocaine solution is used as a solvent (see section 6.6), contraindications to lidocaine, warnings and other relevant information as detailed in the Summary of Product Characteristics of lidocaine must be considered before use (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of benzylpenicillin benzathine is not recommended with:

-*bacteriostatic antibiotics*: based on the general principle not to combine bactericidal and bacteriostatic antibiotics.

Caution should be exercised when co-administering the following:

-*probenecid*: the administration of probenecid leads to inhibition of the tubular secretion of benzylpenicillin, resulting in an increase in the serum concentration and prolongation of the elimination half-life. Furthermore, probenecid inhibits the penicillin transport from the cerebrospinal fluid, so that the concomitant administration of probenecid reduces the penetration of benzylpenicillin into brain tissue even further.

-*methotrexate*: when taken at the same time as benzylpenicillin benzathine, the excretion of methotrexate is reduced. This can lead to increased methotrexate toxicity. The combination with methotrexate is not recommended.

-*anticoagulants*: concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with benzylpenicillin benzathine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Benzylpenicillin benzathine crosses the placenta. 10-30% of maternal plasma concentrations are found in the foetal circulation. High concentrations are also reached in the amniotic fluid. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Benzylpenicillin benzathine can be used during pregnancy when appropriately indicated and with due consideration of the benefits and risks.

Breast-feeding

Benzylpenicillin benzathine is excreted in human milk in small amounts. The concentration in maternal milk may reach 2 to 15% of the mother's serum concentrations.

Although no undesirable effects in infants fed on breast milk have been reported to date, consideration must nevertheless be given to the possibility of sensitisation or interference with the intestinal flora. Breast-feeding should be stopped in the case of occurrence of diarrhoea, candidosis or rash in the child.

In infants also being fed on baby food, mothers should express and discard breast milk during benzylpenicillin benzathine treatment. Breast-feeding can be resumed 24 hours after finishing treatment.

Fertility

No fertility studies have been conducted in humans. Reproductive studies on mice, rats and rabbits have not revealed any negative effects on fertility. No long-term fertility studies on laboratory animals are available.

4.7 Effects on ability to drive and use machines

Due to the occurrence of possible serious undesirable effects (e.g. anaphylactic shock with collapse and anaphylactoid reactions, see also section 4.8), Benzylpenicillin benzathine can have a major influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent and common adverse reactions related to benzylpenicillin benzathine are candidiasis, diarrhoea, nausea and laboratory investigation changes.

Table 2 - Tabulated list of adverse drug reactions by MedDRA System Organ Class.

MedDRA System Organ class	**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)**	**Frequency not known (cannot be estimated from available data)**
Infections and infestations	Candidiasis				
Blood and lymphatic system disorders				Haemolytic anaemia Leukopenia Thrombocytopenia Agranulocytosis	
Immune system disorders			Allergic reactions Urticaria Angioedema Erythema		Serum sickness

			multiform Exfoliative dermatitis Fever Arthralgia Anaphylactic shock with collapse and anaphylactoid reactions (asthma, purpura, gastrointestinal symptoms)		
Gastrointestinal disorders	Diarrhoea Nausea	Stomatitis and glossitis Vomiting			Pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders					Hepatitis Cholestasis
Renal and urinary disorders			Nephropathy Interstitial nephritis		
General disorders and administration site conditions					Pain at the injection site Injection site infiltrates Hoigné syndrome Nicolau syndrome
Investigations	Positive direct Coombs' test False-positive urinary protein determination				

	when precipitation techniques are used (Folin-Ciocalteu-Lowry method, biuret method) False-positive urinary amino acid determination (ninhydrin method) Simulation of pseudobisalbumin aemia when using electrophoresis methods to determine albumin False-positive non-enzymatic urinary glucose detection and urobilinogen detection Increased levels when determining 17-ketosteroids in urine (when the Zimmermann reaction is used) (see section 4.4)				

Description of selected adverse reactions

When treating syphilis, a Jarisch-Herxheimer reaction may occur as a result of bacteriolysis, characterised by fever, chills, general and focal symptoms. In patients with dermatomycosis, para-allergic reactions may occur, as common antigenicity may exist between penicillins and dermatophyte metabolites.

In infants, local reactions are possible.

It cannot be excluded that, in very rare cases and due to the povidone content, povidone may accumulate in the reticuloendothelial system (RES) or local deposits and foreign body granuloma may occur, which may be confused with tumours.

4.9 Overdose

At extremely high doses, penicillins can induce neuromuscular excitability or epileptiform seizures. If overdose is suspected, clinical monitoring and symptomatic measures are indicated. Benzylpenicillin can be haemodialyzed.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Antibacterials for systemic use, beta-lactamase sensitive penicillins.

ATC code: J01CE08

Mechanism of action

For benzylpenicillin benzathine, the mechanism of action is based on an inhibition of bacterial cell wall synthesis (during the growth phase) through a blockade of the penicillin-binding proteins (PBPs), such as transpeptidases. This results in a bactericidal action.

Resistance

Resistance to benzylpenicillin benzathine can be due to the following mechanisms:

-*Inactivation by beta-lactamases:* benzylpenicillin benzathine is not beta-lactamase-resistant and therefore has no effect against beta-lactamase-producing bacteria (e.g. staphylococci or gonococci).

-*Reduced affinity of PBPs for benzylpenicillin benzathine:* the acquired resistance in pneumococci and a few other streptococci to benzylpenicillin benzathine is due to modifications of existing PBPs as a result of mutation. However, the formation of an additional PBP with reduced affinity for benzylpenicillin benzathine is responsible for resistance in methicillin (oxacillin)-resistant staphylococci.

-In Gram-negative bacteria, inadequate penetration of benzylpenicillin benzathine through the outer cell wall can lead to insufficient PBP inhibition.

-Benzylpenicillin benzathine can be actively transported from the cell by efflux pumps.

-Benzylpenicillin benzathine is partially or completely cross-resistant to other penicillins and cephalosporins.

PK/PD relationship

Efficacy largely depends on the length of time that the active substance level remains above the minimum inhibitory concentration (MIC) of the pathogen.

Breakpoints

Table 3 - EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints.

Pathogen	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 0.12 mg/l	> 0.12 mg/l
Streptococcus spp. (Groups A, B, C, G)	≤ 0.25 mg/l	> 0.25 mg/l
Streptococcus pneumoniae #	≤ 0.06 mg/l	> 2 mg/l
Streptococci of the "Viridans" group	≤ 0.25 mg/l	> 2 mg/l
Neisseria meningitidis	≤ 0.06 mg/l	> 0.25 mg/l
Neisseria gonorrhoeae	≤ 0.06 mg/l	> 1 mg/l
Gram-negative anaerobes	≤ 0.25 mg/l	> 0.5 mg/l
Gram-positive anaerobes	≤ 0.25 mg/l	> 0.5 mg/l
Non-species-specific breakpoints *	≤ 0.25 mg/l	> 2 mg/l
* Based mainly on serum pharmacokinetics # Infections other than meningitis		

The prevalence of acquired resistance in individual species may vary geographically and with time for selected species and local information on the resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Table 4 - Commonly susceptible species.

Aerobic Gram-positive micro-organisms
Streptococcus pyogenes
Streptococcus dysgalactiae subsp. equisimilis (Group C & G streptococci)
Streptococci of the "Viridans" group
Other micro-organisms
Treponema pallidum
Information derived from published literature, clinical experience and therapeutic guidelines. Collective name for a heterogeneous group of streptococci species. The resistance rate can vary depending on the streptococci species present.

5.2 Pharmacokinetic properties

Pharmacokinetic data are based on an old dossier and information derived from them are limited. However published literature, clinical experience and therapeutic guidelines can be taken into account.

Absorption

Following intramuscular administration, benzylpenicillin benzathine is absorbed slowly and converted by hydrolysis to benzylpenicillin. Peak plasma levels are reached 24 hours (children) or 48 hours (adults) post-injection.

Distribution

After intramuscular injection serum levels of benzylpenicillin are sustained:

• 14 days after intramuscular injection of 2.4 Million I.U. a serum level of 0.12 µg/ml was measured.

• 21 days after intramuscular injection of 1.2 Million I.U. a serum level of 0.06 µg/ml was measured.

The volume of distribution is around 0.3-0.4 l/kg in adults and about 0.75 l/kg in children. Plasma protein binding is approximately 55%.

Biotransformation and elimination

Elimination largely takes place (50 - 80%) as unchanged substance via the kidneys (85 - 95%) and, to a lesser extent, in active form within the bile (about 5%).

The plasma half-life in adults with healthy kidneys is approximately 30 min.

Kinetics in special patient groups

-*Preterm and newborn infants*: due to the immaturity of kidneys and liver at this age, the serum half-life is up to three hours (and more). The dosing interval must therefore be no shorter than 8 - 12 hours (depending on the degree of maturity).

-*Elderly patients:* elimination processes may also be delayed with advanced age. The dosage should therefore be adjusted to individual renal function.

Administration of lidocaine as a solvent

Lidocaine has no effect on the pharmacokinetic profile of benzylpenicillin benzathine following intramuscular administration.

Clinical practice guidelines recommend the reconstitution of benzylpenicillin benzathine with local anaesthetics, such as lidocaine, to reduce pain at the injection site.

5.3 Preclinical safety data

Reproductive studies in mice, rats and rabbits revealed no negative effects on fertility or on the foetus. No long-term studies on laboratory animals are available with regard to carcinogenicity, mutagenicity and fertility.

6. Pharmaceutical particulars

6.1 List of excipients

Lecithin

6.2 Incompatibilities

Data on compatibility are available with water for injections and lidocaine.

6.3 Shelf life

36 months

Following reconstitution, benzylpenicillin benzathine should be used immediately.

6.4 Special precautions for storage

Store below 30℃, away from light and moisture.

6.5 Nature and contents of container

Molded glass vials sealed with halogenated butyl rubber stoppers with aluminium caps.

Pack of 50 vials.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Reconstitution of the suspension for intramuscular injection:

The suspension must be prepared aseptically.

The contents of the vial should be reconstituted in at least 3.5ml (1.2 Million I.U.), or 5ml (2.4 Million I.U.) of diluent (e.g. water for injections or 1% Lidocaine Injection BP).

Clinical practice guidelines recommend the reconstitution of benzathine benzylpenicillin with local anaesthetics, such as 1% Lidocaine Injection BP, to reduce pain at the injection site.

To reconstitute the suspension for injection, agitate this suspension carefully for at least 20 seconds until a homogeneous suspension is obtained.

The suspension for injection is intended for single use only.

The product should be used immediately after reconstituting the suspension.

In general, a needle of a diameter of at least 900μm (needle gauge: 20) for intramuscular injection is preferred.

Prior to injection, intravascular administration should be excluded by aspiration. The injection site should be changed with repeated injections.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

07116/07481/NMR/2019

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 10 Feb 2022

10. Date of revision of the text

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