HPRA An tÚdarás Rialála Táirgí Sláinte Health Products Regulatory Authority

DEPO-MEDRONE

40 Mg/Ml Suspension for Injection

Pfizer Healthcare Ireland PA0822/122/001

Main Information

Trade Name DEPO-MEDRONE
Active Substances METHYLPREDNISOLONE ACETATE
Strength 40 Mg/Ml
Dosage Form Suspension for Injection
Licence Holder Pfizer Healthcare Ireland
Licence Number PA0822/122/001

Group Information

ATC Code H02AB04 Glucocorticoids

Status

Authorised/Withdrawn Authorised
Licence Issued 05/04/2012
Supply Status Supply through pharmacies only
Dispensing Status Product subject to prescription which may not be renewed (A)
Marketing Status Marketed
Promotion Status Promotion to Healthcare Professionals only
Conditions of Licence

Documents

Summary of Product Characteristics PDF Version
Package Leaflet No document available
Public Assessment Report No document available

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Summary of Product Characteristics

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Depo-Medrone 40 mg/ml Suspension for Injection 1 ml vial

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylprednisolone Acetate 40mg/ml
Each 1ml vial contains 40mg Methylprednisolone Acetate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.
Sterile white aqueous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Depo−Medrone is used in the management of corticosteroid disorders.

4.2 Posology and method of administration

Depo−Medrone may be used by any of the following routes: intramuscular, intra−articular, intralesional, intrarectal, intrabursal, periarticular or into the tendon sheath. It **must not** be used by the intrathecal or intravenous routes (see section 4.3 Contraindications).

Undesirable effects may be minimised by using the lowest effective dose for the minimum period (see section 4.4 Special warnings and precautions for use).

Depo−Medrone vials are intended for single dose use only.

The following may serve as a guide:

Adults: The usual dose is 20 to 120 mg daily or weekly, with adjustment on the basis of the individual requirements of the patient.

Elderly patients: When used according to instructions, there is no information to suggest that a change in dosage is warranted in the elderly. Treatment of elderly patients, however, particularly if long-term, should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age and close clinical supervision is required (see section 4.4 Special warnings and precautions for use).

Children (including infants): Dosage depends principally on the condition and to a lesser extent on body weight and age of the patient.

Intramuscular − for sustained systemic effect:

Allergic conditions (hay fever, asthma, rhinitis, drug reactions), 80 − 120 mg (2 − 3 ml).

Dermatological conditions, 40 − 120 mg (1 − 3 ml).

Rheumatic disorders, collagen disease, SLE, 40 − 120 mg (1 − 3 ml) per week.

Adrenogenital syndrome, 40 mg (1 ml) every two weeks.

On average the effect of a single 2 ml (80 mg) injection may be expected to last approximately two weeks.

In the case of seasonal allergic rhinitis a single injection is frequently sufficient. If necessary, however, a second injection may be given after 2 to 3 weeks.

Intra−articular

Rheumatoid arthritis, osteo-arthritis. The dose of Depo−Medrone depends upon the size of the joint and the severity of the condition. Repeated injections, if needed, may be given at intervals of one to five or more weeks depending upon the degree of relief obtained from the initial injection. A suggested dosage guide is: large joint (knee, ankle, shoulder), 20 − 80 mg (0.5 − 2 ml); medium joint (elbow, wrist), 10 − 40 mg (0.25 − 1 ml); small joint (metacarpophalangeal, interphalangeal, sternoclavicular, acromioclavicular), 4 − 10 mg (0.1 − 0.25 ml).

Intrabursal

Subdeltoid bursitis, prepatellar bursitis, olecranon bursitis. For administration directly into bursae, 4 − 30 mg (0.1 − 0.75 ml). In most cases, repeat injections are not needed.

Intralesional

Keloids, localized lichen planus and simplex, granuloma annulare, alopecia areata, and discoid lupus erythematosus. For administration directly into the lesion for local effect in dermatological conditions, 20 − 60 mg (0.5 − 1.5 ml).

For large lesions, the dose may be distributed by repeated local injections of 20 − 40 mg (0.5 − 1 ml). One to four injections are usually employed. Care should be taken to avoid injection of sufficient material to cause blanching, since this may be followed by a small slough.

Rectal

Ulcerative colitis, 40 − 120 mg (1 − 3 ml). Administer in retention enemas or by continuous drip in 30 − 300 ml of water, three to seven times weekly for two or more weeks.

Periarticular

Epicondylitis. Infiltrate 4 − 30 mg (0.1 − 0.75 ml) into the affected area.

Into the tendon sheath

Tendonitis, tenosynovitis, epicondylitis. For administration directly into the tendon sheath, 4 − 30 mg (0.1 − 0.75 ml). In recurrent or chronic conditions, repeat injections may be necessary.

Special precautions should be observed when administering Depo−Medrone. Intramuscular injections should be made deeply into the gluteal muscles. The usual technique of aspirating prior to injection should be employed to avoid intravascular administration. Doses recommended for intramuscular injection must not be administered superficially or subcutaneously.

Intra−articular injections should be made using precise, anatomical localisation into the synovial space of the joint involved. The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves. Suitable sites for intra−articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal and hip joints.
The spinal joints, unstable joints and those devoid of synovial space are not suitable. Treatment failures are most frequently the result of failure to enter the joint space. Intra−articular injections should be made with care as follows, ensure correct positioning of the needle into the synovial space and aspirate a few drops of joint fluid. The aspirating syringe should then be replaced by another containing Depo−Medrone. To ensure position of the needle, synovial fluid should be aspirated and the injection made. After injection the joint is moved slightly to aid mixing of the synovial fluid and the suspension. Subsequent to therapy care should be taken for the patient not to overuse the joint in which benefit has been obtained. Negligence in this matter may permit an increase in joint deterioration that will more than offset the beneficial effects of the steroid.

Intrabursal injections should be made as follows: the area around the injection site is prepared in a sterile way and a wheal at the site made with 1 percent procaine hydrochloride solution. A 20 to 24 gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place and the aspirating syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

In the treatment of tenosynovitis and tendonitis care should be taken to inject Depo−Medrone into the tendon sheath rather than into the substance of the tendon. Due to the absence of a true tendon sheath, the Achilles tendon should not be injected with Depo−Medrone.

4.3 Contraindications

Depo-Medrone is contraindicated where there is known hypersensitivity to components and in systemic infection unless specific anti-infective therapy is employed.

Depo-Medrone should not be used in the Achilles tendon due to the absence of a true tendon sheath.

Due to its potential for neurotoxicity, Depo−Medrone **must not** be given by the intrathecal route. In addition, as the product is a suspension it **must not** be given by the intravenous route (see section 4.8 Undesirable effects).

4.4 Special warnings and precautions for use

Special Warnings:

1. A Patient Information Leaflet is provided in the pack by the manufacturer.

2. Undesirable effects may be minimised by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity (see section 4.2 Posology and method of administration).

3. Depo−Medrone vials are intended for single dose use only. Any multidose use of the product may lead to contamination.

4. Depo−Medrone is not recommended for epidural, intranasal, intra-ocular, or any other unapproved route of administration. See Undesirable effects section for details of side-effects reported from some non−recommended routes of administration.

5. Due to the absence of a true tendon sheath, the Achilles tendon should not be injected with Depo−Medrone.

6. While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physiochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring dermal and/or subdermal changes may form depressions in the skin at the injection site and the possibility of depigmentation. The degree to which this reaction occurs will vary with the amount of adrenal steroid injected. Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed. In order to minimise the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into the area of the lesion should be made whenever possible. The technique of intra−articular and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

7. Intralesional doses should not be placed too superficially, particularly in easily visible sites in patients with deeply pigmented skins, since there have been rare reports of subcutaneous atrophy and depigmentation.

8. Systemic absorption of methylprednisolone occurs following intra−articular injection of Depo−Medrone. Systemic as well as local effects can therefore be expected.

9. Intra−articular corticosteroids are associated with a substantially increased risk of inflammatory response in the joint, particularly bacterial infection introduced with the injection. Charcot-like arthropathies have been reported particularly after repeated injections. Appropriate examination of any joint fluid present is necessary to exclude any bacterial infection, prior to injection.

10. Following a single dose of Depo−Medrone, plasma cortisol levels are reduced and there is evidence of hypothalamic−pituitary−adrenal (HPA) axis suppression. This suppression lasts for a variable period of up to 4 weeks. The usual dynamic tests of HPA axis function can be used to diagnose evidence of impaired activity (e.g. Synacthen test).

11. Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute rebound exacerbation of disease, acute adrenal insufficiency or polyarteritis, being tapered off over weeks or months according to the dose and duration of treatment. During prolonged therapy any intercurrent illness, trauma, anaesthesia or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

12. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

13. Because rare instances of anaphylactic reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of drug allergy.

14. Corticosteroids may mask some signs of infection, and new infections may appear during their use. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised.

15. Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

16. Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults, particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IVIG) may be indicated. Exposed patients should be advised to seek medical advice without delay.

17. Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

18. The use of Depo−Medrone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

19. Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see section 4.8 Undesirable effects).

20. Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerve and may enhance the establishment of secondary ocular infections due to fungi or viruses.

21. *The following precautions apply for parenteral corticosteroids:* Following intra−articular injection, the occurrence of a marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

    Local injection of a steroid into a previously infected joint is to be avoided.

    Corticosteroids should not be injected into unstable joints.

    Sterile technique is necessary to prevent infections or contamination.

    The slower rate of absorption by intramuscular administration should be recognised.

22. Patients and/or carers should be warned that potentially severe psychiatric adverse reactions **may** occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 Interaction with Other Medicaments and Other Forms of Interaction that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

23. Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects (see section 4.5).

    Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Precautions: Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

1. Osteoporosis (post-menopausal females are particularly at risk).
2. Hypertension or congestive heart failure.
3. Existing or previous history of severe affective disorders (especially previous steroid psychosis).
4. Diabetes mellitus (or a family history of diabetes).
5. History of tuberculosis.
6. Glaucoma (or a family history of glaucoma).
7. Previous corticosteroid-induced myopathy.
8. Liver failure or cirrhosis.
9. Renal insufficiency.
10. Epilepsy.
11. Peptic ulceration.
12. Fresh intestinal anastomoses.
13. Predisposition to thrombophlebitis.
14. Abscess or other pyogenic infections.
15. Ulcerative colitis.
16. Diverticulitis.
17. Myasthenia gravis.
18. Ocular herpes simplex, for fear of corneal perforation.
19. Hypothyroidism.
20. Exanthematous infectious diseases.
21. Cushing's Syndrome.

Use in Children

Corticosteroids cause growth retardation in infancy, childhood and adolescence which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time.

Use in the elderly

The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

4.5 Interaction with other medicinal products and other forms of interaction

1. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse effects associated with the individual use of either drug may be more apt to occur.

2. Drugs that induce hepatic enzymes, such as rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

3. Drugs such as erythromycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decrease their clearance.

4. Steroids may reduce the effects of anticholinesterases in myasthenia gravis. The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

5. The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

6. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in hypothrombinaemia.

7. Steroids have been reported to interact with neuromuscular blocking agents such as pancuronium with partial reversal of the neuromuscular block.

8. Pharmacokinetic enhancers (cobicistat) - CYP3A4 INHIBITORS, which are used to treat HIV infections.

4.6 Fertility, pregnancy and lactation

Corticosteroids cross the placenta. There may be a very small risk of cleft palate and intra-uterine growth retardation in the foetus; there is evidence of harmful effects on pregnancy in animals. Neonates of mothers who received such therapy during pregnancy should be observed for signs of hypo-adrenalism and appropriate measures instituted if such signs exist. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state. Patients with pre-eclampsia or fluid retention require close monitoring.

Methylprednisolone is excreted in breast milk and infants of mothers taking pharmacological doses of steroids should be monitored carefully for signs of adrenal suppression.

4.7 Effects on ability to drive and use machines

None Stated

4.8 Undesirable effects

The incidence of predictable undesirable side-effects associated with the use of corticosteroids, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and duration of treatment (see Special warnings and precautions for use).

PARENTERAL CORTICOSTEROID THERAPY - Anaphylactic reaction or allergic reactions, hypopigmentation or hyperpigmentation, subcutaneous and cutaneous atrophy, sterile abscess, post injection flare (following intra-articular use), Charcot-like arthropathy, rare instances of blindness associated with intralesional therapy around the face and head.

GASTRO-INTESTINAL - Dyspepsia, peptic ulceration with perforation and haemorrhage, abdominal distension, oesophageal ulceration, oesophageal candidiasis, acute pancreatitis, perforation of bowel.

Increases in alanine transaminase (ALT, SGPT) aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE EFFECTS - Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, may suppress reactions to skin tests, recurrence of dormant tuberculosis (see Special warnings and precautions for use).

MUSCULOSKELETAL - Steroid myopathy, osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, aseptic necrosis, muscle weakness.

FLUID AND ELECTROLYTE DISTURBANCE - Sodium and water retention, potassium loss, hypertension, hypokalaemic alkalosis, congestive heart failure in susceptible patients.

DERMATOLOGICAL - Impaired healing, petechiae and ecchymosis, thin fragile skin, skin atrophy, bruising, striae, telangiectasia, acne.

ENDOCRINE/METABOLIC - Suppression of the hypothalamo-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea. Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, negative nitrogen and calcium balance. Increased appetite.

NEUROPSYCHIATRIC - A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood psychological dependence and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, seizures and cognitive dysfunction including confusion and amnesia have been reported for all corticosteroids. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions was estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown. Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of methylprednisolone.

OPHTHALMIC - Increased intra-ocular pressure, glaucoma, papilloedema, cataracts with possible damage to the optic nerve, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease, exophthalmos.

GENERAL - Leucocytosis, hypersensitivity including anaphylaxis, thrombo-embolism, nausea and malaise.

WITHDRAWAL SYMPTOMS - Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see Special warnings and precautions for use).

A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

CERTAIN SIDE-EFFECTS REPORTED WITH SOME NON RECOMMENDED ROUTES OF ADMINISTRATION.

Intrathecal/Epidural: Usual systemic corticoid adverse reactions, headache, meningismus, meningitis, paraplegia, spinal fluid abnormalities, nausea, vomiting, sweating, arachnoiditis, convulsions.

Extradural: Wound dehiscence, loss of sphincter control.

Intranasal: Permanent/temporary blindness, rhinitis.

Ophthalmic: (Subconjunctival) - Redness and itching, abscess, slough at injection site, residue at injection site, increased intra-ocular pressure, decreased vision - blindness, infection.

Miscellaneous injection sites - Scalp, tonsillar fauces, sphenopalatine ganglion: blindness.

4.9 Overdose

No known antidote. There is no clinical syndrome of acute overdosage with Depo−Medrone. Following overdosage the possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. Further traumatic episodes during that period may require special supportive therapy.

Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Methylprednisolone acetate is a synthetic glucocorticoid. An aqueous suspension may be injected directly into joints and soft tissues in the treatment of rheumatoid arthritis, osteoarthritis, bursitis and similar inflammatory conditions. For prolonged systemic effect it may be administered intramuscularly.

5.2 Pharmacokinetic properties

Methylprednisolone acetate is absorbed from joints in a few days, with peak serum levels being reached 2-12 hours after injection.

It is more slowly absorbed following deep intramuscular injection with plasma levels detected up to 17 days afterwards.

Methylprednisolone acetate is less soluble than methylprednisolone.

5.3 Preclinical safety data

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350,
Sodium chloride,
Miripirium chloride,
Sodium hydroxide,
Hydrochloric acid,
Water for injections

6.2 Incompatibilities

None stated.

6.3 Shelf life

Unopened: 5 years
Once opened, use immediately.

6.4 Special precautions for storage

Do not store above 25ºC. Do not freeze.
Keep the vial in the outer carton.

6.5 Nature and contents of container

Type I flint glass vial with a butyl rubber plug and metal seal. Each vial contains 1 ml of Depo-Medrone 40 mg/ml.

Vials packed singly and in 10 vial packs.

Not all pack sizes may be marketed.

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

Depo-Medrone should not be mixed with any other fluid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever suspension and container permit.

Shake well before use.

Discard any remaining suspension after use.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 0822/122/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978
Date of last renewal: 28 January 2006

10 DATE OF REVISION OF THE TEXT

March 2017