Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carmustine 300 mg powder and solvent for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Carmustine 300 mg powder and solvent for concentrate for solution for infusion
Each vial of powder for concentrate for solution for infusion contains 300 mg carmustine.

After reconstitution and dilution (see section 6.6), one ml of solution contains 3.3 mg carmustine.

Excipient with known effect
Carmustine 300 mg Each vial of solvent contains 9 ml ethanol anhydrous (equivalent to 7.11 g).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion.

Powder: Pale yellow dry flakes or dry powder.
Solvent: Clear, colourless solution.

The pH and osmolality of diluted ready-to-use solutions for infusion are
pH: 3.2 to 7.0 diluted in sodium chloride 9 mg/ml (0.9%) or 5% glucose solution for injection.
Osmolality: 340 to 400 mOsmol/l (diluted in glucose 50 mg/ml [5%] solution for injection or sodium chloride 9 mg/ml [0.9%] solution for injection).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carmustine is indicated in adults in the following malignant neoplasms as a single agent or in combination with other antineoplastic agents and/or other therapeutic measures (radiotherapy, surgery):

- Brain tumours (glioblastoma, Brain-stem gliomas, medulloblastoma, astrocytoma and ependymoma), brain metastases
- Secondary therapy in non-Hodgkin's lymphoma and Hodgkin's disease
- Tumours of the gastrointestinal tract
- Malignant melanoma in combination with other antineoplastic medicinal products.
- As conditioning treatment prior to autologous haematopoietic progenitor cell transplantation (HPCT) in malignant haematological diseases (Hodgkin's disease/ Non-Hodgkin's lymphoma

4.2 Posology and method of administration

Carmustine must be administered only by specialists experienced in the field of chemotherapy and under appropriate medical supervision.

Posology
Initial doses
The recommended dose of Carmustine as a single agent in previously untreated patients is 150 to 200 mg/m^2 intravenously every 6 weeks. This may be given as a single dose or divided into daily infusions such as 75 to 100 mg/m2 on two successive days.

When Carmustine is used in combination with other myelosuppressive medicinal products or in patients in whom bone marrow reserve is depleted, the doses should be adjusted according to the haematologic profile of the patient as shown below.

Monitoring and subsequent doses
A repeat course of Carmustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm^3, leukocytes above 4,000/mm^3), and this is usually in six weeks. Blood counts should be monitored frequently and repeat courses should not be given before six weeks because of delayed haematologic toxicity.

Doses subsequent to the initial dose should be adjusted according to the haematologic response of the patient to the preceding dose, in both monotherapy as well as in combination therapy with other myelosuppressive medicinal products. The following schedule is suggested as a guide to dose adjustment:

Table 1

Nadir after prior dose		*Percentage of prior dose to be given, %*
Leucocytes/mm^3	*Platelets/*mm^3	
>4000	>100,000	100
3000 – 3999	75,000 - 99,999	100
2000 – 2999	25,000 - 74,999	70
<2000	<25,000	50

In cases where the nadir after initial dose does not fall in the same row for leucocytes and platelets (e.g. leucocytes >4,000 and platelets <25,000) the value given the lowest percentage of prior dose should be used (e.g. platelets <25,000 then a maximum of 50% of prior dose should be given).

There are no limits for the period of application of carmustine therapy. In case the tumor remains incurable or some serious or intolerable adverse reactions appear, the carmustine therapy must be terminated.

Conditioning treatment prior to HPCT
Carmustine is given in combination with other chemotherapeutic agents in patients with malignant haematological diseases before HPCT at a dose of 300 – 600 mg/m^2 intravenously.

Special populations

Paediatric population
Carmustine is contraindicated in children and adolescents aged <18 years (see section 4.3).

Elderly
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dose range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and take into consideration concomitant disease or therapy with other medicinal products.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and the glomerular filtration rate should be monitored and the dose reduced according to this.

Renal impairment
For patients with renal impairment the dose of carmustine should be reduced if the glomerular filtration rate is reduced.

Method of administration
For intravenous use after reconstitution and further dilution.

By reconstituting the powder with the solvent provided, a solution has to be prepared by adding additional sterile water for injections. Reconstitution and dilution, as recommended, results in a clear, colourless to yellowish stock solution which has to be further diluted with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection.

The resulting ready-to-use solution for infusion should then be administered immediately by intravenous drip over a one- to two-hour period protected from light. The duration of infusion should not be less than one hour, otherwise it leads to burning and pain in the injected area. The injected area should be monitored during the administration.

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

4.3 Contraindications

- Hypersensitivity to the active substance, to other nitrosoureas or to any of the excipients listed in section 6.1.
- Severe bone marrow depression.
- Severe (end-stage) renal impairment.
- Children and adolescents
- Breast-feeding.

4.4 Special warnings and precautions for use

Pulmonary toxicity characterised by pulmonary infiltrates and/or fibrosis has been reported to occur with a frequency ranging up to 30%. This may occur within 3 years of therapy and appears to be dose related with cumulative doses of 1,200-1,500 mg/m ^{2} being associated with increased likelihood of lung fibrosis. Risk factors include smoking, the presence of a respiratory condition, pre-existing radiographic abnormalities, sequential or concomitant thoracic irradiation and association with other agents that cause lung damage. Baseline pulmonary function studies and chest X-ray should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70% of the predicted forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO) are particularly at risk.

An increased risk for pulmonary toxicities upon treatment with conditioning regimes and HPCT for females has been reported. So far, this increased risk is described for the treatment itself including conditioning regimens without carmustine (e.g. TBI or busulfan-cyclophosphamide) or with carmustine (BEAM: carmustine, etoposide, cytarabine and melphalan or CBV: cyclophosphamide, carmustine and etoposide).

High-dose therapy with carmustine (especially with 600 mg/m^2) prior to haematopoietic stem cell transplantation has been shown to increase the risk for incidence and severity of pulmonary toxicities. Therefore, in patients with other risks for pulmonary toxicities, use of carmustine needs to be weighed against the risks.

Upon high-dose therapy with carmustine, the risk and severity for infections, cardiac, hepatic, gastrointestinal, and renal toxicity, diseases of the nervous system and electrolyte abnormalities (hypokalaemia, hypomagnesemia and hypophosphatemia) rises.

Patients with comorbidities and worse disease status have a higher risk for adverse reactions. This needs to be respected especially for elderly patients.

Hepatic and renal function should also be checked prior to treatment and regularly monitored during therapy (see section 4.8).

Neutropenic enterocolitis can occur as therapy-related adverse reactions upon treatment with chemotherapeutic agents.

Carmustine is carcinogenic in rats and mice at doses less than the recommended human dose based on body surface area (see section 5.3).

Bone marrow toxicity is a common and severe toxic adverse reaction of carmustine. Complete blood count should be monitored frequently for at least six weeks after a dose. In case of a decreased number of circulating platelets, leucocytes or erythrocytes either from previous chemotherapy or other cause the dose should be adjusted, see Table 1, section 4.2. Liver, kidney and lung function should be checked and monitored regularly during therapy (see section 4.8). Repeat doses of Carmustine should not be given more frequently than every six weeks.

The bone marrow toxicity of carmustine is cumulative and therefore the dose adjustment must be considered on the basis of nadir blood counts from prior doses (see section 4.2).

Direct administration of carmustine into the carotid artery is regarded as experimental and has been associated with ocular toxicity.

Excipient warning
A dose of 600 mg/m^2 of this medicine administered to an adult weighing 70 kg would result in exposure to 365.66 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 60.94 mg/100 ml. For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml. Co-administration with medicines

containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects. Because this medicine is usually given slowly over 1-2 hours, the effects of alcohol may be reduced.

4.5 Interaction with other medicinal products and other forms of interaction

Phenytoin and dexamethasone
In combination with chemotherapeutic medicinal products reduced activity of antiepileptic medicinal products must be anticipated.

Cimetidine
Concomitant use with cimetidine leads to delayed, major, suspected, increased carmustine toxic effect (due to the inhibition of carmustine metabolism).

Digoxin
Concomitant use with digoxin leads to delayed, moderate, suspected, decreased effect of digoxin (due to the decreased digoxin absorption).

Melphalan
Concomitant use with melphalan leads to increased risk of pulmonary toxicity.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women should use effective contraception to avoid becoming pregnant while on treatment and for at least 6 months after treatment.

Male patients should be advised to use adequate contraceptive measures while on treatment with carmustine and for at least 6 months after treatment.

Pregnancy
Carmustine should not be administered to patients who are pregnant. Safe use in pregnancy has not been established and therefore the benefit must be carefully weighed against the risk of toxicity. Carmustine is embryotoxic in rats and rabbits and teratogenic in rats when given in doses equivalent to the human dose (see section 5.3). If carmustine is used during pregnancy, or if the patient becomes pregnant while taking (receiving) carmustine, the patient should be apprised of the potential hazard to the foetus.

Breast-feeding
It is unknown whether carmustine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Carmustine is contraindicated during breast-feeding and up to seven days post-treatment (see section 4.3).

Fertility
Carmustine may impair male fertility. Males should be advised of potential risk of infertility and to seek fertility/family planning counselling prior to therapy with carmustine.

4.7 Effects on ability to drive and use machines

Carmustine has no or negligible influence on the ability to drive and use machines. However, the possibility will have to be taken into consideration, that the alcohol quantity in these pharmaceutical medicines can impair the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The table includes adverse reactions that were presented during treatment with this medicinal product but may not necessarily have a causal relationship with the medicinal product. Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed may not reflect the rates observed in clinical practice. Adverse reactions are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. When placebo-controlled trials are available, adverse reactions are included if the incidence is ≥ 5% higher in the treatment group.

Tabulated list of adverse reactions

The following table includes adverse reactions of carmustine listed by MedDRA system organ class and frequency convention presented in order of decreasing seriousness: 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 (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Not known	Opportunistic infections (including fatal)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Acute leukaemia, bone marrow dysplasia - following long-term use.
Blood and lymphatic system disorders	Very common	Myelosuppression.
	Common	Anaemia.
Nervous system disorders	Very common	Ataxia, dizziness, headache.
	Common	Encephalopathy (high-dose therapy and dose-limiting).
	Not known	Muscular pain, status epilepticus, seizure, grand mal seizure.
Eye disorders	Very common	Ocular toxicities, transient conjunctival flushing and blurred vision due to retinal haemorrhages.
Cardiac disorders	Very common	Hypotension, due to the alcohol content of the solvent (high-dose therapy).
	Not known	Tachycardia
Vascular disorders	Very common	Phlebitis.
	Rare	Veno-occlusive disease (high-dose therapy).
Respiratory, thoracic and mediastinal disorders	Very common	Pulmonary toxicity, interstitial fibrosis (with prolonged therapy and cumulative dose)* Pneumonitis.
	Rare	Interstitial fibrosis (with lower doses).
Gastrointestinal disorders	Very common	Emetogenic potential. Nausea and vomiting - severe
	Common	Anorexia, constipation, diarrhoea, stomatitis.
Hepatobiliary disorders	Common	Hepatotoxicity, reversible, delayed up to 60 days after administration (high-dose therapy and dose-limiting), manifested by: - bilirubin, reversible increase - alkaline phosphatase, reversible increase - SGOT, reversible increase.
Skin and subcutaneous tissue disorders	Very common	Dermatitis with topical use improves with reduced concentration of compounded product, hyperpigmentation, transient, with accidental skin contact.
	Common	Alopecia, flushing (due to alcohol content of solvent; increased with administration times <1-2 h), injection site reaction.
	Not known	Extravasation hazard: vesicant
Renal and urinary disorders	Rare	Renal toxicity.
Reproductive system and breast disorders	Rare	Gynecomastia.
	Not known	Infertility, teratogenesis.
Metabolism and nutrition disorders	Not known	Electrolyte abnormalities (hypokalemia, hypomagnesemia and hypophosphatemia)

* An increased risk for pulmonary toxicities upon treatment with conditioning regimes and HPCT for females has been reported. So far, this increased risk is described for the treatment itself including conditioning regimes without carmustine (e.g. TBI or busulfan-cyclophosphamide) or with carmustine (BEAM: carmustine, etoposide, cytarabine and melphalan or CBV: cyclophosphamide, carmustine and etoposide).

Description of selected adverse reactions

Myelosuppression
Myelosuppression is very common and begins 7-14 days of administration with recovery 42-56 days of administration. The myelosuppression is dose and cumulative dose related, and often biphasic.

Respiratory, thoracic and mediastinal disorders
Pulmonary fibrosis (with fatal outcome), pulmonary infiltration
Pulmonary toxicity has been observed in up to 30% of patients. In cases where pulmonary toxicity started early (within 3 years of treatment), pulmonary infiltrates and/or pulmonary fibrosis occurred, some of which were fatal. The patients were between 22 months and 72 years old. Risk factors include smoking, respiratory disease, existing radiographic abnormalities, sequential or concomitant thoracic radiation, as well as combination with other active substances that can cause lung damage. The incidence of adverse reactions is probably dose-related; cumulative doses of 1200-1500 mg/m^2 have been associated with an increased likelihood of pulmonary fibrosis. During treatment, lung function tests (FVC, DLCO) should be performed regularly. Patients showing a baseline value of <70% of expected forced vital capacity or carbon monoxide diffusion capacity in these tests are at particular risk.

In patients having received carmustine in childhood or adolescence, cases of extremely delayed-onset pulmonary fibrosis (up to 17 years after treatment) have been described.

Long-term follow-up observation of 17 patients who survived brain tumours in childhood showed that 8 of them succumbed to pulmonary fibrosis. Two of these 8 fatalities occurred within the first 3 years of treatment and 6 of them occurred 8-13 years after treatment. The median age of patients who died on treatment was 2.5 years (1-12 years), the median age of long-term survivors on treatment was 10 years (5-16 years). All patients younger than 5 years of age at the time of treatment died from pulmonary fibrosis; neither the carmustine dose nor an additional vincristine dose or spinal radiation had any influence on the fatal outcome.

All remaining survivors available for follow-up were diagnosed with pulmonary fibrosis. Use of carmustine in children and adolescents < 18 years is contraindicated, see section 4.3.

Pulmonary toxicity also manifested in the post-marketing phase as pneumonitis and interstitial lung disease. Pneumonitis is seen for doses >450 mg/m^2 and interstitial lung disease is seen with prolonged therapy and cumulative dose > 1,400 mg/m^2.

Emetogenic potential
The emetogenic potential is high at doses >250 mg/m^2 and high to moderate in doses ≤250 mg/m^2. Nausea and vomiting are severe and begins within 2-4 h of administration and lasts for 4-6 h.

Renal toxicity
Renal toxicity is rare, but occurs for cumulative doses < 1,000 mg/m^2.

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,
website: www.hpra.ie.

4.9 Overdose

The main symptom of intoxication is myelosuppression. In addition, the following serious adverse reactions may occur: liver necrosis, interstitial pneumonitis, encephalomyelitis. A specialized antidote is not available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, nitrosoureas,
ATC code: L01AD01

Mechanism of action

Carmustine is a cell-cycle phase nonspecific antineoplastic agent of the nitrosourea type, which exerts tumour cytotoxicity via multiple mechanisms. As an alkylating agent, it can alkylate reactive sites on nucleoproteins, thus interfering with DNA and RNA synthesis and DNA repair. It is able to form interstrand crosslinks in DNA, which prevents DNA replication and transcription. In addition, carmustine is known to carbamoylate lysine residues on proteins causing irreversible inactivation of enzymes including glutathione reductase. The carbamoylating activity of carmustine is generally considered less significant than the alkylating activity in its action on tumors, but carbamoylation may serve to inhibit DNA repair.

Pharmacodynamic effects
The antineoplastic and toxic activities of carmustine may be due to its metabolites. Carmustine and related nitrosoureas are unstable in aqueous solutions and degrade spontaneously to reactive intermediates that are capable of alkylation and carbamoylation. The alkylating intermediates are believed to be responsible for the antitumor effect of carmustine. However, opinion is divided over the role of the carbamoylating intermediates as mediators of the biological effects of the nitrosoureas. On one hand, their carbamoylating activity was reported to contribute to the cytotoxic properties of their parent medicinal products by inhibiting DNA repair enzymes. On the other hand, it has been speculated that the carbamoylating species may mediate some of toxic effects of carmustine.

Carmustine crosses the blood-brain barrier readily because of its lipophilic nature.

Paediatric population
Carmustine should not be used in children and adolescents due to high risk of pulmonary toxicity.

5.2 Pharmacokinetic properties

Distribution
Intravenously administered carmustine is rapidly degraded, with no substance intact detectable after 15 minutes. Because of the good lipid solubility and the lack of ionisation at the physiological pH, carmustine is very well transferred through the blood-brain barrier. Levels of radioactivity in the cerebrospinal fluid are at least 50% higher than those measured concurrently in plasma. The kinetic of carmustine in humans is characterised by a two-chamber model. After the intravenous infusion over 1 hour, the carmustine-plasma level drops in a biphasic manner. The half-life α is 1-4 minutes and the half-life β is 18-69 minutes.

Biotransformation
It is presumed that the metabolites of carmustine cause its antineoplastic and toxic activity.

Elimination
Approximately 60-70% of a total dose is excreted in the urine in 96 hours and about 10% as respiratory CO2. The fate of the remainder is undetermined.

5.3 Preclinical safety data

Carmustine was embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. Carmustine affected the fertility of male rats at doses higher than the human dose. Carmustine, at clinically relevant dose levels, was carcinogenic in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
No excipients.

Solvent
Ethanol, anhydrous.

6.2 Incompatibilities

The intravenous solution is unstable in polyvinyl chloride containers. All plastic coming into contact with the carmustine solution for infusion (e.g. infusion set, etc.) should be PVC-free polyethylene plastic, otherwise glass ware should be used.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
2 years.

After reconstitution (reconstituted stock solution)
Chemical and physical in-use stability of reconstituted stock solution has been demonstrated for 24 hours at 2 to 8°C.
After dilution (solution after dilution for infusion)
Chemical and physical in-use stability of solution after dilution for infusion in sodium chloride solution for injection or 5% glucose solution for injection at final concentration of 0.2 mg/ml and stored in a glass or polypropylene container has been demonstrated for 4 hours at 20 to 25°C, protected from light. These solutions will also remain stable for 24 hours** in refrigerator (2 to 8 °C) and a further 3 hours at 20 to 25 °C, protected from light.

From a microbiological point of view, unless the method of opening, reconstitution and dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

**24 hours in-use storage time of final diluted solution is the total time, carmustine is in solution including the time it is reconstituted using ethanol and water for injections.

The solution should be protected from light until end of administration.

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C).

Keep the vials in the outer carton in order to protect from light.

For storage conditions after reconstitution and further dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder:
Amber glass vial sealed with a grey bromobutyl rubber stopper and aluminium seal having polypropylene cap.

Solvent:
Clear glass vial sealed with a chlorobutyl rubber stopper coated using FluroTec film and aluminium seal having polypropylene cap.

Pack sizes:
Pack contains 1 vial of 300 mg powder and 1 vial of 9 ml solvent
Pack contains 10 vials of 300 mg powder and 10 vials of 9 ml solvent

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The carmustine powder for concentrate for solution for infusion contains no preservative and is not intended as a multiple dose vial. Reconstitution and further dilutions should be carried out under aseptic conditions.

The dry frozen product does not contain any preservatives and is suitable only for one use. The lyophilisate can appear as a fine powder, however handling can cause it to appear as a heavier and lumpier lyophilisate than as a powdery lyophilisate due to the mechanical instability of the freeze drying cake. The presence of an oily film can be an indication of melting of the medicinal product. Such products are not accepted for use due to the risk of temperature excursions to more than 30°C. This medicinal product should not be used any further. When you are not clear about the fact whether the product is adequately cooled, then you should immediately inspect each vial in the carton. For verification, hold the vial in bright light.

Reconstitution and dilution of the powder for concentrate for solution for infusion
Dissolve carmustine (powder) with the required quantity of supplied sterile refrigerated ethanol solvent in the primary packaging (brown glass vial). Carmustine must be completely dissolved in ethanol before sterile water for injections is added. Then aseptically add required quantity of sterile water for injection to the alcohol solution. The stock solution needs to be mixed thoroughly.

Powder vial	Solvent vial (ethanol)	Required volume of solvent (ethanol)	Required volume of water for injection.	Concentration of stock solution
50 mg	3 ml	1.5 ml	13.5 ml	3.3 mg/ml
300 mg	9 ml	9 ml	81 ml	3.3 mg/ml

One ml of the reconstituted stock solution contains 3.3 mg carmustine in 10% ethanol. Reconstitution, as recommended, results in a clear, colourless to yellowish stock solution, practically free from visible particles, which should be further diluted immediately to required quantity of either sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution for injection to get final concentration of 0.2 mg/ml. The diluted solution (i.e. the ready-to-use solution) should be mixed for at least 10 seconds before administration. The Ready-to-Use solution should be administered over 1-2 hours.

Administration of the infusion should be performed using a PVC free PE infusion set. During administration of the medicinal product, the glass or polypropylene container shall be used. Further, the ready-to-use solution needs to be protected from light (e.g. using alu-foil wrapped around the container of the ready-to-use solution) and preferably kept at temperatures below 20-25°C as Carmustine degrades faster at higher temperatures.

Infusion of Carmustine in less than one hour may produce intense pain and burning at the site of injection (see section 4.2).

Guidelines for the safe handling and disposal of antineoplastic agents must be observed.

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/250/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st March 2023

10 DATE OF REVISION OF THE TEXT

November 2025