Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cerubidin 20 mg Powder for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Daunorubicin Hydrochloride equivalent to Daunorubicin 20 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for Solution for Infusion.
A microcrystalline, orange-red, sterile powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an antimitotic and cytotoxic for the induction of remissions in acute lymphocytic and myelogenous leukaemias.

Daunorubicin, as part of combination regimen, is indicated for the treatment of acute lymphocytic leukemia and acute myeloid leukemia in children.

4.2 Posology and method of administration

Posology

The effect of Cerubidin/Daunorubicin on the disease process and on normal blood precursors cannot be exactly predicted for any particular case. The difference between the incomplete treatment, a satisfactory remission and overdosage with possible irreversible aplasia of the bone marrow depends on the correct choice of dosage, time intervals and total number of doses.

Daunorubicin should be administered with caution when the neutrophil count is <1,500/mm3. Daunorubicin dose reduction should be considered in case of severe neutropenia.
The number of infusions required varies widely from patient to patient and must be determined in each case according to response and tolerance.

Adults:

40 - 60mg/m^2 on alternate days for a course of up to three infusions.

Acute Myelogenous Leukaemia:
45mg/m^2/day is the recommended dose.

Acute Lymphocytic Leukaemia:
45mg/m^2/day is the recommended dose.

Special populations

Pediatric population:

Cerubidin dose for children (over 2 years) is usually calculated based on the body surface area and adjusted to meet individual requirements of each patient, on the basis of clinical response and the patient's haematological status. Courses may be repeated after 3 to 6 weeks.

Current specialized protocols and guidelines should be consulted for appropriate treatment regimen.

For children over 2 years the maximum cumulative dose is 300 mg/m^2
For children under 2 years of age (or below 0.5 m^2 body surface area), the maximum cumulative dose is 10 mg/kg

Elderly

Use with care in patients with inadequate bone marrow reserves. A dosage reduction of up to 50% is recommended.

Renal and hepatic impairment:
The dosage should be reduced in patients with impaired hepatic or renal function (see section 4.4). A 25% reduction is recommended in patients with serum bilirubin concentrations of 1.2-3mg/100ml and a 50% reduction in cases with serum bilirubin or creatinine concentrations above 3 mg/100ml.

Method of administration
For intravenous administration only.
The solution is given *via* the tubing of a freely running intravenous infusion, over a 20 minute period. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.

Cerubidin/Daunorubicin is extremely irritating to tissues and may only be administered intravenously after dilution. Cerubidin/Daunorubicin should be administrated through a large vein and the infusion should be kept free flowing. When second or subsequent infusions are given, the doses and time intervals on the effect on the previous doses and must be the subject of careful deliberation, examination of the peripheral blood and, under some circumstances, of the bone marrow.

4.3 Contraindications

- Hypersensitivity to daunorubicin and other anthracyclines or to any of the excipients listed in section 6.1.
- Prior treatment with maximum cumulative doses of other anthracyclines such as doxorubicin or epirubicin.
- Use in the management of non-malignant disease.
- Use in the presence of acute infections.
- In patients with uncontrolled coronary insufficiency including those complicated by marked impaired left ventricular function.
- Use in patients with marked marrow depression unless considered essential by the physician/oncologist.
- Use in patients in the presence of oropharyngeal ulceration.
- Use in patients recently exposed to, or with existing chicken pox or herpes zoster.
- Use via intramuscular or subcutaneous routes.
- Breastfeeding

4.4 Special warnings and precautions for use

Special warnings

Daunorubicin should only be administered under the direction of a specialist having the facilities for regular monitoring of clinical, biochemical and haematological effects during and after administration.

Urine, sweat or tear may be coloured in red due to daunorubicin composition. This will last a few days and then return to normal.

Daunorubicin has been shown to be carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

Precautions for use

Caution is indicated when daunorubicin is used concomitantly with phenytoin due to drug-drug interaction potentially affecting both daunorubicin and phenytoin plasma exposure which can lead to seizure (see section 4.5).

Haematopoietic system

Daunorubicin produces bone marrow depression. Daunorubicin should be administered with caution when the neutrophil count is < 1,500/mm3. Febrile neutropenia has been reported when daunorubicin is given in combination with other antineoplastic treatments.
Monitoring of blood counts prior to and during daunorubicin treatment is recommended, and hematological abnormalities should be treated promptly (see sections 4.2 and 4.8).

Secondary malignancies:
Secondary malignancies (including leukaemia) have been reported when daunorubicin was given in combination with other antineoplastic treatments known to be associated with secondary malignancies (see section 4.8). Secondary malignancies may occur during daunorubicin-containing therapy, or several months or years after the end of therapy. Patients should be monitored for secondary malignancies.

Cardiotoxicity
Extreme caution should be exercised when using the product in patients with cardiac disorders or in the elderly. Cardiotoxicity if it occurs is likely to be heralded by either a persistent tachycardia, shortness of breath, swelling of feet and lower limbs or by minor changes in the electrocardiogram and for this reason an electrocardiographic examination should be made at regular intervals during the treatment.

Cardiotoxicity usually appears within 1 to 6 months after initiation of the therapy. It may develop suddenly and not be detected by routine ECG. It may be irreversible and fatal but responds to treatment if detected early.

The risk may be decreased through regular monitoring of left ventricular ejection fraction
(LVEF) during the course of treatment. Initiation of cardio-protective drugs might be considered to limit the risk of cardiomyopathy, while treatment should be discontinued upon the first sign of cardiomyopathy. A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patient with risk factors for increased cardiotoxicity. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). ECG changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity.

The risk of congestive heart failure increases significantly when the total cumulative dosage exceeds 600 mg/m^2 body surface area in adults, 300 mg/m^2 in children over 2 years or 10mg/kg bodyweight in children under 2 years. Cardiotoxicity may be more frequent in children and the elderly. The dosage should be modified if previous or concomitant cardiotoxic drug therapy is used.

Hepatic and renal function
Daunorubicin is mainly metabolised in the liver and eliminated via the bile. Hepatic function should be monitored before starting treatment with daunorubicin in order to prevent complications. The dose should be reduced in case of impaired hepatic function since the toxic effects of the drug may be exacerbated in this population. This should be based on serum bilirubin levels.

An impaired renal function can also lead to increased toxicity. Renal function should therefore be monitored before initiating treatment.
Daunorubicin should be used with care in patients at risk of hyperuricaemia (e.g. in the presence of gout, urate and renal calculi), tumor cell infiltration of the bone marrow and in patients with inadequate bone marrow reserves due to previous cytotoxic drug or radiation therapy. The cumulative dose of daunorubicin should be limited to 400mg/m^2 when radiation therapy to the mediastinum has been previously administered. The dose of daunorubicin should not be repeated in the presence of bone marrow depression or buccal ulceration.

Rapid destruction of a large number of leukaemia cells may cause a rise in the blood uric acid or urea and so it is a wise precaution to check these concentrations three or four times a week during the first week of treatment. Fluids should be administered and allopurinol used in severe cases to prevent the development of hyperuricaemia.

Daunorubicin treatment may lead to hyperuricaemia as a consequence of tumour lysis syndrome.

Infections
Infections should be treated before the start of daunorubicin therapy. If during daunorubicin treatment a patient becomes febrile (regardless of the neutrophil count), treatment with broad spectrum antibiotics should be initiated.

Gastrointestinal disorders
Cases of colitis, entercolitis and neutropenic entercolitis (typhlitis) have been reported in patients treatment with daunorubicin. Treatment discontinuation and prompt appropriate medical management are recommended.

Immunosuppressive effects/Increased sensitivity to infections
The administration of live or live attenuated vaccines to patients whose immune system has been compromised by chemotherapeutic drugs, including daunorubicin, can lead to severe or fatal infections. Patients who receive daunorubicin should not be vaccinated with live vaccines such as yellow fever vaccine. Dead or inactivated vaccines may be administered. Such vaccines may, however, be less effective.

Nervous system disorders
Posterior reversible encephalopathy syndrome (PRES) also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS):
Cases of PRES have been reported with daunorubicin used in combination chemotherapy. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. In patients with PRES, the discontinuation of daunorubicin treatment should be considered (See section 4.8).

General disorders and administration site conditions / Extravasation
Care should be taken to avoid extravasation during intravenous administration. Using catheters or implanted ports reduces the risk of extravasation. All steps should be taking to avoid tissuing and bandages should not be used. Facial flushing or erythematous streaking along the vein indicates too rapid infusion. If tissue necrosis is suspected, the infusion should be stopped immediately and resumed in another vein. Where extravasation has occurred, an attempt should be made to aspirate the fluid back through the needle. The affected area may be injected with hydrocortisone. Sodium bicarbonate (5 ml of 8.4%) may also be injected in the hope that through pH changes the drug will hydrolyse. The opinion of a plastic surgeon should be sought as skin grafting may be required.

Application of ice packs may help decrease local discomfort and also prevent extension. Liberal application of corticosteroid cream and dressing the area with sterile gauze should then be carried out.

Each patient should be given a clinical and bacteriological examination to determine whether infection is present; any infection should be adequately eliminated before treatment with Daunorubicin which might depress the bone marrow to the point where anti-infective agents would no longer be effective. If facilities are available, patients should be treated in a germ-free environment or, where it is not possible, reverse barrier nursing and aseptic precautions should be employed. Anti-infective therapy should be employed in the presence of suspected or confirmed infection and during a phase of aplasia. It should be continued for some time after the marrow has regenerated. Care should also be used in patients at risk of infection. Personnel handling this product should wear protective clothing and be trained in good handling techniques.

Fertility
Daunorubicin inhibits fertility. Amenorrhea and azoospermia may occur. The severity of this will depends on the dose. Both men and women should take contraceptive measures during and after treatment (see section 4.6). For male or female patients who intend to have a child after completing treatment, genetic counselling is recommended. Male patients should be informed about the possibility of storing their semen before starting treatment with daunorubicin due to the risk of irreversible infertility.

4.5 Interaction with other medicinal products and other forms of interaction

Immunosuppressive agents: immunosuppressive effect of daunorubicin can be more pronounced when daunorubicin is concomitantly administered with other immunosuppressive agents.

The combination of daunorubicin with phenytoin (and by extrapolation fosphenytoin) can lead to risk of seizure since daunorubicin reduces the gastrointestinal absorption of phenytoin, or risk of increased toxicity or decreased efficacy of daunorubicin since both phenytoin and fosphenytoin increase hepatic metabolism (see section 4.4).

Yellow fever vaccine with daunorubicin is not recommended due to the risk of fatal systemic vaccine disease.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in men and women

Women of childbearing potential should be advised to avoid pregnancy while taking daunorubicin and should be informed of the potential danger to the foetus. Women of childbearing potential should undergo pregnancy test before starting daunorubicin. Men with fertile sexual partners should use effective contraception during treatment and for 4 months after the last dose of daunorubicin. Women should use effective contraception during treatment and for 7 months after the last dose of daunorubicin.

Fertility
Daunorubicin could cause chromosomal damage to human spermatozoa. For male or female patients who intend to have a child after completing treatment, genetic counselling is recommended. Male patients should be informed about the possibility of storing their semen before starting treatment with daunorubicin due to the risk of irreversible infertility.

Pregnancy
There are no data on the use of daunorubicin in pregnant women. Based on results from animal studies and its mechanism of action, daunorubicin should not be used during pregnancy, unless the clinical condition of the woman requires treatment and justifies the potential risk to the foetus (see section 5.3).

If the medicinal product is used during pregnancy, or if the patient becomes pregnant while receiving daunorubicin, the woman should be informed of the potential hazard to the foetus. In any case, cardiologic examination and a blood count are recommended in foetuses and newborns born to mothers who received treatment during pregnancy.

Breast-feeding
It is not known whether daunorubicin is excreted in human milk. Because of the potential for serious adverse reactions in breast-feeding children, breastfeeding is contraindicated during treatment with daunorubicin (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, confusion, seizures and visual disturbances have been observed in patients treated with daunorubicin combination therapy (see section 4.4). Moreover, daunorubicin causes episodes of nausea and vomiting, which in some cases may affect the ability to drive or use machines. Therefore, patients should be warned of the possible impact of the side effects on their ability to drive or use machines, and be advised not to drive or use machines if they experience these side effects during treatment.

4.8 Undesirable effects

Adverse reactions associated with daunorubicin obtained from clinical studies and post-marketing surveillance are listed in the table below.
Adverse reactions are listed by system organ class and can occur in the following frequencies: Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Table 1: Adverse reactions

System Organ class	***Adverse Reaction***
Infectionsandinfestations	*Very common:Infections[a]*
Neoplasms benign and malignant(includingcysts and polyps)	*Not known: Leukaemia[b,c], Myelodysplastic syndrome*
Immunesystemdisorders	*Not known: Anaphylactic reaction/Anaphylactoid reaction*
Metabolismandnutrition disorders	*Not known: Tumor lysis syndrome[c], Hyperuricaemia, Dehydration*
Nervoussystemdisorders	*Not known: Posterior Reversible Encephalopathy Syndrome[c d]*
Bloodandlymphatic systemdisorders[c]	*Very common: Bone marrow failure, Myelosuppression[c], Thrombocytopenia, Neutropenia, Leukopenia, Anaemia* *Not known:Febrile neutropenia[d]*
Cardiacdisorders	*Common: Cardiac failure congestive, Cardiotoxicity* *Rare: Cardiomyopathy* *Not known: Restrictive cardiomyopathy, Myocardial infarction, Supraventricular tachyarrhythmia[e], myocardial*

	ischaemia, Myocarditis/pericarditis
Vasculardisorders	*Not known: Shock, Haemorrhage, Phlebosclerosis, Thrombophlebitis, Hot flush*
Respiratory, thoracic and mediastinal disorders	*Not known: Hypoxia, Pulmonary toxicity*
Gastrointestinal disorders	*Common: Abdominal pain, Mucosal inflammation, Diarrhoea, Vomiting, Nausea* *Uncommon: Enterocolitis, Stomatitis* *Not known: Neutropenic colitis, Colitis, Oesophagitis, Mouth ulceration, Glossitis*
Skin and subcutaneous tissue disorders[d]	*Common: Alopecia* *Uncommon: Urticaria, Rash* *Not known: Angioneurotic oedema, Recall phenomenon, Nail pigmentation, Skin hyperpigmentation, Dermatitis contact, Erythema, Pruritis*
Renal and urinary disorders	*Not known: Nephrotic syndrome*[c]*, Uric acid nephropathy*[c]*, Chromaturia*[c,f]
Reproductive system and breast disorders	*Not known:Infertility*[c]*, Azoospermia, Amenorrhea Oligospermia*
Congenital, familial and genetic disorders	*Not known: Aplasia*
General disorders and administration site conditions	*Common: Pyrexia*[c] *Uncommon: Extravasation*[g] *Rare: Injection site necrosis* *Not known: Death, Pain, Infusion site phlebitis*[c]*, Chills*
Investigations	*Uncommon: Electrocardiogram abnormal*[h] *Not known: Electrocardiogram QT prolonged, Hepatic enzymes increased (including blood bilirubine increased, aspartate aminotransferase increased, blood alkaline phosphatase increased)*

1. Including severe infections (including septic shock, sepsis/septicaemia and pneumonia) which can sometimes be fatal.
2. Secondary malignancies, including acute myeloid leukaemia, have been reported in association with daunorubicin when used in combination with other antineoplastic treatments known to be associated with secondary malignancies.
3. See section 4.4 Special warnings and precautions for use.
4. Fatal outcome has been reported.
5. Such as sinus tachycardia, premature ventricular contractions, heart block
6. Urine may be coloured red for several days after administration.
7. Immediate local pain/burning sensation, severe cellulitis, painful ulceration.
8. Such as nonspecific ST-T wave changes, low voltage QRS complex, T waves.

Local Adverse reactions
Two kinds of local adverse reactions are reported:

- Extravasation with risk of tissue necrosis: the infusion must be stopped, a maximum of infiltrated product aspirated and a cold dressing applied. A corticosteroid may possibly be injected or dimethyl sulfoxide applied topically. Daily surveillance is required. Indwelling i.v catheters and Portacath devices reduce the risk of extravasation.
- Recall of skin reaction due to prior radiotherapy, consisting of pain and erthyema which may last several days.

Cardiotoxicity

Acute toxicity:

- Onset within 48 hours
- ECG modification may occur: arrhythmias, in particular prolonged QT interval usually with no clinical signs. In the event of arrhythmia, treatment can be continued but any associated electrolyte imbalance (hypokalemia, hyponatremia, etc.) must be corrected.
- Early onset of acute myopericarditis is rare.

Chronic toxicity

- Cardiomyopathy which may progress to congestive heart failure; this potentially fatal condition requires specialized care.
- Chronic toxicity is correlated to the total cumulative dose administered.

Prevention

Cardiotoxicity may be prevented by:

- Clinical monitoring
- Regular monitoring of cardiac function by evaluating ventricular performance using echocardiography or radionuclide scanning. These tests should be performed before the first administration and repeated regularly. Treatment should be discontinued if any significant change occurs.
- Some cardioprotective drugs can limit risks of toxicity.

Blood and lymphatic system disorders

Very common: Bone marrow failure.

Bone marrow depression (very common): in every patient bone marrow function will be depressed by treatment with daunorubicin and in a variable proportion of cases, severe aplasia will develop. Risk of sepsis, severe opportunistic infections may occur with bone marrow depression.

Frequency not known: febrile neutropenia, including with fatal outcomes, has been reported.

Leucopenia is usually more significant than thrombocytopenia. The nadir for leucopenia usually occurs between 10-14 days and recovery occurs gradually over the next 1-2 weeks. Bone marrow depression must be anticipated in every case by eliminating infection before the treatment, by isolating the patient from infection during the treatment and by means of supportive therapy. This includes the continuous administration of anti-infective agents, the administration of platelet-rich plasma or fresh whole blood transfusion and, under some circumstances, the transfusion of white cell concentrates.

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

In the event of overdose, all the adverse reactions may be exacerbated. Blood and bone marrow counts should be performed regularly and cardiological, radiological, and ultrasound investigations carried out to define appropriate symptomatic treatment if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cerubidin is an anthracycline glycoside antibiotic and is a potent antileukaemia agent. It also has immunosuppressant effects.

The exact mechanism of the antineoplastic action of daunorubicin is uncertain but may involve binding to DNA and RNA by intercalation between base pairs and inhibition of DNA and RNA synthesis by template disordering and steric obstruction. Daunorubicin is most active in the S phase of cell division but is not cycle phase-specific. Tumour cell cross-resistance has been observed between daunorubicin and doxorubicin.

No controlled paediatric studies have been conducted.

The literature mentions the use of daunorubicin in treatment regimens for Acute Myelogenous Leukaemia and Acute Lymphocytic Leukaemia, including paediatric age groups. However, due to the ongoing search for a balance in gain or maintenance of efficacy and a decrease in toxicity the use of daunorubicin in the treatment of paediatric ALL and AML is fluctuating in clinical practice, mainly depending on risk stratification and specific subgroups. Published studies suggest no differences in safety profile between paediatric patients and adults.

5.2 Pharmacokinetic properties

Daunorubicin is rapidly taken up by the tissues, especially by the kidneys, spleen liver and heart. It does not cross the blood brain barrier. Subsequent release of the drug and its metabolites from the tissues is slow (T½ = 55 hours). Daunorubicin is rapidly metabolised in the liver. The major metabolite, daunorubicinol is also active. Daunorubicin is excreted slowly in the urine, mainly as metabolites with 25% excreted in the first 5 days. Biliary excretion also makes a significant (40%) contribution to elimination.

5.3 Preclinical safety data

Daunorubicin is genotoxic and carcinogenic in rats and mice. Daunorubicin has been shown to induce chromosomal damage in the in vitro chromosomal aberration test on human lymphocytes, and in vivo on human lymphocytes and on human and rat bone marrow cells. Daunorubicin induced mutagenicity in the bacterial reverse mutation (Ames) test.

Daunorubicin showed teratogenic and embryotoxic effects in animal studies. Furthermore, daunorubicin caused testicular atrophy and total aplasia of spermatocytes in the seminiferous tubules in dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-Mannitol

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
The reconstituted product is incompatible with heparin sodium injection and dexamethasone sodium phosphate injection.

6.3 Shelf life

3 years.
The product after first opening and reconstitution of the powder should be used within 24 hours (see 6.4 for storage details). Once the reconstituted solution has been diluted in the infusion medium, it should be used immediately.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original container. If prepared aseptically, the reconstituted solution may be stored for up to 24 hours in a refrigerator at 2 – 8ºC protected from light. The reconstituted solution further diluted in infusion medium should be used immediately.

6.5 Nature and contents of container

Uncoloured Type III (Ph. Eur.) neutral glass vial fitted with butyl rubber stopper and aluminium overseal.
The vials are available in packs of 1 or 10 vials.

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

The contents of the vial should be reconstituted with water for injections Ph.Eur. 4ml to give a solution of concentration 5 mg per ml. The calculated dose of Cerubidin should be further diluted with normal saline to give a final concentration of 1 mg per ml. Once diluted the infusion should be given immediately. The solution should be infused over a 20 minute period into the tubing, or side arm, of a well placed, rapidly flowing i.v. infusion of normal saline (to minimise extravasation and possible tissue necrosis).

Alternatively, cerubidin may be added to a mini bag of sodium chloride injection 0.9% w/v and this solution infused into the side arm of a rapidly flowing infusion of normal saline.

Special Protection Information

Cerubidin should only be handled by staff experienced with cytotoxic drugs. Reconstitution should be carried out in a designated area. Protective clothing (including gloves and eye protection) should be worn. Double gloving is recommended for dealing with major spillages.
Waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (it should be noted that the patient's body fluids and excreta will contain appreciable amounts of antineoplastic agents and they should be treated as hazardous waste). All staff exposed to cerubidin should be recorded and monitored. Pregnant staff should not handle cerubidin.

Spill or Leaks Procedures

Daunorubicin infusion may be neutralised with sodium hypochlorite prior to disposal of unused drug or if vial is accidentally broken. The neutralised drug can be disposed of in the sink.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
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8 MARKETING AUTHORISATION NUMBER

PA0540/096/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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