Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aciclovir 500 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg aciclovir (as the sodium salt).

Excipient(s) with known effect
This medicinal product contains 2.27 mmol (or 52.2 mg) sodium per vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aciclovir is indicated in immunosuppressed patients for:

- Infections with the *Varicella zoster* (VZV) virus
- Infection with the *Herpes simplex* (HSV) virus

Aciclovir is indicated in immunocompetent patients for:
VZV infections

- Severe shingles due to the extent of lesions or their capacity for progression
- Chickenpox in pregnant women where the rash occurs 8-10 days before delivery.
- Varicella in neonates
- Neonates before any rash, when the onset of chickenpox occurred in the mother within 5 days before and 2 days after childbirth
- Severe forms of chickenpox in children under 1 year of age
- Complicated chickenpox, especially varicella pneumonia

HSV infections

- Severe primary genital herpes infection
- Treatment of acute herpetic gingivostomatitis, when functional discomfort makes oral treatment impossible
- Kaposi-Juliusberg dermatitis (eczema herpeticum)
- Treatment of herpetic meningoencephalitis

4.2 Posology and method of administration

Posology
Dosage for patients with normal kidney function is given below. In patients with abnormal kidney function, dosage must be adapted according to the level of renal impairment (see paragraph, Patients with renal impairment).
Regarding recommendations for the duration of treatment, see paragraph, Duration of treatment.
Dosage in patients with normal renal function
Adults and adolescents (>12 years of age)

- *Varicella zoster* virus (VZV) infections: 10 mg/kg every 8 hours; 10-15 mg/kg every 8 hours in pregnant women
- *Herpes simplex* virus (HSV) (except meningoencephalitis): 5 mg/kg every 8 hours.
- Herpetic meningoencephalitis: 10 mg/kg every 8 hours.

Paediatric population
In children over 3 months of age
In children between 3 months and 12 years of age, the dosage must be calculated according to body weight.

- HSV infection (except meningoencephalitis) or VZV infections: 10 mg/kg every 8 hours, with a maximum dose of 400 mg every 8 hours.
- HSV meningoencephalitis or VZV infection in immunosuppressed children: 20 mg/kg every 8 hours, with a maximum dose of 800 mg every 8 hours.

Neonates
In neonates and infants up to 3 months of age, the dosage is calculated according to body weight.

- Known or suspected neonatal herpes, the recommended regimen is 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease confined to the skin and mucous membranes.

Dosage in patients with renal impairment
The interval between two doses and the dosage should be adjusted according to creatinine clearance in mL/min for adults and adolescents and in mL/min/1.73 m^2 for infants and children under 13 years of age. Caution is advised when administering aciclovir by infusion to patients with impaired renal function. In such patients, special care should be taken to ensure adequate fluid intake.
The following dosage adjustments are proposed.

Dosage adjustment recommended in adults and adolescents > 12 years with impaired renal function:

Creatinine clearance	**Recommended dose unit and dosing frequency according to indication**	
	HSV or VZV infections (*except meningoencephalitis*)	**VZV infections in immunocompromised children or herpetic meningoencephalitis**
25-50 mL/min	5 mg/kg body weight every 12 hours	10 mg/kg body weight every 12 hours
10-25 mL/min	5 mg/kg body weight every 24 hours	10 mg/kg body weight every 24 hours
0 (anuria) to 10 mL/min	2.5 mg/kg body weight every 24 hours	5 mg/kg body weight every 24 hours
Patients on haemodialysis	2.5 mg/kg body weight every 24 hours and after haemodialysis	5 mg/kg body weight every 24 hours and after haemodialysis

Dosage adjustment in children ≤ 12 years, infants and neonates with impaired renal function:

Creatinine clearance (mL/min/1.73 m^2)	**Recommended dose unit and dosing frequency by indication**	
	HSV or VZV infections (except meningoencephalitis)	**VZV infections in immunocompromised patients or with herpetic meningoencephalitis**
25- 50 mL/min/1.73 m^2	10 mg/kg of body weight twice a day	20 mg/kg of body weight twice a day
10-25 mL/min/1.73 m^2	5 mg/kg of body weight twice a day	10 mg/kg of body weight twice a day
0 (anuria) to 10 mL/min/1.73 m^2	2.5 mg/kg of body weight twice a day	5 mg/kg of body weight twice a day
Patients on haemodialysis	2.5 mg/kg of body weight twice a day after hemodialysis	5 mg/kg of body weight twice a day after hemodialysis

Elderly
The possibility of renal impairment in elderly patients must be taken into account and the dosage should be adjusted according to creatinine clearance (see section "Dosage in patients with renal impairment").

Adequate fluid intake must be ensured.

Obese patients
In obese patients who receive aciclovir intravenously based on their actual body weight, increased plasma concentrations may be obtained. A dose reduction should therefore be considered in obese patients, especially in patients with renal impairment or in elderly patients.

Duration of treatment
The duration of treatment is generally 5 days, but it can be adjusted depending on the patient's condition and response to treatment. The duration is:

- 8-10 days for infections with the *Varicella zoster* virus
- 10 days for the treatment of herpetic meningoencephalitis; it must be adjusted according to the patient's condition and his/her response to treatment
- 5-10 days for other infections with the *Herpes simplex* virus
- 14 days for the treatment of neonatal herpes for mucocutaneous infections (skin/eye/mouth)
- 21 days for the treatment of neonatal herpes for disseminated disease or disease of the central nervous system.

The duration of prophylactic treatment with Aciclovir is determined by the length of the risk period.

Method of administration
Strictly intravenous use:
Each dose should be injected slowly intravenously (by pump or infusion) **over at least one hour.**
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance - aciclovir, or to valaciclovir, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Special warnings
This medicinal product does not represent a treatment or prophylaxis of post-zoster pain.
Concomitant use of other nephrotoxic medicinal products increases the risk of renal impairment. Caution is required when administering aciclovir IV with other nephrotoxic medicinal products.
At the onset of renal pain, renal impairment and discontinuation of treatment must be considered.

Precautions for use
The patient's hydration status
Adequate fluid intake must be ensured particularly in patients at risk of dehydration, especially the elderly, as well as in patients receiving IV aciclovir or high doses of oral aciclovir.

Patients with renal impairment and elderly subjects
As aciclovir is eliminated via the kidneys, the dosage must be adjusted to creatinine clearance (see section 4.2).
Elderly subjects are likely to have reduced renal function and a reduction in the aciclovir dosage should therefore be considered in these patients.
Neurological disorders (see section 4.8) are likely to occur more frequently in patients with renal impairment and in elderly patients with potentially reduced renal function.
Elderly subjects and/or patients with renal impairment must be closely monitored to identify these undesirable neurological effects, which are usually reversible after discontinuation of treatment (see section 4.8).

Precautions relating to intravenous administration
Intravenous doses must be given as an infusion over at least one hour to avoid precipitation of aciclovir in the kidneys; rapid or bolus injections must be avoided.
When administered in an infusion bag, the reconstituted aciclovir solution must be diluted, taking care not to exceed the maximum concentration of 5 mg/mL of aciclovir per bag (see sections 4.8 and 6.6).
For patients receiving aciclovir as an IV infusion at high doses (for example, to treat herpetic encephalitis), particular attention should be paid to renal function, especially when patients are dehydrated or have impaired renal function. The reconstituted aciclovir solution for IV infusion has an approximate pH of 11.0 and must not be administered orally.

Cases of dilution errors have been reported with the administration of aciclovir by injection. It is important to strictly observe the procedures for reconstitution and dilution when administering aciclovir in an infusion bag (see section 6.6).

Prolonged treatment
Prolonged treatment or repeated administration of aciclovir in severely immunosuppressed patients may lead to selection of viral strains with reduced susceptibility to aciclovir, which may result in a lack of response to continued treatment with aciclovir (see section 5.1).

Excipient with known effect
500 mg vial:
This medicinal product contains 52.2 mg sodium per vial, equivalent to 2.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations to be taken into account

- Other nephrotoxic medicinal products

Risk of increased nephrotoxicity
Concomitant use of medicinal products with inherent renal toxicity increases the risk of nephrotoxicity. If such a combination is necessary, kidney function tests must be more closely monitored.
Aciclovir is eliminated in the urine mainly in unchanged form by active renal tubular secretion.
Any co-medication that competes with this mechanism may increase aciclovir plasma concentrations.
Probenecid and cimetidine increase the AUC of aciclovir by this mechanism and reduce the renal clearance of aciclovir. However, no dose adjustment is necessary due to the wide therapeutic index of aciclovir.
In patients receiving intravenous aciclovir, caution is necessary when co-administering medicinal products that compete with aciclovir for elimination, due to the potential increase in plasma levels of one or all of these medicines or their metabolites. Increases in plasma AUCs of aciclovir and the inactive metabolite of mycophenolate mofetil, an immunosuppressant used in transplant patients, have been observed with co-administration of these medicines.
Particular care is also needed (with monitoring for changes in renal function) when co-administering aciclovir intravenously with medicinal products that affect other aspects of renal physiology (for example ciclosporin or tacrolimus).

- Lithium

If **lithium** is administered concomitantly with high doses of IV aciclovir, serum lithium should be closely monitored due to the potential for lithium toxicity.

- Theophylline

Increases of approximately 50% in the AUC of total **theophylline** administered were shown in a clinical study conducted in 5 male subjects during co-administration with aciclovir. Assaying of plasma concentrations is recommended when co-administered with aciclovir.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies have shown a teratogenic effect in one species and at very high doses. However, systemic administration of aciclovir in internationally accepted standard tests do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown an increase in the number of birth defects amongst aciclovir exposed subjects compared with the general population and any birth defects showed no uniqueness or consistent pattern to suggest a common cause.
However, only epidemiological studies would verify the absence of risk.

The use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks.

Breastfeeding
Following oral administration of 200 mg five times a day, aciclovir has been detected in human breast milk at concentrations ranging from 0.6 to 4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir doses of up to 0.3 mg/kg/day.
In view of the above and the seriousness of the conditions intended to be treated with Aciclovir breast-feeding should be avoided.

Fertility
There is no information on the effect of aciclovir on human female fertility.
In a study of 20 male patients with normal sperm count, oral acyclovir administered at doses of up to 1g per day for up to six months has been shown to have no clinically significant effect on sperm count, motility or morphology. Findings in animal fertility studies are included in section 5.3.

4.7 Effects on ability to drive and use machines

Aciclovir for solution for injection (IV) is usually used in hospitalised patients and information on the ability to drive and use machines generally has no significance.
No studies have been performed to assess the effects of aciclovir on the ability to drive or use machines.

4.8 Undesirable effects

The frequency categories assigned to the adverse reactions below have been established on the basis of clinical trial data to classify adverse reactions, in the knowledge that this incidence may vary depending on the indication.
The frequency of other adverse reactions could not be estimated from spontaneous reports due to the lack of appropriate data for calculating their frequency.

The following convention has been used for classifying adverse reactions according to their frequency:
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)

Blood and lymphatic system disorders:
Frequency not known: Thrombocytopenia, leukopenia.
Immune system disorders:
Frequency not known: Anaphylactic reactions.
Nervous system disorders:
Frequency not known: Headache, feelings of drunkenness.
Balance disorders, ataxia and dysarthria may be associated or observed in isolation and indicate a cerebellar syndrome.
Sometimes severe neurological disorders are possible, which may reflect symptoms of encephalopathy and include confusion, agitation, tremors, myoclonus, convulsions, hallucinations, psychosis, drowsiness and coma.
These usually resolve upon discontinuation of treatment.
These neurological signs are usually observed in patients with renal impairment who have received doses above the recommended dosage or in elderly patients (see section 4.4). However, they may be observed in the absence of these contributing factors. The presence of these symptoms should trigger an investigation into possible overdose (see section 4.9).
Respiratory, thoracic and mediastinal disorders:
Frequency not known: Dyspnoea.
Gastrointestinal disorders:
Common: Nausea, vomiting, diarrhoea, abdominal pain.
Hepatobiliary disorders:
Common: Reversible increases in serum bilirubin and hepatic enzymes.
Frequency not known: Acute liver injury.
Skin and subcutaneous tissue disorders:
Common: pruritus, rash, hives
Isolated cases of angioedema
Renal and urinary disorders:
Common: Increased urea and blood creatinine.

Rapid increases in plasma urea and creatinine levels might be related to peak plasma concentrations, as well as the patient's hydration status. To avoid this effect, the medicinal product must not be administered by intravenous bolus injection, but rather as a slow infusion over a period of one hour (see section 4.2).

Frequency not known: acute renal failure, especially in elderly subjects or in patients with renal impairment if the dosage is exceeded, renal pain.
Renal pain may be associated with renal impairment (see section 4.4).
The risk of acute renal failure is promoted by any situation of overdose and/or dehydration, or by combination with nephrotoxic medicinal products. Investigations into these risk factors should be made, regardless of the patient's age.
The risk of renal impairment can be avoided by respecting the dosage, the precautions for use (especially maintenance of adequate hydration) and a slow rate of administration (see sections 4.2, 4.4).

General disorders and administration site conditions:
Frequency not known: Fatigue, fever.
Common: Inflammatory skin lesions or phlebitis at the injection site, which can exceptionally lead to necrosis, in the event of extravasation or insufficient dilution of the solution.
These inflammatory lesions are related to the alkaline pH of this medicinal product.
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 the HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Signs and symptoms
Overdose of intravenous aciclovir has led to an increase in serum creatinine, blood urea and subsequent renal impairment. Neurological effects such as confusion, hallucinations, agitation, convulsions and coma have been described in association with overdose.

Management
Patients must be closely monitored to detect any signs of toxicity.
Haemodialysis significantly increases the elimination of aciclovir from the bloodstream and may therefore be considered as a management option in cases of symptomatic overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct-acting antivirals, nucleosides and nucleotides excluding reverse-transcriptase inhibitors, ATC code: J05AB01.

Aciclovir is a specific inhibitor of the herpes virus, with *in vitro* activity against *Herpes simplex* virus types 1 and 2 and *Varicella zoster* virus (VZV).
Aciclovir, after having been phosphorylated to aciclovir triphosphate, inhibits viral DNA synthesis. The first stage of phosphorylation is mediated solely by a specific viral enzyme.
For HSV and VZV viruses, this enzyme is a viral thymidine kinase, which is present only in cells infected with the virus.
The phosphorylation of aciclovir monophosphate to di- and triphosphate is mediated by cellular kinases. Aciclovir triphosphate is a selective competitive inhibitor of viral DNA polymerase, and the incorporation of this nucleoside analogue stops the elongation of the DNA chain, thereby interrupting the synthesis of viral DNA. Viral replication is thus blocked.
Due to its dual selectivity, aciclovir does not interfere with the metabolism of healthy cells.
The study of a large number of clinical isolates during curative or preventive treatment with aciclovir has shown that a decrease in sensitivity to aciclovir is extremely rare in immunocompetent subjects. In immunocompromised subjects (such as recipients of organ and bone marrow transplants, subjects receiving cancer chemotherapy and subjects infected with human immunodeficiency virus (HIV)), decreased susceptibility has occasionally been found.
The rare cases of resistance observed are generally due to deficient viral thymidine kinase and are manifested by lower virulence. A few cases of decreased sensitivity to aciclovir have been observed following changes in either thymidine kinase or viral DNA polymerase. The virulence of these viruses does not appear to be altered.

Clinical studies

There is no information on the effect of oral or injectable (IV) forms of aciclovir on fertility in women.
In a study of 20 male patients with normal sperm count, orally administered aciclovir at doses of up to 1 g per day for a duration of up to 6 months was not shown to have any clinically significant effect on the number of spermatozoa, their mobility or their morphology.

5.2 Pharmacokinetic properties

Absorption
Aciclovir is only partially absorbed by the intestine.
Following doses of 200 mg of aciclovir administered every four hours to adults, the maximum average concentrations in a state of equilibrium (C_{ssmax}) reach 0.7 µg/mL (3.1 µM).
After doses of 400 mg and 800 mg were given every four hours to adults, an increase in the C_{ssmax} proportionally lower than the dose was observed, with rates reaching 1.2 and 1.8 µg/mL (5.3 and 8 µM).
Distribution
Aciclovir is distributed to tissues including the brain, kidneys, lungs, liver, muscles, vaginal secretions and herpetic vesicular fluid.
The average volume of distribution of 26 L shows that aciclovir is distributed through the total volume of body water. The apparent values after oral administration (Vd/F) range from 2.3 to 17.8 L/kg.
Aciclovir is poorly bound to plasma proteins (9-33%) and drug interactions involving displacement of aciclovir from its binding sites are not expected.
Levels in cerebrospinal fluid are approximately 50% of steady-state plasma concentrations.

Biotransformation
Aciclovir is mainly excreted by the kidney unchanged. The 9-(carboxy-methoxymethyl) guanine, the main metabolite in aciclovir, accounts for around 10 - 15 % of the dose excreted in urine.

Elimination
Average systemic exposure ($ASC_{0-\infty}$) to aciclovir varies between 1.9 and 2.2 µg*h/mL after a 200 mg dose. In adults, the terminal plasma half-life of aciclovir after aciclovir IV is administered is around 2.9 hours. Renal clearance of aciclovir (CLr=14,3 L/h) is much higher than clearance of creatinine, showing that a tubular secretion, alongside glomerular filtration, helps the drug to be eliminated by the kidneys. The half-life and total clearance of aciclovir is dependent on kidney function. As a result, it is recommended to adapt the dosage to patients suffering from renal impairment. The terminal plasma half-life in neonates (0-3 months) treated with doses of 10 mg/kg, administered as a one-hour infusion every 8 hours, was 3.8 hours.
In elderly subjects, total body clearance decreases with increasing age and is associated with decreased creatinine clearance, although there is little change in the plasma terminal half-life.
In patients with chronic renal failure, the mean terminal half-life was 19.5 hours. The mean half-life of aciclovir was 5.7 hours during haemodialysis. Plasma levels of aciclovir decreased by approximately 60% during dialysis.

5.3 Preclinical safety data

Mutagenicity
The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir is unlikely to pose a genetic risk to man.

Carcinogenicity
Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

Teratogenicity
Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice.
In a non-standard test in rats, foetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Fertility
Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Two-generation studies in mice did not reveal any effect of (orally administered) aciclovir on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (used to adjust pH).

6.2 Incompatibilities

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

6.3 Shelf life

30 months

After reconstitution for 500 mg:
Chemical and physical in-use stability has been demonstrated for 24 hours at 23-27°C under artificial light and at 2-8°C when dissolved in 20 ml of water for injections or sodium chloride 9 mg/mL (0.9 %) solution for injection.

After dilution for 500 mg:
Chemical and physical in-use stability has been demonstrated for 12 hours at 23-27°C at a concentration of Aciclovir 5.0 mg/ml after dilution with the compatible solutions mentioned in section 6.6.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C or than the times stated above for the chemical and physical in-use stability, whichever is the shorter unless opening/reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Any unused solution should be discarded.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

500 mg:
Clear type-I glass vials with capacity of 20 ml closed with 20 mm bromobutyl rubber stopper and 20 mm aluminum seals, with turn-off coloured (yellow) plastic caps.

Pack sizes: 1, 5 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Should be prepared immediately prior to use. Any unused solution must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Reconstitution:
Aciclovir should be reconstituted using the following volumes of either water for injections or sodium chloride 9 mg/mL (0.9 %) solution for injection to provide a solution containing 25 mg aciclovir per ml:

Formulation volume of fluid for reconstitution
250 mg vial 10 ml
500 mg vial 20 ml
From the calculated dose, the appropriate number and strength of vials to be used should be determined.
To reconstitute each vial the recommended volume of infusion fluid is to be added and shaked gently until the contents of the vial have dissolved completely.

Administration

The required dose of Aciclovir should be administered by slow intravenous infusion over a one-hour period.
After reconstitution Aciclovir may be administered by a controlled-rate infusion pump. Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.
The required volume of reconstituted solution to the chosen infusion solution should be added, as recommended below, and shaked well to ensure adequate mixing occurs.
For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum, it is recommended that dilution is based on 4 ml reconstituted solution (100 mg aciclovir) added to 20 ml of infusion fluid.
For adults, it is recommended that infusion bags containing 100 ml of infusion fluid are used, even when this would give an aciclovir concentration substantially below 0.5% w/v. Thus, one 100 ml infusion bag may be used for any dose between 250 mg and 500 mg aciclovir (10 and 20 ml of reconstituted solution) but a second bag must be used for doses between 500 mg and 1000 mg.
When diluted in accordance with the recommended schedules, Aciclovir is known to be compatible with the following infusion fluids:

- Sodium chloride 9 mg/mL (0.9 %) solution for injection
- Sodium Chloride Intravenous Infusion (0.45%w/v)
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion
- Sodium Chloride (0.45% w/v) and Glucose (2.5% w/v) Intravenous Infusion
- Compound Sodium Lactate Intravenous Infusion (Hartmann's Solution).

Aciclovir when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v.
Since no antimicrobial preservative is included, reconstitution and dilution must be carried out under full aseptic conditions, immediately before use, and any unused solution discarded.
The reconstituted or diluted solutions should not be refrigerated.
Should any visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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