SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Synastone 50 mg/ml, Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methadone hydrochloride 50 mg/ml (50 mg in 1 ml total volume)

For excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

(Colourless, isotonic solution)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of opioid addiction as a narcotic abstinence syndrome suppressant. The use of injectable methadone for this indication must be initiated by physicians with adequate expertise and experience in addiction therapy.
The use of methadone in opiate addiction must be part of a broader treatment programme including regular treatment reviews and must be supervised by specialist services.

4.2 Posology and method of administration

Treatment goals and discontinuation:

Before initiating treatment with Synastone 50mg/ml, solution for injection, a treatment strategy including treatment duration and treatment goals should be agreed together with the patient in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with methadone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4). In absence of adequate pain control, the possibility of tolerance and progression of underlying disease should be considered (see section 4.4).

Method of administration:
Intramuscular, intravenous or subcutaneous injection. Volumes greater than 2ml given intramuscularly may need to be in divided doses at different sites.

Adults:
Initially 10-20mg per day, increasing by 10-20mg per day until there are no signs of withdrawal or intoxication.

This must be managed by physicians with suitable experience. The initial dose, safe dosage increments and the establishment of a dose that prevents withdrawal symptoms needs to be individualised. The degree of tolerance or neuroadaptation, any additional consumption of oral methadone or other opiates and the cumulative potential of methadone treatment (as opposed to shorter acting opiates), along with the general health of the patient must be taken into account. Typical doses for heavily-addicted users can be fatal to those without such neuroadaptation.

The usual dose of injectable methadone, when the addict is stabilised may need to exceed 100mg daily in order to prevent symptoms of opiate withdrawal.

The aims of treatment should include allowing patients to reduce any criminality and improve their health and social productivity.

Elderly and debilitated patients:
If repeated doses are required, use with caution due to the long plasma half-life. There may be a greater risk of respiratory depression, with or without any associated renal or hepatic impairment in this age group.

Children:
As methadone has not been studied in children, it should not be used in children under the age of 16 years.

Liver disease:
In patients with severe liver damage, the dose of methadone should be carefully controlled as there is a risk that methadone might precipitate porto-systemic encephalopathy.

Renal Impairment:

The dose may need to be reduced in moderate or severe renal impairment.

4.3 Contraindications

When using injectable methadone in the treatment of opioid addiction, the following are contraindicated:

1. Patients not already receiving methadone (because of the high methadone concentration).

2. Patients with known hypersensitivity to methadone.

3. Patients with respiratory depression and obstructive airways disease.

4. Use during an acute asthma attack.

5. Concurrent administration with monoamine oxidase inhibitors or within 2 weeks of discontinuation of treatment with them.

6. Phaeochromocytoma. Opiates may induce the release of endogenous histamine and stimulate catecholamine release.

7. Risk of paralytic ileus.

8. Comatose patients.

4.4 Special warnings and precautions for use

Opioid Use Disorder (abuse and dependence)
Methadone is an opioid analgesic and is highly addictive in its own right. It is controlled under the Misuse of Drugs Act 1971 (Schedule 2).
It has a long half-life and can therefore accumulate. A single dose which will relieve symptoms may, if repeated on a daily basis, lead to accumulation and possible death.

As with other opioids, tolerance, physical, and/or psychological dependence may develop upon repeated administration of methadone.
It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Abuse or intentional misuse of Synastone 50mg/ml, solution for injection may result in overdose and/or death.
The risk of developing Opioid Use Disorder is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with methadone hydrochloride. The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician and patient with review at regular intervals (usually at least three-monthly, depending on clinical progress).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations.

Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Hypoglycaemia

Hypoglycaemia has been observed in the context of methadone overdose or dose escalation. Regular monitoring of blood sugar is recommended during dose escalation (see section 4.8 and section 4.9).

Respiratory depression

Due to the slow accumulation of methadone in the tissues, respiratory depression may not be fully apparent for a week or two. Asthma may be exacerbated due to histamine release. Concomitant treatment with other agents with CNS depressant activity is not advised due to the potential for CNS and respiratory depression (see also section 4.5 Interactions).

Cardiac effects

Cases of QT interval prolongation and torsades de pointes have been reported during treatment with methadone, particularly at higher doses (> 100 mg/d). Methadone should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of:

- history of cardiac conduction abnormalities,

- advanced heart disease or ischaemic heart disease,
- liver disease,
- family history of sudden death,
- electrolyte abnormalities, i.e. hypokalaemia, hypomagnesaemia,
- concomitant treatment with drugs that have a potential for QT-prolongation,
- concomitant treatment with drugs which may cause electrolyte abnormalities,
- concomitant treatment with cytochrome P450 CYP 3A4 inhibitors (see section 4.5).

In patients with recognised risk factors for QT prolongation, or in case of concomitant treatment with drugs that have a potential for QT-prolongation, ECG monitoring is recommended prior to methadone treatment, with further ECG test at dose stabilisation. ECG monitoring is recommended, in patients without recognised risk factors for QT prolongation, before dose titration above 100 mg/d and at seven days after titration.

Pregnancy and risks to the neonate (see also section 4.6 Pregnancy and Lactation)
Female addicts who discover they are pregnant will require specialised care from obstetric and paediatric staff with experience in such management. Methadone should not be withdrawn abruptly and infants require careful monitoring for signs of respiratory depression and/or opioid withdrawal.

There are reports of neonates and children exposed to methadone during pregnancy developing visual disorders, including reduced visual acuity, strabismus and nystagmus. The causal relationship to methadone in isolation has not been established as factors such as other drugs taken during pregnancy e.g. benzodiazepines, intake of alcohol, and drugs used to treat neonatal abstinence syndrome e.g. phenobarbital, could play a role in the adverse reactions seen. However, there is sufficient evidence to suggest that an association is possible and therefore consideration of this risk should be taken during prescribing decisions.

Hepatic disorders
Special care should be taken with patients with severe liver damage, as there is a risk that methadone might precipitate porto-systemic encephalopathy or precipitate coma.

Adrenal insufficiency
Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Renal impairment
Reduce doses to avoid increased and prolonged effect, increased cerebral sensitivity.

Decreased Sex Hormones and increased prolactin

Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Other warnings
Methadone should be used with great caution in patients with acute alcoholism, convulsive disorders and head injuries.

Methadone, as with other opiates, has the potential to increase intracranial pressure especially where it is already raised.

Children (under 16): Even at low doses, methadone is a special hazard to children if ingested accidentally. Children under 6 months, particularly neonates, may be more sensitive to respiratory depression than adults.

The drug should be used with caution in elderly or debilitated patients due to its long half-life. It should also be used with caution in patients with hypothyroidism, adrenocortical insufficiency, prostatic hyperplasia, hypotension, shock, biliary tract disorders, inflammatory or obstructive bowel disorders or myasthenia gravis.

Local reactions at the site of injection can occur and therefore these sites should be inspected regularly. Injections may be painful.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Methadone and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Methadone concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Synastone contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Methadone is metabolised by the liver cytochrome P450 isoenzymes including CYP 3A4. CYP 1A and CYP 2D6. Interactions are likely with enzyme inhibitors or inducers.

Cytochrome P450 3A4 inhibitors
Methadone clearance is decreased when co-administered with drugs which inhibit CYP3A4 activity, such as some anti-HIV agents, macrolide antibiotics, cimetidine and azole antifungal agents (since the metabolism of methadone is mediated by the CYP3A4 isoenzyme). Please see further details of specific interactions with antiviral-HIV agents, erythromycin, cimetidine and fluconazole/ketoconazole/voriconazole given later in this section.

Monoamine Oxidase Inhibitors
The concurrent use of MAOIs is contraindicated (see 4.3 Contraindications) as they may prolong and enhance the respiratory depressant effects of methadone. Severe CNS excitation, delirium, hyperpyrexia, convulsions or respiratory depression is possible with concurrent use of opiates and MAOIs. With moclobemide, either CNS excitation or depression (hypertension or hypotension) is possible.

CNS drugs
Concomitant use of other CNS depressants is not advised. Hypnotics (including benzodiazepines, chloral hydrate and chlormethiazole) and anxiolytics may increase the general depressant effects of methadone. Antipsychotics may enhance the sedative effects and hypotensive effects of methadone.

The plasma concentrations of methadone may be increased by fluvoxamine and, to a lesser extent, fluoxetine and theoretically other SSRIs due to decreased methadone metabolism. There may be increased sedation with tricyclic antidepressants.

There is an increased risk of ventricular arrhythmias when methadone is given with the CNS stimulant, atomoxetine.

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Opioid agonists
Concomitant use of pethidine and other opioid agonist analgesics is not advised because of the potential for additive effects on CNS depression, respiratory depression and hypotension.

Opioid antagonists
Naloxone and naltrexone antagonise the analgesic, CNS and respiratory depressant effects of methadone and can rapidly precipitate withdrawal symptoms (see section 4.9 Overdose). Similarly buprenorphine and pentazocine may precipitate withdrawal symptoms.

Alcohol

Alcohol may enhance the sedative and hypotensive effects of methadone and increase respiratory depression.

Antibacterials
Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of methadone may be necessary.

Plasma levels of methadone may increase with concurrent administration of ciprofloxacin due to inhibition of CYP 1A2 and CYP 3A4. Reduced serum concentrations of ciprofloxacin may occur.

Erythromycin theoretically may increase methadone levels due to decreased methadone metabolism.

Rifabutin may decrease methadone levels due to increased metabolism.

Antiviral drugs used in HIV
Plasma concentrations of methadone may be reduced by the nucleoside reverse transcriptase inhibitor, abacavir, the protease inhibitors, nelfinavir, ritonavir and fosamprenavir which are metabolised by cytochrome P450 enzyme systems, and the non-nucleoside reverse transcriptase inhibitors, efavirenz and nevirapine, which interact with a number of drugs metabolised in the liver. Methadone may increase the plasma concentration of the nucleoside reverse transcriptase inhibitor, zidovudine.

Anticonvulsants
Phenytoin and carbamazepine increase the metabolism of methadone. Adjustment of the dose of methadone should be considered.

Barbiturates
May stimulate hepatic enzymes that increase methadone metabolism, reducing methadone levels. There may be increased sedation and additive CNS depression.

Cyclizine and other sedating antihistamines
May have additive psychoactive effects; antimuscarinic effects at high doses.

Fluconazole, ketoconazole and voriconazole
May raise methadone levels, due to decreased methadone metabolism. Reducing the dose of methadone should be considered.

Grapefruit juice
There are several anecdotal reports of raised methadone levels due to decreased methadone metabolism.

Cimetidine
Retards oxidative hepatic drug metabolism by binding to microsomal cytochrome P450. The metabolism of methadone may be inhibited leading to increased plasma concentrations and opiate action.

Antimuscarinics
Concomitant antimuscarinics (e.g. atropine and synthetic anticholinergics) may increase the risk of severe constipation and/or urinary retention.

Drugs affecting gastric emptying
Domperidone and metoclopramide may increase the speed of onset but not the extent of methadone absorption by reversing the delayed gastric emptying associated with opioids. Conversely, methadone may antagonise the effect of domperidone/metoclopramide on gastro-intestinal activity.

Serotonergic drugs
Serotonergic syndrome may occur with concomitant administration of methadone with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

pH of urine
Drugs that acidify (e.g. ascorbic acid) or alkalinise (e.g. sodium bicarbonate) the urine may have an effect on clearance of methadone as it is increased at acidic pH and decreased at alkaline pH.

Gabapentinoids
The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.

Cannabidiol
Concomitant administration of cannabidiol may result in increased plasma concentrations of methadone.

Effects of methadone on other drugs
Methadone may have an effect on other drugs as a consequence of reduced gastro-intestinal motility. Methadone may delay the absorption of the antiarrhythmic, mexiletine. Methadone may increase desimipramine levels by up to a factor of two.

In patients taking drugs affecting cardiac conduction, or drugs which may affect electrolyte balance there is a risk of cardiac events when methadone is taken concurrently.

The hypnotic effect of sodium oxybate may be enhanced by opioid analgesics; concomitant use should be avoided.

Co-administration of methadone with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of methadone with potential decrease in clinical

efficacy. Therefore, caution is advised when metamizole and methadone are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Reports of visual disorders have been reported in neonates and children following exposure to methadone during pregnancy. Although other factors have also been present, there is sufficient evidence to suggest that an association is possible (see section 4.4).

Female addicts who discover they are pregnant will require specialised care from obstetric and paediatric staff with experience in such management.

A careful risk/benefit assessment should be made before administration to pregnant women because of possible adverse effects on the foetus and neonate including respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. In labour there is a risk of gastric stasis and inhalation pneumonia in the mother.

Lactation:
Administration to nursing women is not recommended as methadone hydrochloride may be secreted in breast milk and may cause respiratory depression in the infant. Methadone is excreted in breastmilk at low levels. The decision to recommend breastfeeding should take into account clinical specialist advice and consideration should be given to whether the woman is on a stable maintenance dose of methadone and any continued use of illicit substances. If breastfeeding is considered, the dose of methadone should be as low as possible. Prescribers should advise breastfeeding women to monitor the infant for sedation and breathing difficulties and to seek immediate medical care if this occurs. Although the amount of methadone excreted in breast milk is not sufficient to fully suppress withdrawal symptoms in breast-fed infants, it may attenuate the severity of neonatal abstinence syndrome. If it is necessary to discontinue breastfeeding it should be done gradually, as abrupt weaning could increase withdrawal symptoms in the infant.

4.7 Effects on ability to drive and use machines

Patients should not drive or use machines while taking methadone.
Methadone may cause drowsiness and reduce alertness and the ability to drive after the administration of methadone.

"This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  o The medicine has been prescribed to treat a medical or dental problem and
  o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  o It was not affecting your ability to drive safely"

4.8 Undesirable effects

Methadone is associated with undesirable effects similar to other opioid analgesics. There are no modern clinical studies available that can be used to determine the frequency of undesirable effects. Therefore, all the undesirable effects listed are classed as "frequency unknown".

Endocrine Disorders:-
Hyperprolactinaemia.

Metabolism and nutrition disorders:-
Hypoglycaemia.

Psychiatric Disorders:-
Dependence (see section 4.4), confusion, mood change including euphoria and dysphoria, hallucinations, restlessness, sleep disturbances.

Nervous System Disorders:-
Drowsiness, dizziness, vertigo.

Eye Disorders:-
Dry eyes, visual disturbances such as miosis, nystagmus[1], strabismus[1], visual acuity reduced[1].

Cardiac Disorders:-
Bradycardia, tachycardia, palpitations, QT prolongation, torsades de pointes.

Vascular Disorders:-

Orthostatic hypotension.

Respiratory, Thoracic & Mediastinal Disorders:
Respiratory depression (see also section 4.9 overdose), central sleep apnoea syndrome, dry nose.

Gastrointestinal Disorders:-
Nausea, vomiting (particularly at the start of treatement), constipation, biliary spasm, dry mouth.

Skin & Subcutaneous tissue Disorders:-
Sweating, facial flushing, rashes (urticaria, pruritus), oedema.

Musculoskeletal, Connective Tissue & Bone Disorders:-
Muscle rigidity

Renal & Urinary Disorders:-
Micturition difficulties, urinary retention, ureteric spasm

Reproductive System & Breast Disorders:-
Decreased libido, dysmenorrhoea, amenorrhoea, sexual dysfunction

General Disorders & Administration Site Conditions:-
Uncommon: drug withdrawal syndrome
Not known: hypothermia

[1]Visual effects have been reported in infants and children exposed to methadone during pregnancy.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Signs:
Similar to those for morphine.
Toxic leukoencephalopathy, respiratory depression, extreme somnolence progressing to stupor or coma, cyanosis, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension have been observed with methadone overdose.

Hypoglycaemia has been reported.

In severe overdosage, apnoea, circulatory collapse, pulmonary oedema, cardiac arrest and death may occur.

Treatment:
Treatment is supportive. Patients should be kept conscious wherever possible.

A patent airway must be established with assisted or controlled ventilation. Narcotic antagonists may be required if there is evidence of significant respiratory or cardiovascular depression. However, treatment with these antagonists must be repeated as necessary because of the longer duration of depressant activity of methadone (36 to 48 hours) compared to the antagonists (1 to 3 hours). Nalorphine or Levallorphine should be given intravenously as soon as possible and repeated every 15 minutes if necessary. In a person addicted to narcotics, administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome. In such cases, use of an antagonist should be avoided unless there is serious respiratory depression when they should be administered with great care.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in opioid dependence. ATC code: N07BC
Methadone is a drug of addiction and repeated administration can result in dependence and tolerance. Cross-tolerance with other opioids can occur.
It is a synthetic opioid analgesic similar to morphine although less sedative. It acts on the CNS system and smooth muscles via the peripheral nervous system.
The analgesic effect of methadone occurs about 10 to 20 minutes following parenteral administration. Miosis and respiratory depression can occur for more than 24 hours after a single dose. Methadone also reduces heart rate, systolic blood pressure and body temperature. Sedation is seen in some patients receiving repeated doses and sudden cessation of treatment can result in withdrawal symptoms.
Like morphine, it also has effects on bowel motility, biliary tone and secretion of pituitary hormones as well as on cough suppression. Methadone also causes the release of histamine from mast cells resulting in a number of allergic-type reactions.

5.2 Pharmacokinetic properties

Methadone is rapidly absorbed following injection, however there are wide inter-individual variations.
Methadone is widely distributed in the tissues, diffuses across the placenta and is excreted in breast milk. It is extensively protein bound.
It is metabolised in the liver (forming inactive metabolites) and excreted via the bile and urine. Urinary excretion is pH-dependent, the lower the pH the greater the clearance.
Methadone has a prolonged half-life (15 to 40 hours) and can accumulate on repeated administration.

5.3 Preclinical safety data

There is no additional information relevant to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.
Keep container in the outer carton.

6.5 Nature and contents of container

1 ml clear glass (Ph. Eur. Type I) one-point-cut ampoules containing 1 ml solution for injection.

Pack size: 10 ampoules per carton.

6.6 Special precautions for disposal

Methadone is controlled under the Misuse of Drugs Act 1971 (Schedule 2).

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
Middlesex
HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0610

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2003 / 3 March 2009

10 DATE OF REVISION OF THE TEXT

14/05/2025