

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-dydramol Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Dihydrocodeine Tartrate 10 mg & Paracetamol 500 mg.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White, flat, bevel edge tablets with plain on one face and break line on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Analgesic for the relief of mild to moderate pain.

4.2 Posology and method of administration

Posology:

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with Co-dydramol in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Adults: Initially one or, if necessary, two tablets every 4 hours to a maximum of 8 tablets daily.

Elderly

Dosage should be reduced in the elderly.

Paediatric Population:

Children 16-18 years:

Initially one or, if necessary, two tablets every 4 hours to a maximum of 8 tablets in 24 hours.

Children 12 - 15 years:

1 tablet every 4-6 hours when necessary to a maximum of 4 doses in 24 hours.

Children under 12 years:

Not recommended.

Method of Administration:

For oral administration.

It is recommended that this product should be taken during or after meals.

4.3 Contraindications

- Hypersensitivity to dihydrocodeine tartrate, other opioids or paracetamol or to any of the excipients listed in section 6.1.
- Respiratory depression.
- Obstructive airways disease.
- Diarrhoea caused by poisoning until the toxic material has been eliminated, or diarrhoea associated with pseudomembranous colitis.
- Liver disease

4.4 Special warnings and precautions for use

Co-dydramol should be used with caution in patients with:

- Hepatic function impairment (avoid if severe) and those with non-cirrhotic alcoholic liver disease. The hazards of overdose are greater in those with alcoholic liver disease.
- Prolonged use of co-dydramol may cause hepatic necrosis. Patients should be advised not to exceed the recommended dose and not to take other paracetamol-containing products concurrently.
- Renal function impairment.
- Hypothyroidism (risk of depression and prolonged CNS depression is increased). Dosage should be reduced.
- Inflammatory bowel disease - risk of toxic megacolon.
- Asthma attacks. Opioids should not be administered during an asthma attack, and it should be administered with due care to persons liable to such attack.
- Convulsions - may be induced or exacerbated.
- Drug abuse, dependence (including alcoholism), enhanced instability, suicidal ideation or attempts - predisposed to drug abuse.
- Head injuries or conditions where intracranial pressure is raised.
- Gall bladder disease or gall stones - opioids may cause biliary contraction
- Gastro-intestinal surgery - use with caution after recent GI surgery as opioids may alter GI motility.
- Prostatic hypertrophy or recent urinary tract surgery.

- Adrenocortical insufficiency, e.g. Addison's Disease;
- Hypotension and shock.
- Myasthenia gravis.
- Pheochromocytoma - opioids may stimulate catecholamine release by inducing the release of endogenous histamine.
- Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.

The risk-benefit of continued use should be assessed regularly by the prescriber.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain

relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. 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.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

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 Co-dydramol.

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 newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of co-dydramol 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 co-dydramol 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).

Alcohol should be avoided. When dihydrocodeine is prescribed for chronic use, care should be taken to avoid unnecessary increase in dosage.

The risk-benefit of continued use should be assessed regularly by the prescriber.

The label will have the following warnings:

- Do not take with anything else containing paracetamol while taking this medicine.
- Contains paracetamol.
- Talk to your doctor at once if you take too much of this medicine, even if you feel well.
- Do not take more medicine than the label tells you to. If you do not get better, talk to you doctor.

The label will also state (to be displayed prominently on outer pack – not boxed):

- Do not take for longer than directed by your prescriber as taking dihydrocodeine regularly for a long time can lead to addiction.

The leaflet will state in a prominent position in the “before taking” section:

- Do not take for longer than directed by your prescriber.
- Taking dihydrocodeine regularly for a long time can lead to addiction, which might cause you to feel restless and irritable when you stop the tablets.
- Taking a painkiller for headaches too often or for too long can make them worse.
- Talk to your doctor at once if you take too much of this medicine, even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

Important information regarding the ingredients of this medicine

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol can interact with the following:

- Drugs which alter gastric emptying time (e.g. cimetidine, ethyl alcohol, oral steroid contraceptives). These drugs reduce or delay peak paracetamol blood levels;
- Metoclopramide or domperidone increases the speed of absorption of paracetamol;
- Colestyramine reduces paracetamol absorption;
- Drugs which interfere with the metabolism of paracetamol by competition with metabolic pathways or substrates e.g. anticonvulsants (phenytoin), hepatic enzyme inducers, alcohol, barbiturates, tricyclic antidepressants. A poor diet (low protein) may also have a similar effect on the risk of serious paracetamol toxicity to hepatic enzyme inducers. Patients who have taken barbiturates, tricyclic antidepressants and alcohol may show diminished ability to metabolise large doses of paracetamol, the plasma half-life of which may be prolonged;
- The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
- Alcohol can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol.
- Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risk factors (see section 4.4)

Dihydrocodeine can interact with the following:

- CNS depressants - enhanced sedative and/or hypotensive effect with alcohol, anaesthetics, hypnotics, anxiolytics, antipsychotics, hydroxyzine, tricyclic antidepressants;
- Antibacterials, e.g. ciprofloxacin, - avoid premedication with opioids as reduced plasma ciprofloxacin concentration;
- Monoamine Oxidase Inhibitors (MAOIs) or have taken these within the last 2 weeks - use only with extreme caution;
- Cyclizine
- Mexiletine - delayed absorption;
- Metoclopramide and domperidone - antagonise GI effects;
- Cisapride - possible antagonism of GI effects;

- Dopaminergics (e.g. selegiline) - possible risk of hyperpyrexia and CNS toxicity. This risk is greater with pethidine but with other opioids the risk is uncertain;
- Ulcer healing drugs - cimetidine inhibits the metabolism of opioid analgesics;
- Anticholinergics (e.g. atropine) - risk of severe constipation which may lead to paralytic illness, and/or urinary retention;
- Antidiarrhoeal drugs (e.g. loperamide, kaolin) - increased risk of severe constipation;
- Antihypertensive drugs (e.g. guanethidine, diuretics) - enhanced hypotensive effect;
- Opioid antagonists (e.g. buprenorphine, naltrexone, naloxone);
- Neuromuscular blocking agents - additive respiratory depressant effects.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Paracetamol:

A large amount of data on pregnant women indicate neither malformative, nor fetol/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Risk benefit must be considered because opioid analgesics cross the placenta. Studies in animals have shown opioids to cause delayed ossification in mice and increased resorption in rats.

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.

During labour opioids enter the foetal circulation and may cause respiratory depression in the neonate. Administration during labour may depress

respiration in the neonate and an antidote for the child should be readily available.

As with all medicines, use should be avoided during the first trimester.

Breast-feeding

Paracetamol is excreted in breast milk but not in a clinically significant amount.

Administration to nursing woman is not recommended as dihydrocodeine may be secreted in breast milk and may cause respiratory depression in the infant.

4.7 Effects on ability to drive and use machines

Opioid analgesics can impair mental function and can cause blurred vision and dizziness. Patients should make sure they are not affected before driving or operating machinery.

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:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not Known (cannot be estimated from the available data).

At the recommended dosage, paracetamol may cause the following side effects:

System Organ Class	Frequency	ADR
Immune system disorders	Rare	Allergic reactions (skin rash, drug fever, mucosal lesions)
Metabolism and nutrition disorders	Not known	High anion gap metabolic acidosis
Nervous system disorders	Not known	Drowsiness, impaired mental functions
Gastrointestinal disorders	Very rare	Acute pancreatitis ¹
Vascular disorders	Not known	Toxic myocarditis
Blood and lymphatic system disorders	Not known	Methaemoglobinaemia, neutropenia, pancytopenia, leukopenia, haemolytic anaemia, agranulocytosis, thrombocytopenia
Renal and urinary disorders	Uncommon	Nephrotoxicity
	Not known	Papillary necrosis ²
Skin and subcutaneous tissue disorder	Very rare	Cases of serious skin reactions have been reported.

¹ Pancreatitis is more likely to occur at above normal doses

² Reported after prolonged administration

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year, and liver damage has been reported after daily ingestion of excessive amounts for shorter periods.

A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol, nor was the control of their disease improved after paracetamol withdrawal.

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Adverse effects of opioid treatment which have been reported include:

System Organ Class	Frequency	ADR
Immune system disorders	Not known	Allergic reactions (may be caused by histamine release) (rash, urticaria, difficulty breathing, increased sweating, redness or flushed face), anaphylactic shock, angioedema
Nervous system disorders	Not known	Confusion, drowsiness, vertigo, dizziness, changes in mood, hallucinations, CNS excitation (restlessness/excitement), convulsions, mental depression, headache, trouble sleeping, or nightmares, raised intracranial pressure, tolerance or dependence, trembling, unusual tiredness or weakness, malaise, miosis, hypothermia
Psychiatric disorders	Not known	Drug dependence (see section 4.4)
Gastrointestinal disorders	Not known	Constipation ¹ , GI irritation, biliary spasm, nausea, vomiting, loss of appetite, dry mouth, paralytic ileus or toxic megacolon, abdominal pain.
Vascular disorders	Not known	Bradycardia, palpitations, hypotension
Eye disorders	Not known	Blurred or double vision
Renal and urinary disorders	Not known	Ureteral spasm, antidiuretic effect
Skin and subcutaneous tissue disorders	Not known	Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption
General disorders and administration site conditions	Uncommon	Drug withdrawal syndrome

¹ If constipation occurs it can be treated with a gentle laxative

Withdrawal

Abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, nausea, vomiting, sweating and increase in heart rate, respiratory rate and blood pressure. Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Regularly prolonged use of dihydrocodeine is known to lead to addiction and tolerance. Symptoms of restlessness and irritability may result when treatment is then stopped.

Prolonged use of a painkiller for headaches can make them worse.

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.

Paracetamol:

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Symptoms:

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal/stomach pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding coma and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria may develop even in the absence of severe liver damage. Cardiac arrhythmias have been reported.

Risk factors:-

If the patient

- Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Regularly consumes ethanol in excess of recommended amounts.
- Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Treatment

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the NPIS or a liver unit.

Dihydrocodeine

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.

Symptoms

Acute overdosage with dihydrocodeine can be manifested by somnolence progressing to stupor or coma, miotic pupils, rhabdomyolysis, non-cardiac pulmonary oedema, bradycardia, hypotension and respiratory depression or apnoea.

Management

Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

In the case of massive overdosage, administer naloxone intravenously (0.4 to 2 mg for an adult and 0.01 mg/kg body weight for children) if the patient is in a coma or respiratory depression is present. Repeat the dose at 2 minute intervals if there is no response, or by an infusion. An infusion of 60% of the initial dose per hour is a useful starting point. A solution of 10 mg made up in 50 ml dextrose will produce 200 micrograms/ml for infusion using an IV pump (dose adjusted to the clinical response). Infusions are not a substitute for frequent review of the patient's clinical state. Intramuscular naloxone is an alternative in the event that IV access is not possible.

As the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. Naloxone is a competitive antagonist and large doses (4 mg) may be required in seriously poisoned patients. For less severe overdosage, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to dihydrocodeine overdosage. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on dihydrocodeine. In such cases, an abrupt or complete reversal of opioid effects may precipitate pain and an acute withdrawal syndrome.

Consider activated charcoal (50 g for adults, 10-15 g for children), if an adult presents within 1 hour of ingestion of more than 420mg or a child more than 3mg/kg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, ATC code: N02BE71

Paracetamol has analgesic and antipyretic effects. It is only a weak inhibitor of prostaglandin biosynthesis, although there is some evidence to suggest that it may be more effective against enzymes in the CNS than those in the periphery. This fact may partly account for its ability to reduce fever (a central action) and to induce analgesia.

Dihydrocodeine tartrate is an opioid analgesic. Dihydrocodeine is a centrally acting analgesic which produces its effects by its action at opioid binding sites within the CNS.

5.2 Pharmacokinetic properties

Dihydrocodeine is absorbed from the gastrointestinal tract. Dihydrocodeine is metabolised by O- and N-demethylation in the liver to morphine, norcodeine and other metabolites. It is excreted almost entirely by the kidney, mainly as conjugates with glucoric acid.

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 0.5-2 hours after ingestion. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations. Paracetamol is metabolised predominantly in the liver and excreted in the urine mainly as the glucoronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause tissue damage. The elimination half-life varies from about 1-3 hours.

The pharmacokinetics of dihydrocodeine may be similar to those of codeine.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Starch
- Polyvinylpyrrolidone
- Sodium Starch Glycollate
- Stearic Acid
- Colloidal Silicon Dioxide
- Talc
- Potable Water.

6.2 Incompatibilities

None.

6.3 Shelf life

36 months for opaque plastic containers.
24 months for blisters.

6.4 Special precautions for storage

Store below 25°C. Protect from light and moisture. Keep out of the sight and reach of children.

6.5 Nature and contents of container

Co-Dydramol tablets are packed in the following containers and closures and pack sizes.

Opaque plastic containers composed of polypropylene tubes fitted with polyethylene made tamper-evident closures in pack sizes of 10, 12, 20, 24, 25, 30, 50, 100, 250, 500 and 1,000 tablets.

Opaque plastic containers composed of either, high density polypropylene or high density polyethylene with a tamper evident or child resistant tamper evident closure composed of high density polyethylene in pack sizes of 10, 12, 20, 24, 25, 30, 50, 100, 250, 500 and 1,000 tablets.

Blister packs of 20µm hard aluminium foil laminated to 15µm rigid PVC film, and 250µm white opaque PVC film, containing 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0353

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 July 2004

10 DATE OF REVISION OF THE TEXT

06/02/2025