SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Palladone 2 mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Palladone 2 mg/ml*:*

1 ampoule contains 2 mg hydromorphone hydrochloride (corresponding to 1.77 mg hydromorphone) in 1 ml solution.

Excipient(s) with known effect:

1 ml contains 0.153 mmol of sodium (3.52 mg/ml of sodium).

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially ‘sodium-free’

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain in cancer.

Palladone injection is indicated in adults and adolescents aged >12 years.

4.2 Posology and method of administration

Method of administration

Intravenous injection or infusion
Subcutaneous injection or infusion

The medicinal product is to be visually inspected prior to use. Only clear solutions free from particles should be used.

After opening, this medicinal product should be used immediately (please refer to section 6.3).

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

Posology
The dosing of ***Palladone*** injection has to be adjusted to the patients' severity of pain and to their individual response. The dose should be titrated until optimum analgesic effect is achieved.

While the dose to be administered should be sufficient to achieve appropriate analgesia, the aim should also be to keep the dose as small as possible in the individual case.

Duration of treatment:
Palladone injection should not be administered longer than absolutely necessary.

Treatment goals and discontinuation:
Before initiating treatment with ***Palladone*** injection, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, 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 in order to minimise the risk of addiction and drug withdrawal syndrome. When a patient no longer requires therapy with hydromorphone, it may be advisable to taper the daily dose gradually to prevent withdrawal symptoms. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Palladone 10 mg/ml injection is not suitable for initial opioid therapy. This higher strength may only be used as individual doses in patients who have no longer sufficiently responded to lower doses of hydromorphone preparations (***Palladone*** 2 mg) or comparably strong analgesics within the scope of chronic pain therapy. The reservoir of a pain pump can also be filled with individual doses of 10 mg/ml as the dose control is secured by the pump calibration.

Age	**Bolus**	**Infusion**
Adults and adolescents (> 12 years)		
subcutaneous (s.c.) use	1-2 mg s.c. every 3-4 hours	0.15-0.45 mg/h 0.004 mg/kg

		bodyweight/h
intravenous (i.v.) use	1-1.5 mg i.v. every 3-4 hours to be injected slowly over at least 2-3 minutes	0.15-0.45 mg/h 0.004 mg/kg bodyweight/h
PCA (s.c. and i.v.)	0.2 mg bolus, stop interval 5-10 min.	
Paediatric population (< 12 years)	Not recommended	

Transferring patients between oral and parenteral hydromorphone:
Switching patients from parenteral hydromorphone to oral hydromorphone should be guided by the sensitivity of the individual patient. The oral starting dose should not be overestimated (for oral bioavailability see section 5.2).

Paediatric population:
Palladone injection is not recommended for use in children under 12 years of age as the safety and efficacy has not yet been established. No data are available.

Elderly patients
Elderly patients (as a rule over 75 years) may require a lower dosage than other adults to achieve adequate analgesia.

Patients with hepatic and/or renal impairment
These patients may require lower doses than other patient groups to achieve adequate analgesia. They should be carefully titrated to clinical effect (see Section 5.2).

4.3 Contraindications

Hydromorphone is contra-indicated in patients with:

- Known hypersensitivity to hydromorphone or to any of the excipients listed in section 6.1.
- Severe respiratory depression with hypoxia and/or hypercapnia
- Severe chronic obstructive pulmonary disease
- Severe bronchial asthma
- Cor pulmonale,
- Coma
- Acute abdomen
- Paralytic ileus
- Concurrent administration of mono-amine oxidase inhibitors or within two weeks of discontinuation of their use.

4.4 Special warnings and precautions for use

Hydromorphone should be used with caution in the debilitated elderly and in patients with:

- Severely impaired respiratory function
- Sleep apnoea
- CNS depressants co-administration (see below and section 4.5)
- Head injury, intracranial lesions or increased intracranial pressure, reduced level of consciousness of uncertain origin
- Hypotension with hypovolaemia
- Pancreatitis
- Hypothyroidism
- Toxic psychosis
- Prostatic hypertrophy
- Adrenocortical insufficiency (e.g., Addison's disease)
- Severely impaired renal function
- Severely impaired hepatic function
- Convulsive disorders
- Alcoholism
- Delirium tremens
- Biliary tract diseases, biliary or ureteric colic
- Obstructive or inflammatory bowel disorders
- Reduced respiratory reserve
- Constipation

In all these patients, reduced dosage may be advisable.

<u>Sleep-related breathing disorders</u>
The major risk of opioid excess is respiratory depression.

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent manner (see section 4.8). Opioids may also cause worsening of pre-existing sleep apnoea (see section 4.8). In patients who present with CSA, consider decreasing the total opioid dosage.

<u>Risk from concomitant use of sedative medicines such as benzodiazepines (and other CNS depressants)</u>
Concomitant use of ***Palladone*** injection 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 ***Palladone*** injection 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).

Tolerance and Opioid Use Disorder (abuse and dependence)
Tolerance, physical and/or psychological dependence may develop upon repeated administration of opioids such as hydromorphone.

Repeated use of ***Palladone*** injection can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of ***Palladone*** injection may result in overdose and/or death. The risk of developing OUD 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).

Before initiating treatment with ***Palladone*** injection and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

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 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 hydromorphone.

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.

Palladone injection should not be used where the occurrence of paralytic ileus is possible. Should paralytic ileus be suspected or occur during use, hydromorphone treatment must be discontinued immediately.

Palladone injection should be used with caution pre- or intraoperatively and within the first 24 hours postoperatively.

Patients about to undergo additional pain-relieving procedures (e.g. surgery, plexus blockade) should not receive hydromorphone for 4 hours prior to the intervention. If further treatment with ***Palladone*** injection is indicated, the dosage should be adjusted to the post-operative requirement.

Opioids, such as hydromorphone, may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

It should be emphasised that patients, once adjusted (titrated) to an effective dose of a specific opioid, should not be changed to other opioid analgesics without clinical assessment and careful retitration as necessary. Otherwise a continuous analgesic action is not ensured.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system (CNS):
The concomitant use of opioids with sedative medicines such as benzodiazepines or other drugs that depress the CNS 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). Drugs which depress the CNS include, but are not limited to: other opioids, anxiolytics, hypnotics and sedatives (including benzodiazepines), anaesthetics (e.g. barbiturates), antiemetics, antidepressants, antipsychotics (e.g. phenothiazines), antihistamines and alcohol.

Alcohol may also enhance the pharmacodynamic effects of hydromorphone; concomitant use should be avoided.

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

Medicinal products with an anticholinergic effect (e.g. psychotropics, antiemetics, antihistamines or antiparkinsonian medicinal products) may enhance the anticholinergic undesirable effects of opioids (e.g. constipation, dry mouth or urinary retention).

Concurrent administration of hydromorphone and mono-amine oxidase inhibitors or within two weeks of discontinuation of their use is contraindicated (see section 4.3).

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no well-controlled studies of hydromorphone in pregnant women. Hydromorphone should not be used in pregnancy unless clearly necessary.

Palladone injection is not recommended during pregnancy and labour due to impaired uterine contractility. Regular use in 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 pregnant women, 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.

Breast-feeding
Administration to nursing women is not recommended as hydromorphone is excreted into breast milk in low amounts and may cause respiratory depression in the infant.

Fertility
Non clinical toxicology studies in rats have not shown any effects on male or female fertility or sperm parameters.

4.7 Effects on ability to drive and use machines

Hydromorphone may impair the ability to drive and use machines. This is particularly likely at the initiation of treatment with hydromorphone, after dose increase or product rotation and if hydromorphone is combined with alcohol or other CNS depressant substances. Patients stabilised on a specific dosage will not necessarily be restricted. Patients should therefore consult with their physician whether driving or the use of machinery is permitted.

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 you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence'). This defence applies when:
  - 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.
- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected)."

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

4.8 Undesirable effects

The following frequency categories form the basis for classification of the undesirable effects:

Term	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
Not known	Frequency cannot be estimated from the available data

Immune system disorders:
Not known: hypersensitivity (including oropharyngeal swelling), anaphylactic reactions

Metabolism and nutrition disorders
Common: decreased appetite

Psychiatric disorders:
Common: anxiety, confusional state, insomnia
Uncommon: agitation, depression, euphoric mood, hallucinations, nightmares
Not known: drug dependence (see section 4.4), dysphoria

Nervous system disorders:
Very common: dizziness, somnolence
Common: headache
Uncommon: tremor, myoclonus, paraesthesia
Rare: sedation, lethargy
Not known: convulsions, dyskinesia, hyperalgesia (see section 4.4), central sleep apnoea syndrome

Eye disorders:
Uncommon: visual impairment
Not known: miosis

Cardiac disorders:
Rare: bradycardia, palpitations, tachycardia

Vascular disorders:
Uncommon: hypotension
Not known: flushing

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea
Rare: respiratory depression, bronchospasm

Gastrointestinal disorders:

Very common: constipation, nausea
Common: abdominal pain, dry mouth, vomiting
Uncommon: dyspepsia, diarrhoea, dysgeusia
Not known: paralytic ileus

Hepato-biliary disorders:
Uncommon: hepatic enzymes increased
Rare: elevation of pancreatic enzymes

Skin and subcutaneous tissue disorders:
Common: pruritus, hyperhidrosis
Uncommon: rash
Not known: urticaria

Renal and urinary disorders:
Common: urinary urgency
Uncommon: urinary retention

Reproduction system and breast disorders:
Uncommon: decreased libido, erectile dysfunction

General disorders and administration site conditions:
Common: asthenia, injection site reactions
Uncommon: drug withdrawal syndrome, fatigue, malaise, peripheral oedema
Very rare: injection site induration (particularly after repeated s.c. administration)
Not known: drug tolerance, drug withdrawal syndrome neonatal

Paediatric population:
For infants born to mothers receiving hydromorphone see section 4.6.

Description of selected adverse reactions

Drug dependence
Repeated use of *Palladone* injection can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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

4.9 Overdose

Signs of hydromorphone intoxication and overdose include miosis, bradycardia, respiratory depression, hypotension, somnolence progressing to stupor and coma, and pneumonia aspiration. Circulatory failure and deepening coma may occur in more severe cases and may lead to a fatal outcome. 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.

Toxic leukoencephalopathy has been observed with hydromorphone overdose.

In unconscious patients with respiratory arrest intubation and assisted respiration may be required. An opioid antagonist (e.g. naloxone 0.4 mg) should be administered intravenously. Individual administration of the antagonist should be repeated at 2 to 3-minute intervals as necessary.

Close monitoring (at least for 24 hours) is required, since the effect of the opioid antagonist is shorter than that of hydromorphone, so that repeated occurrence of the signs of overdose like respiratory insufficiency are to be expected.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics; opioids; natural opium alkaloid

ATC code: N02A A03.

Hydromorphone is a μ-selective, full opioid agonist. Hydromorphone and related opioids produce their major effects on the central nervous system and the intestine.

The effects are primarily analgesic, anxiolytic, antitussive and sedative. Moreover, mood swings, respiratory depression, reduced gastrointestinal motility, nausea, vomiting and alteration of the endocrine and vegetative nervous system may occur.

Endocrine System
See section 4.4.

Other Pharmacological Effects
Preclinical studies indicate various effects of opioids on components of the immune system. The clinical significance of these findings is unknown.

5.2 Pharmacokinetic properties

The onset of action after intravenous and subcutaneous injection is usually within 5 minutes and 5-10 minutes, respectively. The duration of action is 3-4 hours after intravenous or subcutaneous injection. After epidural administration of 1 mg hydromorphone hydrochloride, a latency of 22.5 ± 6 minutes was observed until full analgesia was achieved. The effect was maintained for 9.8 ± 5.5 hours (n=84 patients aged 22-84).

Hydromorphone hydrochloride crosses the placenta barrier. According to published data, hydromorphone is excreted into breast milk at low amounts.

Plasma protein binding of hydromorphone is low (< 10 %). This percentage of 2.46 ng/ml remains constant up to very high plasma levels of 81.99 ng/ml, which are only very rarely achieved with very high hydromorphone doses.

Hydromorphone hydrochloride has a relatively high distribution volume of 1.22 ± 0.23 l/kg (C.I.: 90 %: 0.97 – 1.60 l/kg) (n = 6 male subjects), which suggests a pronounced tissue uptake.

The course of the plasma concentration time curves after single administration of hydromorphone hydrochloride 2 mg i.v. or 4 mg oral to 6 healthy volunteers in a randomised cross-over study revealed a relatively short elimination half-life of 2.64 ± 0.88 hours (1.68-3.87 hours)

Hydromorphone is metabolised by direct conjugation or reduction of the keto group with subsequent conjugation. After absorption, hydromorphone is primarily metabolised to hydromorphone-3-glucuronide, hydromorphone-3-glucoside and dihydroisomorphine-6-glucuronide. Smaller portions of the metabolites dihydroisomorphine-6-glucoside, dihydromorphine and dihydroisomorphine have also been found. Hydromorphone is metabolised via the liver; a smaller portion is excreted unchanged via the kidneys.

Hydromorphone metabolites were found in plasma, urine and human hepatocyte test systems. There are no indications of hydromorphone being metabolised in vivo via the cytochrome P 450 enzyme system. In vitro, hydromorphone has a minor inhibition effect (IC50 > 50 µM) on recombinant CYP isoforms, including CYP1A2, 2A6, 2C8, 2D6 and 3A4. Hydromorphone is therefore not expected to inhibit the metabolism of other active substances which metabolise via these CYP isoforms.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

No effects on male or female fertility or sperm parameters were observed in rats at oral hydromorphone doses of 5 mg/kg/day (30 mg/m^2/day, which is 1.4 times higher than the expected human dose on a body surface area basis).

Hydromorphone was not teratogenic in rats and rabbits at doses that caused maternal toxicity. Reduced foetal development was found in rabbits at doses of 50 mg/kg (developmental no-effect level was established at a dose of 25 mg/kg or 380 mg/m^2 at an active substance exposure (AUC) almost four times above the one expected in humans). No evidence of foetal toxicity was observed in rats treated with oral hydromorphone doses as high as 10 mg/kg (308 mg/m^2 with an AUC about 1.8 times above the one expected in humans).

Perinatum and postpartum rat pup (F1) mortality was increased at doses of 2 and 5 mg/kg/day and bodyweights were reduced during lactation period.

Long-term carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous

Sodium citrate

Sodium chloride

Sodium hydroxide solution (4%) (for pH-adjustment)

Hydrochloric acid 3.6% (for pH-adjustment)

Water for injections

6.2 Incompatibilities

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

Cyclizine lactate was found to precipitate in the presence of Palladone injection unless the solution is sufficiently diluted with water for injection. It is recommended that water for injection be used as a diluent as cyclizine was found to precipitate in the presence of 0.9 % saline.

6.3 Shelf life

3 years unopened.

After opening, use immediately.

Chemical and physical in-use stability has been demonstrated for 7 days at 4°C, 25°C and 37°C except for diluted solutions in polycarbonate syringes which should not be stored beyond 24 hours (see 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, unless opening/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

The ampoules should be stored in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1, clear, neutral glass ampoules in packs of 5 x 1 ml ampoules.

6.6 Special precautions for disposal

No evidence of incompatibility was observed between ***Palladone*** injection and representative brands of injectable forms of the following drugs, when stored in high and low dose combinations in polypropylene syringes over a 24 hour period at ambient temperature (25°C).

Hyoscine butylbromide
Hyoscine hydrobromide
Dexamethasone sodium phosphate
Haloperidol
Midazolam hydrochloride
Metoclopramide hydrochloride
Levomepromazine hydrochloride
Glycopyrronium bromide
Ketamine hydrochloride

No evidence of incompatibility was observed between ***Palladone*** injection, undiluted or diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion, glucose 50 mg/ml (5%) solution for infusion or water for injections and representative brands of polypropylene syringes, polyethylene and PVC tubing and PVC or EVA infusion bags

Incompatibilities were observed with diluted solutions of 50 mg/ml when stored in polycarbonate syringes beyond 24 hours at 25°C. Whereas no evidence of incompatibility was found when the same preparations were stored at 4°C up to 7 days.

Inappropriate handling of the undiluted solution after opening of the original ampoule, or of the diluted solutions may compromise the sterility of the product.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL16950/0163

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

12/11/2025