

## **1. NAME OF THE MEDICINAL PRODUCT**

SINEMET CR 50mg/200mg Prolonged-release Tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet of Sinemet CR contains carbidopa (equivalent to 50 mg of anhydrous carbidopa) and 200 mg levodopa.

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Prolonged-release tablets.

Peach-coloured, oval-shaped tablet, deep score on one side, 521 on the other.

The scoreline is not intended to facilitate breaking of the tablet.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Antiparkinson agent.

Idiopathic Parkinson's disease, in particular to reduce off-period in patients who previously have been treated with levodopa/decarboxylase inhibitors, or with levodopa alone and who have experienced motor fluctuations. The experience is limited with Sinemet CR and Half Sinemet CR in patients who have not been treated with levodopa before.

### **4.2 Posology and method of administration**

To be taken orally.

Sinemet CR and Half Sinemet CR tablets contain a 1:4 ratio of carbidopa to levodopa (Sinemet CR: carbidopa 50 mg/levodopa 200 mg, Half Sinemet CR 25 mg/100 mg per tablet). The daily dosage of Sinemet CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment

period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

Sinemet CR and Half Sinemet CR may only be administered as whole tablets. So that the controlled release properties of the product can be maintained, tablets should not be chewed, crushed, or halved.

Standard antiparkinson drugs, other than levodopa alone, may be continued while Sinemet CR or Half Sinemet CR are being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, Sinemet CR or Half Sinemet CR can be given to patients receiving supplemental pyridoxine (vitamin B<sub>6</sub>).

### **Initial Dose**

#### **Patients currently treated with conventional levodopa/decarboxylase inhibitor combinations**

Dosage with Sinemet CR should be substituted initially at an amount that provides no more than approximately 10% more levodopa per day when higher dosages are given (more than 900 mg per day). The dosing interval between doses should be prolonged by 30 to 50% at intervals ranging from 4 to 12 hours. It is recommended to give the smaller dose, if divided doses are not equal, at the end of the day. The dose needs to be titrated further depending on clinical response, as indicated below under 'Titration'. Dosages that provide up to 30% more levodopa per day may be necessary.

A guide for substitution of Sinemet CR treatment for conventional levodopa/decarboxylase inhibitor combinations is shown in the table below:

#### **Guideline for Conversion from Sinemet to Sinemet CR**

| <b>Sinemet</b>                | <b>Sinemet CR</b>             |                                      |
|-------------------------------|-------------------------------|--------------------------------------|
| Daily Dosage<br>Levodopa (mg) | Daily Dosage<br>Levodopa (mg) | Dosage Regimen                       |
| 300 - 400                     | 400                           | 1 Tablet x 2 daily                   |
| 500 - 600                     | 600                           | 1 Tablet x 3 daily                   |
| 700 - 800                     | 800                           | 4 Tablets in 3 or more divided doses |
| 900 - 1000                    | 1000                          | 5 Tablets in 3 or more divided doses |
| 1100 - 1200                   | 1200                          | 6 Tablets in 3 or more divided doses |
| 1300 - 1400                   | 1400                          | 7 Tablets in 3 or more divided doses |
| 1500 - 1600                   | 1600                          | 8 Tablets in 3 or more divided doses |

Half Sinemet CR is available to facilitate titration when 100 mg steps are required.

#### **Patients currently treated with levodopa alone**

Levodopa must be discontinued at least eight hours before therapy with Sinemet CR is started. In patients with mild to moderate disease, the initial recommended dose is one tablet of Sinemet CR twice daily.

### **Patients not receiving levodopa**

In patients with mild to moderate disease, the initial recommended dose is one tablet of Sinemet CR twice daily. Initial dosages should not exceed 600 mg per day of levodopa, nor be given at intervals of less than six hours.

### **Titration**

Following initiation of therapy, doses and dosing intervals may be increased or decreased, depending upon therapeutic response. Most patients have been adequately treated with two to eight tablets per day of Sinemet CR administered as divided doses at intervals ranging from four to twelve hours during the waking day. Higher doses (up to 12 tablets) and shorter intervals (less than four hours) have been used, but are not usually recommended.

When doses of Sinemet CR are given at intervals of less than 4 hours, or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day. In some patients the onset of effect of the first morning dose may be delayed for up to one hour compared with the response usually obtained from the first morning dose of Sinemet.

An interval of at least three days between dosage adjustments is recommended.

### **Maintenance**

Because Parkinson's disease is progressive, periodic clinical evaluations are recommended and adjustment of the dosage regimen of Sinemet CR or Half Sinemet CR may be required.

### **Addition of other antiparkinson medication**

Anticholinergic agents, dopamine agonists and amantadine can be given with Sinemet CR or Half Sinemet CR. Dosage adjustment of Sinemet CR or Half Sinemet CR may be necessary when these agents are added to an existing treatment regimen for Sinemet CR or Half Sinemet CR.

### **Interruption of therapy**

Patients should be observed carefully if abrupt reduction or discontinuation of Sinemet CR or Half Sinemet CR is required, especially if the patient is receiving antipsychotics (see 4.4 'Special warnings and precautions for use').

## **Use in Children**

Safety and effectiveness of Sinemet CR or Half Sinemet CR in infants and children have not been established, and its use in patients below the age of 18 is not recommended.

### **4.3 Contraindications**

Sinemet CR or Half Sinemet CR should not be given when administration of a sympathomimetic amine is contraindicated.

Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with Sinemet CR or Half Sinemet CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with Sinemet CR or Half Sinemet CR. Sinemet CR or Half Sinemet CR may be administered concomitantly with the manufacturer's lowest recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g. selegiline hydrochloride). (See 4.5 'Interactions with other medicinal products and other forms of interaction').

Sinemet CR or Half Sinemet CR is contraindicated in patients with known hypersensitivity to any component of this medication, and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, Sinemet CR or Half Sinemet CR should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

Use in patients with severe psychoses.

### **4.4 Special warnings and precautions for use**

When patients are receiving levodopa monotherapy, levodopa must be discontinued at least eight hours before therapy with Sinemet CR or Half Sinemet CR is started (at least 12 hours if slow-release levodopa has been administered).

Dyskinesias may occur in patients previously treated with levodopa alone because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed. The occurrence of dyskinesias may require dosage reduction.

Sinemet CR and Half Sinemet CR are not recommended for the treatment of drug-induced extrapyramidal reactions or for the treatment of Huntington's chorea.

Based on the pharmacokinetic profile of Sinemet CR the onset of effect in patients with early morning dyskinesias may be slower than with conventional Sinemet. The incidence of dyskinesias is slightly higher during treatment with Sinemet CR than with conventional Sinemet (16.5% vs 12.2%) in advanced patients with motor fluctuations.

Sinemet CR or Half Sinemet CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or with a history of peptic ulcer disease or of convulsions.

Care should be exercised in administering Sinemet CR or Half Sinemet CR to patients with a history of recent myocardial infarction who have residual atrial, nodal, or ventricular arrhythmia. In such patients, cardiac function should be monitored with particular care during the period of initial dosage administration and titration.

As with levodopa, Sinemet CR or Half Sinemet CR may cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone or levodopa/decarboxylase inhibitor combination should be observed carefully when Sinemet CR or Half Sinemet CR is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa and use of Sinemet CR or Half Sinemet CR may cause recurrence. Dosage reduction may be required. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of carbidopa-levodopa combinations is reduced abruptly or discontinued, especially if the patient is receiving antipsychotics.

Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

Patients with chronic wide-angle glaucoma may be treated cautiously with Sinemet CR or Half Sinemet CR, provided the intraocular pressure is well controlled and the patient monitored carefully for changes in intraocular pressure during therapy.

Periodic evaluations of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

*Melanoma:* Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using SINEMET for any indication.

Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

If general anaesthesia is required, Sinemet CR or Half Sinemet CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medicine.

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/ levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Sinemet CR or Half Sinemet CR. Review of treatment is recommended if such symptoms develop.

**Laboratory Tests:** Abnormalities in various laboratory tests have occurred with carbidopa-levodopa preparations and may occur with Sinemet CR or Half Sinemet CR. These include elevations of liver function tests such as alkaline phosphatase SGOT (AST), SGPT (ALT), LDH, bilirubin, blood urea nitrogen and positive Coombs test.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glycosuria.

Decreased haemoglobin and haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported with standard Sinemet.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Caution should be exercised when the following drugs are administered concomitantly with Sinemet CR or Half Sinemet CR:

##### **Antihypertensive agents**

Symptomatic postural hypotension has occurred when levodopa/decarboxylase inhibitor combinations were added to the treatment of patients receiving some antihypertensive drugs. Therefore when therapy with Sinemet CR or Half Sinemet CR is started, dosage adjustment of the antihypertensive drug may be required.

##### **Antidepressants**

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations. (For patients receiving monamine oxidase inhibitors, see 4.3 'Contraindications').

**Anticholinergics**

Anticholinergics may affect the absorption and thus the patient's response.

**Iron**

Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulphate or ferrous gluconate.

**Other drugs**

Dopamine D2 receptor antagonists (e.g. phenothiazines, butyrophenones and risperidone) and isoniazid may reduce the therapeutic effects of levodopa. The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with Sinemet CR or Half Sinemet CR should be observed carefully for loss of therapeutic response.

Use of Sinemet CR with dopamine-depleting agents (e.g., reserpine and tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (see 4.3 'Contraindications').

Since levodopa competes with certain amino acids, the absorption of levodopa may be impaired in some patients on a high protein diet.

The effect of simultaneous administration of antacids with Sinemet CR or Half Sinemet CR on the bioavailability of levodopa has not been studied.

**4.6 Fertility, pregnancy and lactation**

There are insufficient data to evaluate the possible harmfulness of this substance when used in human pregnancy. (See 5.3 'Preclinical Safety Data'). It is not known whether carbidopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in breast milk was reported. Sinemet CR or Half Sinemet CR should not be given during pregnancy and to nursing mothers.

**4.7 Effects on ability to drive and use machines**

No data are known about the effect of this product on the ability to drive. Side effects such as dizziness or somnolence may effect the ability to drive or operate machinery.

Patients being treated with levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 4.4 'Special warnings and precautions for use')

## 4.8 Undesirable effects

In controlled clinical trials in patients with moderate to severe motor fluctuations Sinemet CR or Half Sinemet CR did not produce side-effects which were unique to the controlled-release formulation.

The side-effect reported most frequently was dyskinesia (a form of abnormal involuntary movements). A greater incidence of dyskinesias was seen with Sinemet CR than with Sinemet.

Other side-effects that also were reported frequently (above 2%) were: nausea, hallucinations, confusion, dizziness, chorea and dry mouth.

Side effects occurring less frequently (1-2%) were: dream abnormalities, dystonia, insomnia, depression, asthenia, vomiting and anorexia.

Other side effects reported in clinical trials or in post-marketing experience include:

**Body as a whole:** chest pain, muscle cramps, syncope.

**Cardiovascular:** palpitation, orthostatic effects including hypotensive episodes.

**Gastrointestinal:** constipation, diarrhoea, dyspepsia, gastrointestinal pain, dark saliva.

**Hypersensitivity:** angioedema, urticaria, pruritus.

**Metabolic:** weight loss.

**Nervous System/Psychiatric:** Neuroleptic malignant syndrome, (See section 4.4 'Special warnings and precautions for use'), agitation, anxiety, decreased mental acuity, paraesthesia, disorientation, fatigue, headache, extrapyramidal and movement disorders, falling, gait abnormalities, on-off phenomenon, increased libido, psychotic episodes including delusions, hallucinations and paranoid ideation. Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

**Respiratory:** dyspnoea

**Skin:** flushing, alopecia, skin rash, dark sweat.

**Special senses:** blurred vision.

**Urogenital:** dark urine.

Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side-effects with Sinemet CR are listed below.

**Infections and infestations:** Urinary tract infections (very common)

**Cardiovascular:** Cardiac irregularities, hypertension, phlebitis.

**Gastrointestinal:** Bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, gastrointestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.

**Haematologic:** Leukopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis.

**Nervous system/psychiatric:** Ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm, trismus, activation of latent Horner's syndrome. Euphoria, dementia, and depression with or without suicidal tendencies, Dopamine Dysregulation Syndrome.

**Dopamine Dysregulation Syndrome (DDS)** is an addictive disorder seen in some patients treated with carbidopa/ levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

**Impulse control disorders:** Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Sinemet CR or Half Sinemet CR (see section 4.4 'Special warnings and precautions for use').

**Skin:** Increased sweating.

**Special senses:** Diplopia, dilated pupils, oculogyric crises.

**Urogenital:** Urinary retention, urinary incontinence, priapism.

**Miscellaneous:** Weight gain, oedema, weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see 4.3 'Contraindications'). Henoch-Schönlein purpura. Convulsions have occurred; however, a causal relationship with levodopa or levodopa/carbidopa combinations has not been established.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: [www.hpra.ie](http://www.hpra.ie)

## **4.9 Overdose**

Management of acute overdosage with Sinemet CR or Half Sinemet CR is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of Sinemet CR.

Electrocardiographic monitoring should be instituted and the patient observed carefully for the development of arrhythmias; if required, appropriate antiarrhythmic therapy

should be given. The possibility that the patient may have taken other drugs as well as Sinemet CR or Half Sinemet CR should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Dopa and dopa derivatives, ATC code: N04BA02.

Sinemet CR and Half Sinemet CR are a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor, and levodopa, the metabolic precursor of dopamine, in a polymer-based controlled-release tablet formulation, for use in the treatment of Parkinson's disease. Sinemet CR and Half Sinemet CR are particularly useful to reduce 'off' time in patients treated previously with a conventional levodopa/decarboxylase inhibitor combination who have had dyskinesias and motor fluctuations.

Patients with Parkinson's disease treated with preparations containing levodopa may develop motor fluctuations characterised by end-of-dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations ('on-off' phenomenon) is characterised by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely understood, it has been demonstrated that they can be attenuated by treatment regimens that produce steady plasma levels of levodopa.

Levodopa relieves the symptoms of Parkinson's disease by being decarboxylated to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits only the extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and subsequent conversion to dopamine. This normally obviates the necessity for large doses of levodopa at frequent intervals. The lower dosage reduces or may help eliminate gastrointestinal and cardiovascular side-effects, especially those which are attributed to dopamine being formed in extracerebral tissues.

Sinemet CR and Half Sinemet CR are designed to release their active ingredients over a four-six hour period. With this formulation there is less variation in plasma levodopa levels and the peak plasma level is 60% lower than with conventional Sinemet, as established in healthy volunteers.

In clinical trials, patients with motor fluctuations experienced reduced 'off'-time with Sinemet CR when compared with Sinemet. The reduction of the 'off'-time is rather small (about 10%) and the incidence of dyskinesias increases slightly after administration of Sinemet CR compared to standard Sinemet. Global ratings of improvement and activities of daily living in the 'on' and 'off' state, as assessed by both patient and physician, were better during therapy with Sinemet CR than with Sinemet. Patients considered Sinemet CR to be more helpful for their clinical fluctuations, and preferred it over Sinemet. In patients without motor fluctuations, Sinemet CR under controlled conditions, provided the same therapeutic benefit with less frequent dosing than with Sinemet. Generally, there was no further improvement of other symptoms of Parkinson's disease.

## **5.2 Pharmacokinetic properties**

The pharmacokinetics of levodopa following administration of Sinemet CR were studied in young and elderly healthy volunteers. The mean time to peak plasma levodopa level after Sinemet CR was approximately two hours compared to 0.75 hours with Sinemet. The mean peak plasma levodopa levels were 60 percent lower with Sinemet CR than with Sinemet. The *in vivo* absorption of levodopa following administration of Sinemet CR was continuous for 4 to 6 hours. In these studies, as with patients, plasma levodopa concentrations fluctuated in a narrower range than with Sinemet. Because the bioavailability of levodopa from Sinemet CR relative to Sinemet is approximately 70 percent, the daily dosage of levodopa in the controlled release formulation will usually be higher than with conventional formulations. There was no evidence that Sinemet CR released its ingredients in a rapid or uncontrolled fashion.

The pharmacokinetics of levodopa following administration of Half Sinemet CR were studied in patients with Parkinson's disease. Chronic three month, open-label, twice daily dosing with Half Sinemet CR (range: 50 mg carbidopa, 200 mg levodopa up to 150 mg carbidopa, 600 mg levodopa per day) did not result in accumulation of plasma levodopa. The dose-adjusted bioavailability for one Half Sinemet CR tablet was equivalent to that for one Sinemet CR tablet. The mean peak concentration of levodopa following administration of one Half Sinemet CR tablet was approximately 50% greater than that following one Sinemet CR tablet. Mean time-to-peak plasma levels may be slightly less for Half Sinemet CR than for Sinemet CR.

It is not known whether or not to what extent the absorption is influenced by a protein rich diet. The bioavailability may be influenced by drugs which affect the gastrointestinal propulsion.

## **5.3 Preclinical safety data**

The medicine has appeared harmful in animal trials (visceral and skeletal malformations in rabbits). For reproductive toxicity, see section 4.6.

# **6. PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

Hyprolose  
Magnesium Stearate  
Poly (Vinyl Acetate-Crotonic Acid) Copolymer  
Quinoline Yellow 10 Aluminium Lake E104  
Red Iron Oxide E172

## **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Bottles: Do not store above 30°C. Keep the bottle tightly closed.

Blisters: Do not store above 25°C. Store in the original package in order to protect from light.

### **6.5 Nature and contents of the container**

Amber glass or HDPE bottles of 56 or 84 tablets.

OPA/Alu/PVC//Alu blister packs of 60 tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Organon Pharma (Ireland) Limited  
2 Dublin Landings  
North Wall Quay - North Dock  
Dublin, D01 V4A3  
Ireland.

## **8. MARKETING AUTHORISATION NUMBER(S)**

PA23198/004/005

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first Authorisation: 10 December 1991

Date of last Renewal: 10 December 2006

## **10. DATE OF REVISION OF THE TEXT**

December 2025