

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Esteprin 75 mg gastro-resistant tablets

Esteprin 100 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 75 mg acetylsalicylic acid.

Each gastro-resistant tablet contains 100 mg acetylsalicylic acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

75 mg: White, oval, biconvex gastro-resistant tablets, 9.2 x 5.2 mm.

100 mg: White, round, biconvex gastro-resistant tablets with a diameter of 7.2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Secondary prevention of myocardial infarction.
- Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris.
- History of unstable angina pectoris, except during the acute phase.
- Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG).
- Coronary angioplasty, except during the acute phase.
- Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out.

Esteprin is not recommended in emergency situations. It is restricted to secondary prevention with chronic treatment.

4.2 Posology and method of administration

Posology

Adults

Secondary prevention of myocardial infarction:

The recommended dose is 75-150 mg once daily.

Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris:

The recommended dose is 75-150 mg once daily.

History of unstable angina pectoris, except during the acute phase:

The recommended dose is 75-150 mg once daily.

Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG):

The recommended dose is 75-150 mg once daily.

Coronary angioplasty, except during the acute phase:

The recommended dose is 75-150 mg once daily.

Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out:

The recommended dose is 75-300 mg once daily.

Elderly

In general, acetylsalicylic acids should be used with caution in elderly patients who are more prone to adverse events. The usual adult dose is recommended in the absence of severe renal or hepatic impairment (see sections 4.3 and 4.4). Treatment should be reviewed at regular intervals.

Paediatric population

Acetylsalicylic acid should not be administered to children and adolescents younger than 16 years, except on medical advice where the benefit outweighs the risk (see section 4.4).

Method of administration

For oral use.

The tablets should be swallowed whole with sufficient fluid (1/2 glass of water). Due to the gastro resistant coating the tablets should not be crushed, broken or chewed because coating prevents irritant effects on the gut.

Esteprin can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- History of asthma caused by salicylates or substances with a similar mechanism of action, especially non-steroidal anti-inflammatory drugs (NSAIDs);
- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages;
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia;
- Severe hepatic impairment;
- Severe renal impairment;
- Doses >100 mg/day during the third trimester of pregnancy (see section 4.6);
- Methotrexate used at doses >15mg/week (see section 4.5).

4.4 Special warnings and precautions for use

Esteprin is not suitable for use as an anti-inflammatory/analgesic/antipyretic.

Additional regular, frequent intake of other salicylates or other nonsteroidal antiphlogistics/antirheumatics should be avoided.

Increased risk of haemorrhage and duodenal or gastric ulcer

Caution should be exercised in patients with gastrointestinal disorders (e.g. gastritis).

There is an increased risk of haemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction). Temporary discontinuation of treatment may be necessary. Prolongation of bleeding time may occur.

Esteprin is not recommended during menorrhagia where it may increase menstrual bleeding.

Esteprin should be used with caution in patients with severe not sufficiently controlled heart failure.

Esteprin is to be used with caution in cases of hypertension and when patients have a past history of gastric or duodenal ulcer or haemorrhagic episodes or are undergoing therapy with anticoagulants.

Concomitant treatment with Esteprin and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage (see section 4.5). If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox (see section 4.5).

Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

Renal and hepatic impairment

Acetylsalicylic acid should be used with caution in patients with moderately impaired renal or hepatic function (contraindicated if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Hypersensitivity reactions

Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria). The medicine should be discontinued at the appearance of any sign of hypersensitivity.

Caution should be exercised in patients with hypersensitivity to other non-steroidal anti-inflammatory drugs (NSAIDs).

Skin reactions

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid (see section 4.8). Esteprin should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cases of fixed drug eruption (FDE) and generalized bullous fixed drug eruption (GBFDE) have been reported in association with acetylsalicylic acid (see section 4.8). Acetylsalicylic acid should not be reintroduced in patients with history of FDE or GBFDE related to acetylsalicylic acid.

Paediatric population

This medicinal product is not recommended for use in adolescents/children under 16 years of age unless the benefits outweigh the risks. Acetylsalicylic acid may be a contributory factor in the causation of Reye's Syndrome in some children.

Elderly patients

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Where prolonged therapy is required, patients should be reviewed regularly.

Gout

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks (see section 4.5 and 4.8).

Risk of hypoglycaemia

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Esteprin taken at over dosage (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

Methotrexate (used at doses >15 mg/week):

The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Estepirin is contraindicated (see section 4.3).

Not recommended combinations

Uricosuric agents, e.g. probenecid, sulfinpyrazone

Salicylates reverse the effect of probenecid and sulfinpyrazone. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants e.g. coumarin, heparin, warfarin

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored (see section 4.4).

Anti-platelet agents (e.g. clopidogrel and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine)

Increased risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics, e.g. sulphonylureas

Salicylics may increase the hypoglycaemic effect of sulphonylureas.

Digoxin and lithium

Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Diuretics and antihypertensives

NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.

Diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Carbonic anhydrase inhibitors (acetazolamide)

May result in severe acidosis and increased central nervous system toxicity

Systemic corticosteroids

The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4).

Methotrexate (used at doses <15 mg/week):

The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Other NSAIDs

Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Ibuprofen

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Cyclosporin, tacrolimus

Concomitant use of NSAIDs and cyclosporin or tacrolimus may increase the nephrotoxic effect of cyclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Valproate

Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin

Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Metamizole

Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose acetylsalicylic acid for cardioprotection.

Alcohol

Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy

Low doses (up to and including 100 mg/day):

Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of above 100 mg/day and up to 500 mg/day:

There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, Esteprin use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Esteprin should not be given unless clearly necessary. If Esteprin is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Esteprin for several days from gestational week 20 onward. Esteprin should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, acetylsalicylic acid at doses higher than 100 mg/day is contraindicated during the third trimester of pregnancy (see sections 4.3). Doses up to and including 100 mg/day may only be used under strict obstetric monitoring.

Breastfeeding

Low quantities of salicylates and of their metabolites are excreted into the breast milk. Since adverse effects for the infant have not been reported up to now, short-term use of the recommended dose does not require suspending lactation. In cases of long-term use and/or administration of higher doses, breastfeeding should be discontinued.

Fertility

There are no controlled studies regarding the potential effect of acetylsalicylic acid on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with Esteprin . Based on the pharmacodynamic properties and the side effects of acetylsalicylic acid, no influence on the reactivity and the ability to drive or use machines is expected.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse reactions are listed by system organ class and frequency. The following convention has been used for the classification of frequencies: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

MedDRA SOC	Adverse Reactions	Frequency
Blood and lymphatic system disorders	Increased bleeding tendencies.	<i>Common</i>
	Thrombocytopenia, agranulocytosis, aplastic anaemia.	<i>Rare</i>

	Cases of bleeding with prolonged bleeding time such as epistaxis and gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).	<i>Not known</i>
Immune system disorders	Hypersensitivity reactions (including cutaneous reactions), angio-oedema, allergic oedema, anaphylactic reactions including shock.	<i>Rare</i>
Metabolism and nutrition disorders	Hyperuricemia	<i>Not known</i>
Nervous system disorders	Intracranial haemorrhage	<i>Rare</i>
	Headache, vertigo.	<i>Not known</i>
Ear and labyrinth disorders	Tinnitus.	<i>Not known</i>
Vascular disorders	Haemorrhagic vasculitis.	<i>Rare</i>
Respiratory, thoracic and mediastinal disorders	Rhinitis, dyspnoea.	<i>Uncommon</i>
	Bronchospasm, asthma attacks.	<i>Rare</i>
Gastrointestinal disorders	Dyspepsia.	<i>Common</i>
	Severe gastrointestinal haemorrhage, nausea, vomiting.	<i>Rare</i>
	Gastric or duodenal ulcers and perforation.	<i>Not known</i>
Hepatobiliary disorders	Hepatic insufficiency.	<i>Not known</i>
Skin and subcutaneous tissue disorders	Urticaria	<i>Uncommon</i>
	Stevens-Johnson syndrome, Lyell syndrome, purpura, erythema nodosum, erythema multiforme.	<i>Rare</i>
	Pruritus, rash, fixed drug eruption	<i>Not known</i>
Reproductive system and breast disorders	Menorrhagia	<i>Rare</i>
Investigations	Hepatic enzyme increased	<i>Not known</i>

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 national reporting system listed in [Appendix V](#).

4.9 Overdose

Although considerable inter-individual variations are involved, it can be considered that the toxic dose is about 200 mg/kg in adults and 100 mg/kg in children. The lethal dose of acetylsalicylic acid is 25-30 grams. Plasma salicylate concentrations above 300 mg/l indicate intoxication. Plasma concentrations above 500 mg/l in adults and 300 mg/l in children generally cause severe toxicity. Overdose may be harmful for elderly patients and particularly for small children (therapeutic overdose or frequent accidental intoxications may be fatal).

Symptoms of moderate intoxications

Tinnitus, hearing disorders, headache, vertigo, confusion and gastrointestinal symptoms (nausea, vomiting and abdominal pain).

Symptoms of severe intoxications

Symptoms are related to severe disruption of the acid-base balance. In the first instance hyperventilation occurs, which results in respiratory alkalosis. Respiratory acidosis ensues due to suppression of the respiratory centre. In addition, metabolic acidosis occurs as a result of the presence of salicylate.

Since younger children are often not seen until they have reached a late stage of intoxication, they are usually in the stage of acidosis.

Furthermore, the following symptoms may occur: hyperthermia and perspiration, resulting in dehydration: feelings of restlessness, disturbance of the electrolyte balance (e.g. potassium loss), gastrointestinal bleeding, dizziness, drowsiness, delirium, lethargy, shallow breathing, renal function disorder, cerebral and pulmonary oedema, respiratory and metabolic disorder, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system may lead to coma, cardiovascular collapse or respiratory arrest.

Treatment of overdose

If a toxic dose has been ingested, hospital admission is required. In the event of moderate intoxication, inducing the patient to vomit should be attempted.

If this fails, gastric lavage may be attempted during the first hour after ingestion of a substantial amount of the medicine. Afterwards, administer activated carbon (adsorbent) and sodium sulphate (laxative). Activated charcoal may be given as a single dose (50 g for an adult, 1 g/kg body weight for a child up to 12 years).

Alkalinisation of the urine (250 mmol NaHCO₃, for three hours) whilst checking urine pH levels.

In the event of severe intoxication, haemodialysis is to be preferred.

Other symptoms to be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. heparin, ATC code: B01AC06.

Mechanism of action

Acetylsalicylic acid inhibits the platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A₂ synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatous lesions.

Inhibition of TXA₂-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

Pharmacodynamic effects

The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption.

Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

Because of the inhibition of prostaglandin synthesis, acetylsalicylic acid belongs to the group of acid-forming NSAIDs with analgesic, antipyretic, and antiphlogistic properties.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly.

In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

Absorption

After oral administration, acetylsalicylic acid is rapidly and completely absorbed from the gastrointestinal tract. The principal site of absorption is the proximal small intestine. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process. The degree of hydrolysis is dependent on the rate of absorption.

After intake of Esteprin gastro-resistant tablets the maximum plasma levels of acetylsalicylic acid and salicylic acid are reached after about 5 hours and 6 hours, respectively, following administration in the fasted state. If the tablets are taken with food, maximum plasma levels are reached approximately 3 hours later than in the fasted state.

Distribution

Acetylsalicylic acid as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. The degree of protein binding of salicylic acid is strongly dependant of both the salicylic acid and albumin concentration. The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight. Salicylic acid slowly diffuses into the synovial fluid, crosses the placental barrier and passes into breast milk.

Biotransformation

Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates, and traces of gentisic acid.

Elimination

Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2-3 hours after low doses, 12 hours after usual analgetic doses and 15-30 hours after high therapeutic doses or intoxication.

Excretion

Salicylic acid and its metabolites are predominantly excreted via the kidneys.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented.

In experimental animal studies, salicylates have shown no other organ injury than renal damage.

In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications. Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Maize starch
Silica, colloidal anhydrous
Stearic acid

Film-coating:

Methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister (PVC/Aluminium).

Pack sizes:

10, 20, 28, 30, 50, 56, 60, 90, 100 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2011-05-05/2016-05-05

10. DATE OF REVISION OF THE TEXT

2025-08-29