

SUMMARY OF PRODUCT CHARACTERISTICS GLUCOWELL-MET 50/1000 MG FILM COATED TABLET

1. Name of the Medicinal Product

Glucowell-Met film coated tablets 50: 1000 mg

2. Qualitative and Quantitative Composition

Each film coated tablet contains 50 mg Vildagliptin and 1000 mg Metformin Hydrochloride.

3 Pharmaceutical Form

Film coated Tablets

4 Clinical Particulars

4.1 Therapeutic Indications

It is indicated in the treatment of type 2 diabetes mellitus:

- i.It is indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral antidiabetic drugs or who are already treated with the combination of vildagliptin and metformin as separate tablets.
- ii.It is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients in whom metformin and a sulphonylurea.
- iii.It is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients where insulin and metformin alone do not provide adequate glycaemic control.

4.2 Posology and Method of administration

Posology

Adults

The dose of antihyperglycaemic therapy with Glucowell-Met should be individualised on the basis of the patient's current regimen, effectiveness and tolerability, not exceeding the maximum recommended daily dose of 100 mg vildagliptin. Glucowell-Met may be initiated at either the 50 mg/850 mg or

50 mg/1000 mg tablet strength twice daily, one tablet in the morning and the other in the evening.

- For patients inadequately controlled at their maximal tolerated dose of metformin monotherapy:

The starting dose of Glucowell-Met should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

- For patients switching from co-administration of vildagliptin and metformin as separate tablets:

Glucowell-Met should be initiated at the dose of vildagliptin and metformin already being taken.

- For patients inadequately controlled on dual combination with metformin and a sulphonylurea:

The doses of Glucowell-Met should provide vildagliptin as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. If Glucowell-Met is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

- For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin:

The dose of Glucowell-Met should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

The safety and efficacy of vildagliptin and metformin as triple oral therapy in combination with a thiazolidinedione have not been established.

Special populations

Elderly (≥ 65 years)

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Glucowell-Met should have their renal function monitored regularly.

Renal impairment

Glucowell-Met should not be used in patients with creatinine clearance < 60 ml/min.

Hepatic impairment

Glucowell-Met should not be used in patients with hepatic impairment, including those with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal. (ULN)

4.3 Contraindication

- Hypersensitivity to the active substances or to any of the excipients.
- Diabetic ketoacidosis or diabetic pre-coma
- Renal failure or renal dysfunction defined as creatinine clearance < 60 ml/min
- Acute conditions with the potential to alter renal function, such as:
 - dehydration,

- severe infection,
- shock,
- intravascular administration of iodinated contrast agents.
- Acute or chronic disease which may cause tissue hypoxia, such as:
 - cardiac or respiratory failure,
 - recent myocardial infarction,
 - shock.
- Hepatic impairment
- Acute alcohol intoxication, alcoholism

4.4 Special warnings and precautions for use

General

Glucoowell-Met is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes.

Lactic acidosis

Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients have occurred primarily in diabetic patients with significant renal failure. In patients with impaired liver function, lactate clearance may be restricted. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

Diagnosis of lactic acidosis

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased pH, lactate levels above 5 mmol/l and increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medication should be discontinued and the patient hospitalised immediately.

Renal impairment

As metformin is excreted by the kidney, serum creatinine concentrations should be monitored regularly:

- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Renal impairment in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become further impaired when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID.

Hepatic impairment

Patients with hepatic impairment, including those with pre-treatment ALT or AST > 3x ULN, should not be treated with Glucoowell-Met.

Liver enzyme monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with Glucoowell-Met to know the patient's baseline value. Liver function should be monitored during treatment with Glucoowell-Met at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with LFTs at regular intervals and evaluation to confirm the finding and be followed thereafter with frequent LFTs until the abnormality(ies) return(s) to normal. Should an increase in ALT or AST greater persist, withdrawal of Glucoowell-Met therapy is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Glucoowell-Met.

Following withdrawal of treatment with Glucoowell-Met and LFT normalisation, treatment with Glucoowell-Met should not be re-initiated.

Skin disorders

Skin lesions, including blistering and ulceration have been reported with vildagliptin in extremities of monkeys in non-clinical toxicology studies. As no skin lesions were not observed at an increased incidence in clinical trials, there was limited experience in patients with diabetic skin complications. Further, no post-marketing reports of bullous and exfoliative skin lesions. Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders or ulceration, is recommended. Acute pancreatitis

Use of vildagliptin has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

Hypoglycaemia

Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. A lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Surgery

As Glucowell-Met contains metformin, the treatment should be discontinued 48 hours before elective surgery with general anaesthesia and should not be restarted earlier than 48 hours afterwards.

Administration of iodinated contrast agent

The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure. Therefore, due to the metformin active substance, the treatment should be discontinued prior to, or at the time of, the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for Glucowell-Met. The following statements reflect the information available on the individual active substances. Vildagliptin has a low potential for interactions with co-administered medicinal products. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme, it does not inhibit or induce CYP 450 enzymes, it is not likely to interact with active substances that are substrates, inhibitors or inducers of these enzymes. Results from clinical trials conducted with the oral antidiabetics pioglitazone, metformin and glyburide in combination with vildagliptin have shown no clinically relevant pharmacokinetic interactions in the target population.

Drug-drug interaction studies with digoxin (P-glycoprotein substrate) and warfarin (CYP2C9 substrate) in healthy subjects have shown no clinically relevant pharmacokinetic interactions after co-administration with vildagliptin. Drug-drug interaction studies in healthy subjects were conducted with valsartan and simvastatin. In these studies, no clinically relevant pharmacokinetic interactions were observed after co-administration with vildagliptin. No interactions have not been established in the target population.

Combination with ACE-inhibitors

There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors.

As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thyroid products and sympathomimetics.

Metformin

Combinations not recommended

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the active substance of Glucowell-Met. Consumption of alcohol and medicinal products containing alcohol should be avoided.

Cationic active substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common transport systems and hence delay the elimination of metformin, which may increase the risk of lactic acidosis. A study in healthy volunteers showed that cimetidine 400 mg twice daily, increased metformin systemic exposure (AUC) by 50%. Therefore, close monitoring of glycaemic control, dose adjustment within the limits of the approved dosage and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered with metformin. Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation with the risk of lactic acidosis. The treatment should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Combinations requiring precautions for use

Glucocorticoids, beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring is recommended, especially at the beginning of treatment. If necessary, the dosage of Glucowell-Met may need to be adjusted during concomitant therapy and on its discontinuation.

Angiotensin converting enzyme (ACE) inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antihyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of Glucowell-Met in pregnant women. For vildagliptin studies in animals have shown reproductive toxicity. For metformin, studies in animals have not shown reproductive toxicity. Studies in animals performed with vildagliptin and metformin have shown no teratogenicity, but foetotoxic effects at maternotoxic doses. The potential risk for humans is unknown. Glucowell-Met should not be used during pregnancy.

Breast-feeding

Studies in animals have shown excretion of both metformin and vildagliptin in milk. It is unknown whether vildagliptin is excreted in human milk, but it is known to be excreted in human milk in low amounts. Due to both the potential risk of neonate hypoglycaemia related to metformin and the lack of human data with vildagliptin, Glucowell-Met should not be used during breast-feeding.

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. Patients who may experience dizziness as an adverse reaction should not drive vehicles or use machines.

4.8 Undesirable effects

- Angioedema (rare: may affect up to 1 in 1,000 people): Symptoms include swollen face, tongue or throat, difficulty swallowing, difficulty breathing, sudden onset of rash or hives, which may indicate “angioedema”.
- Liver disease (hepatitis) (rare): Symptoms include yellow skin and eyes, nausea, loss of appetite or dark-coloured urine, which may indicate liver disease.
- Inflammation of the pancreas (pancreatitis) (frequency not known): Symptoms include severe and persistent pain in the abdomen (stomach) that may radiate through to your back, as well as nausea and vomiting.

Other side effects

Some patients have experienced the following side effects while taking Glucowell-Met:

- Very common (may affect more than 1 in 10 people): nausea, vomiting, diarrhoea, pain in and around the stomach (abdominal pain), loss of appetite, dizziness, affect up to 1 in 10 people): dizziness, headache, trembling that cannot be controlled, metallic taste, low blood glucose.
- Uncommon (may affect up to 1 in 100 people): joint pain, tiredness, constipation, swollen hands, ankle or feet (oedema).
- Very rare (may affect up to 1 in 10,000 people): sore throat, runny nose, fever; signs of a high level of lactic acid in the blood (known as lactic acidosis), drowsiness or dizziness, severe nausea or vomiting, abdominal pain, irregular heart beat or deep, rapid breathing; redness of the skin, itching, changes in skin levels (paleness, tiredness, mental symptoms such as confusion or memory disturbances). Some patients have experienced the following side effects while taking Glucowell-Met and a sulphonylurea: □ Common: dizziness, tremor, weakness, low blood glucose, excessive sweating. Some patients have had hypoglycaemia while taking Glucowell-Met and insulin:
 - Common: headache, chills, nausea (feeling sick), low blood glucose, heartburn. □ Uncommon: diarrhoea, flatulence.

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacy Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

4.9 Overdose

No data are available with regard to overdose of Glucowell-Met.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties

Glucowell-Met combines two antihyperglycaemic agents with complimentary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the islet enhancer class, and metformin hydrochloride, a member of the biguanide class.

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor. Metformin acts primarily by decreasing hepatic glucose production.

Pharmacodynamic effects

Vildagliptin

Vildagliptin acts primarily by inhibiting DPP-4, the enzyme responsible for the degradation of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which are dependent insulinotropic polypeptide).

The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity resulting in increased fasting and postprandial endogenous incretin hormones GLP-1 and GIP.

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose secretion. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including Model Assessment-β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting glucose production, leading to reduced glycaemia.

The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptin treatment.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion.

produce hypoglycaemia or increased weight gain.

Metformin may exert its glucose-lowering effect via three mechanisms:

- by reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis;
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of specific types of membrane transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in short-term or long-term clinical studies: metformin reduces serum levels of total cholesterol, LDL cholesterol and triglycerides.

5.2 Pharmacokinetic Properties

Vildagliptin

Absorption

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} compared to dosing in the fasting state. However, the

magnitude of change is not clinically significant, so that vildagliptin can be given with or without food. The absolute bioavailability is 85%.

Distribution

The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution at steady-state after intravenous administration (V_{ss}) is 71 litres, suggesting extravascular distribution.

Biotransformation

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmaceutical grade vildagliptin, the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of dose). DPP-4 contributes to the elimination of vildagliptin based on an *in vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolised by CYP 450 enzymes to any quantifiable extent. The metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. *In vitro* studies show that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolised by CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination

Following oral administration of [¹⁴C] vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose was recovered in the faeces. Of the unchanged vildagliptin accounted for 23% of the dose after oral administration. After intravenous administration to healthy subjects, the renal clearances of vildagliptin are 41 and 13 l/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours and after oral administration is approximately 3 hours.

Linearity / non-linearity

The C_{max} for vildagliptin and the area under the plasma concentrations versus time curves (AUC) increased in an approximately dose proportional manner over the therapeutic dose range.

Characteristics in patients

Gender: No clinically relevant differences in the pharmacokinetics of vildagliptin were observed between male and female healthy subjects within a wide range of body mass index (BMI). DPP-4 inhibition by vildagliptin is not affected by gender.

Age: In healthy elderly subjects (≥ 70 years), the overall exposure of vildagliptin (100 mg once daily) was increased by 32%, with an 18% increase in peak plasma concentration as compared to young healthy subjects (18-40 years). These changes are not considered to be clinically relevant, however. DPP-4 inhibition by vildagliptin is not affected by age.

Hepatic impairment: In subjects with mild, moderate or severe hepatic impairment (Child-Pugh A-C) there were no clinically significant changes (maximal increase of 15%) in the exposure to vildagliptin.

Renal impairment: In subjects with mild, moderate, or severe renal impairment, systemic exposure to vildagliptin was increased (C_{max} 8-66%; AUC 15-100%) and renal clearance was reduced compared to subjects with normal renal function.

Ethnic group: Limited data suggest that race does not have any major influence on vildagliptin pharmacokinetics.

Metformin

Absorption

After an oral dose of metformin, the maximum plasma concentration (C_{max}) is achieved after about 2.5 h.. Absolute bioavailability of a 500 mg oral dose is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are independent of metformin doses and dosing schedules, steady state plasma

concentrations are reached within 24-48 h and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) were reached even at maximum doses.

Food slightly delays and decreases the extent of the absorption of metformin. Following administration of a dose of 850 mg, the plasma peak concentration was decreased by 25% and time to peak plasma concentration was prolonged by 35 minutes. The clinical relevance of this decrease is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The mean volume of distribution (V_d) ranged between 63-276 litres.

Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Metformin is eliminated by renal excretion. Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is proportional to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

5.3 Preclinical safety data

Animal studies of up to 13-week duration have been conducted with the combined substances in Glucowell-Met. No new toxicities associated with the combination were identified. The following data are findings from studies performed with vildagliptin or metformin individually.

Vildagliptin

Intra-cardiac impulse conduction delays were observed in dogs with a no-effect dose of 15 mg/kg (7-fold human exposure based on C_{max}).

Accumulation of foamy alveolar macrophages in the lung was observed in rats and mice. The no-effect dose in rats was 25 mg/kg (5-fold human exposure) and in mice 750 mg/kg (142-fold human exposure).

Gastrointestinal symptoms, particularly soft faeces, mucoid faeces, diarrhoea and, at higher doses, faecal blood were observed in dogs. A no-effect level was observed in rats. Vildagliptin was not mutagenic in conventional *in vitro* and *in vivo* tests for genotoxicity.

A fertility and early embryonic development study in rats revealed no evidence of impaired fertility, reproductive performance or early embryonic development with vildagliptin. Embryofetal toxicity was evaluated in rats and rabbits. An increased incidence of wavy ribs was observed in rats in association with reduced litter parameters, with a no-effect dose of 75 mg/kg (10-fold human exposure). In rabbits, decreased foetal weight and skeletal variations indicative of delayed ossification were noted only in the presence of severe maternal toxicity, with a no-effect dose of 50 mg/kg (9-fold human exposure). A pre- and postnatal development study in rats. Findings were only observed in association with maternal toxicity at ≥ 150 mg/kg and included a transient decrease in body weight and reduced litter size in the next generation.

A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. Another two-year carcinogenicity study was conducted in mice at oral doses up to 900 mg/kg. An increased incidence of mammary adenocarcinomas and haemangiosarcomas was observed with a no-effect dose of 500 mg/kg (59-fold human exposure). (5-fold human exposure), respectively. The increased incidence of these tumours in mice is considered not to represent a significant risk to humans. The genotoxicity of vildagliptin and its principal metabolite, the occurrence

of tumours only in one species, and the high systemic exposure ratios at which tumours were observed.

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at doses ≥ 5 mg/kg/day. These were consistently located on the face, feet, ears and tail). At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), only blisters were observed. They were reversible after treatment and were not associated with histopathological abnormalities. Flaking skin, peeling skin, scabs and tail sores with correlating histopathological changes were observed at doses ≥ 20 mg/kg/day (approximately 3 times human AUC exposure at the 100 mg dose). Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day and were reversible in the monkeys treated at 160 mg/kg/day during a 4-week recovery period.

Metformin

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

6 Pharmaceutical Particulars

6.1 List of Excipients

- Ludipress
- Magnesium stearate BP

COATING

Hypromellose BP,
Propylene Glycol BP
Titanium Dioxide BP
Purified Talc BP
Tartrazine yellow lake colour
Isopropyl Alcohol BP
Purified Water BP

6.2 Incompatibilities

Not applicable.

7.0 Marketing Authorization Holder

Cosmos Limited
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8 Marketing Authorization Number

H2019/CTD5986/1380ER/R1

9 Date of first authorization/renewal of the authorization

September 29 2025

10. Date of revision of the text

September 29 2025