Summary of Product Characteristics

EMPAFLO TRIO XR 10/5/1000 mg

(Empagliflozin 10 mg / Linagliptin 5 mg / Metformin Hydrochloride 1000 mg prolonged-release, bilayer film-coated tablets)

---

1. Name of the medicinal product

EMPAFLO TRIO XR 10/5/1000 mg

Empagliflozin / Linagliptin / Metformin Hydrochloride prolonged-release bilayer film-coated tablets 10 mg / 5 mg / 1000 mg

2. Qualitative and quantitative composition

Each bilayer film-coated tablet contains empagliflozin 10 mg, linagliptin 5 mg, and metformin hydrochloride 1000 mg (as prolonged-release), equivalent to 780 mg of metformin base.

Excipients with known effect

Each tablet contains lactose (as lactose monohydrate) and mannitol (E421).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Bilayer film-coated tablet (prolonged-release).

Light yellow to yellow, biconvex, caplet-shaped film-coated tablets, plain on both sides.

4. Clinical particulars

4.1 Therapeutic indications

EMPAFLO TRIO is indicated as an adjunct to diet and exercise for the treatment of adults with type 2 diabetes mellitus:

- in patients not adequately controlled on their maximally tolerated dose of metformin together with empagliflozin and/or linagliptin; or
- in patients already being treated with the free combination of empagliflozin, linagliptin and metformin.

EMPAFLO TRIO is not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (see section 4.3).

4.2 Posology and method of administration

Posology

The recommended dose is one tablet (empagliflozin 10 mg / linagliptin 5 mg / metformin 1000 mg) once daily. The dose of the combination should follow the current dose of each of the individual components taken; in patients switching from the individual components, the same total daily doses of empagliflozin, linagliptin and metformin already being taken should be maintained. When used

in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be required to reduce the risk of hypoglycaemia (see sections 4.4, 4.5 and 4.8).

Special populations

Renal impairment

Renal function should be assessed before initiation and periodically thereafter. This medicinal product is contraindicated in patients with an eGFR below 30 mL/min/1.73 m² and in end-stage renal disease or dialysis (see section 4.3). Because the glucose-lowering efficacy of empagliflozin is reduced at an eGFR below 60 mL/min/1.73 m² and the metformin dose may need to be reduced, the fixed-dose combination may be unsuitable in moderate renal impairment, and treatment with the individual components allowing appropriate dose titration should be considered.

Hepatic impairment

This medicinal product should not be used in patients with hepatic impairment, owing to the metformin component and the risk of lactic acidosis and the limited experience with empagliflozin in severe hepatic impairment (see sections 4.3 and 4.4).

Elderly

As metformin and empagliflozin are excreted via the kidney, renal function and the risk of volume depletion should be assessed regularly, particularly in patients 75 years and older, in whom experience is limited.

Paediatric population

The safety and efficacy of this medicinal product in children and adolescents below 18 years of age have not been established.

Method of administration

For oral use. The tablet should be taken once daily with a meal to reduce the gastrointestinal effects associated with metformin. Tablets should be swallowed whole with water and must not be split, crushed or chewed. Patients should be advised to continue their diet with an adequate distribution of carbohydrate intake during the day. If a dose is missed, it should be taken as soon as the patient remembers, unless it is almost time for the next dose, in which case the missed dose should be skipped; a double dose should not be taken.

4.3 Contraindications

- Hypersensitivity to the active substances, to any other SGLT2 inhibitor or DPP-4 inhibitor, or to any of the excipients listed in section 6.1.
- Diabetic ketoacidosis, diabetic pre-coma.
- Severe renal impairment (eGFR below 30 mL/min/1.73 m²), end-stage renal disease, or patients on dialysis.
- Acute conditions with the potential to alter renal function, such as dehydration, severe infection or shock.

- Acute or chronic disease which may cause tissue hypoxia, such as cardiac or respiratory failure, recent myocardial infarction, or shock.
- Hepatic impairment, acute alcohol intoxication, alcoholism.
- Acute metabolic acidosis (such as lactic acidosis or diabetic ketoacidosis).

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication associated with the metformin component, most often occurs in acute worsening of renal function, cardiorespiratory illness or sepsis. Metformin accumulation occurs in acute worsening of renal function and increases the risk. In the event of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and medical advice sought. Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma; if suspected, treatment should be stopped and the patient hospitalised immediately. Diagnostic laboratory findings include decreased blood pH (< 7.35), increased plasma lactate (> 5 mmol/L), and an increased anion gap and lactate/pyruvate ratio.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported with SGLT2 inhibitors including empagliflozin; in a number of cases the presentation was atypical, with only moderately increased blood glucose (below 14 mmol/L). The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, or unusual fatigue or sleepiness. If DKA is suspected or diagnosed, treatment should be discontinued immediately. Treatment should be interrupted in patients hospitalised for major surgery or acute serious medical illness, with monitoring of ketones, and may be restarted once ketone values are normal and the condition is stable. Restarting treatment in patients with a previous DKA on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.

Renal function

The glucose-lowering efficacy of empagliflozin is dependent on renal function. Assessment of renal function is recommended before initiation and at least yearly thereafter, before starting concomitant medicinal products that may reduce renal function, and more frequently in patients with declining renal function or the elderly.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of necrotising fasciitis of the perineum (Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors, including empagliflozin. This is a rare but serious and potentially life-threatening event

requiring urgent surgical intervention and antibiotic treatment. Patients should be advised to seek medical attention if they experience a combination of pain, tenderness, erythema or swelling in the genital or perineal area, with fever or malaise. If Fournier's gangrene is suspected, treatment should be discontinued and prompt treatment instituted.

Risk of volume depletion

Osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure; caution is required in patients for whom this could pose a risk (e.g. known cardiovascular disease, antihypertensive therapy with a history of hypotension, or patients aged 75 years and older). In conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status and electrolytes is recommended, and temporary interruption of treatment should be considered until the fluid loss is corrected.

Urinary tract and genital infections

Genital mycotic infections and urinary tract infections have been reported with empagliflozin. Temporary interruption should be considered in patients with complicated urinary tract infections.

Acute pancreatitis

Use of DPP-4 inhibitors, including linagliptin, has been associated with a risk of acute pancreatitis. Patients should be informed of the characteristic symptom of persistent, severe abdominal pain. If pancreatitis is suspected, treatment should be discontinued; if acute pancreatitis is confirmed, treatment should not be restarted. Caution is advised in patients with a history of pancreatitis.

Bullous pemphigoid

Bullous pemphigoid has been reported with linagliptin. If bullous pemphigoid is suspected, treatment should be discontinued.

Hypoglycaemia

Empagliflozin and linagliptin alone have a low risk of hypoglycaemia; however, when used with a sulphonylurea or insulin the risk is increased, and a lower dose of the sulphonylurea or insulin may be required.

Surgery and administration of iodinated contrast media

This medicinal product must be discontinued at the time of, or prior to, surgery under general, spinal or epidural anaesthesia, and may be restarted no earlier than 48 hours afterwards, provided renal function has been re-evaluated and found stable. Intravascular administration of iodinated contrast media may lead to contrast-induced nephropathy, resulting in metformin accumulation and a risk of lactic acidosis; treatment must be stopped prior to, or at the time of, the imaging procedure and not restarted until at least 48 hours afterwards, provided renal function has been re-evaluated and found stable.

Cardiac function and lower-limb amputation

Experience with empagliflozin in patients with heart failure classified as NYHA III–IV is limited. An increase in cases of lower-limb amputation (primarily of the toe) has been observed with another SGLT2 inhibitor; as for all diabetic patients, routine preventative foot-care should be counselled.

Vitamin B12

Metformin may decrease vitamin B12 absorption, very rarely resulting in clinically significant deficiency. Measurement of serum vitamin B12 levels should be considered in patients with megaloblastic anaemia or symptoms suggestive of neuropathy.

Excipients

This medicinal product contains lactose; patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take it. It also contains mannitol, which may have a mild laxative effect.

Urine laboratory assessment

Owing to the mechanism of action of empagliflozin, patients will test positive for glucose in their urine.

4.5 Interaction with other medicinal products and other forms of interaction

- Iodinated contrast media: must be avoided concomitantly; treatment should be stopped before or at the time of imaging and withheld for at least 48 hours afterwards (see section 4.4).
- Diuretics: empagliflozin may add to the diuretic effect of thiazide and loop diuretics and increase the risk of dehydration and hypotension; loop diuretics also increase the risk of lactic acidosis with metformin.
- Insulin and sulphonylureas: increased risk of hypoglycaemia; a lower dose may be required (see sections 4.2 and 4.4).
- Cationic medicinal products eliminated by renal tubular secretion (e.g. cimetidine): may increase metformin exposure; closer monitoring of glycaemic control and dose adjustment may be needed.
- Medicinal products with intrinsic hyperglycaemic activity (e.g. corticosteroids, beta-2 agonists and, again, diuretics): more frequent blood glucose monitoring may be required, particularly on initiation.
- Alcohol: increases the risk of lactic acidosis with metformin, particularly in fasting, malnutrition or hepatic impairment; excessive intake should be avoided.
- Inducers of UGT / P-gp / CYP3A4 (e.g. rifampicin): co-administration decreased linagliptin exposure by about 40% and may reduce the efficacy of both linagliptin and empagliflozin; monitoring of glycaemic control is advised.

- Lithium: empagliflozin may increase renal lithium excretion and reduce blood lithium levels; more frequent monitoring of serum lithium is advised after initiation and dose changes.
- ACE inhibitors and angiotensin-II antagonists: may reduce renal function; caution is advised, particularly in combination with diuretics and NSAIDs.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data on the use of empagliflozin and linagliptin in pregnant women, and animal studies with empagliflozin have shown adverse effects on postnatal renal development. When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes be managed with insulin rather than this medicinal product to maintain blood glucose as close to normal as possible. This medicinal product should not be used during pregnancy; if a patient wishes to become pregnant or becomes pregnant, treatment should be discontinued and switched to insulin as soon as possible.

Breast-feeding

Available non-clinical data in animals have shown excretion of empagliflozin, linagliptin and metformin in milk, and empagliflozin may affect developing kidney maturation. A risk to newborns or infants cannot be excluded. This medicinal product should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted with the combination. Non-clinical studies with the individual active substances did not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

This medicinal product has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, particularly when it is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of this combination corresponds to the known safety profiles of its active substances. The most frequently reported reactions are gastrointestinal symptoms associated with metformin (which occur mainly on initiation and resolve spontaneously in most cases), urinary tract and genital infections and increased urination associated with empagliflozin, and hypoglycaemia when used with a sulphonylurea or insulin. The most serious reactions are lactic acidosis, diabetic ketoacidosis, pancreatitis and necrotising fasciitis of the perineum (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions are listed below by system organ class and frequency, based on the safety profiles of the individual components (E = empagliflozin, L = linagliptin, M = metformin). Frequency categories are defined as: 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); and not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Common	Urinary tract infection (including pyelonephritis and urosepsis) (E)
	Common	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections (E)
	Common	Nasopharyngitis (L)
	Rare	Necrotising fasciitis of the perineum (Fournier's gangrene) (E)
Immune system disorders	Uncommon	Hypersensitivity (L); angioedema, urticaria (E, L)
Metabolism and nutrition disorders	Common	Hypoglycaemia (when used with a sulphonylurea or insulin) (E, L)
	Common	Thirst (E)
	Rare	Diabetic ketoacidosis (E)
	Very rare	Lactic acidosis (M); decrease of vitamin B12 absorption during long-term use (M)
Nervous system disorders	Common	Taste disturbance (M)
Vascular disorders	Uncommon	Volume depletion (E)
Respiratory, thoracic and mediastinal disorders	Common	Cough (L)
Gastrointestinal disorders	Very common	Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite (M) — these occur most commonly on initiation and resolve spontaneously in most cases
	Common	Constipation (E, L)
	Uncommon	Pancreatitis (L)
	Rare	Mouth ulceration (L)
Hepatobiliary disorders	Very rare	Abnormal liver function tests or hepatitis, resolving on discontinuation of metformin (M)
Skin and subcutaneous tissue disorders	Common	Pruritus (E); rash (E, L)
	Very rare	Skin reactions such as erythema, pruritus and urticaria (M)
	Not known	Bullous pemphigoid (L)
Renal and urinary disorders	Common	Increased urination (E)
	Uncommon	Dysuria (E)
	Very rare	Tubulointerstitial nephritis (E)
Investigations	Common	Amylase increased (L); lipase increased (L)

System Organ Class	Frequency	Adverse reaction
	Uncommon	Haematocrit increased (E); serum lipids increased (E); blood creatinine increased / glomerular filtration rate decreased (E)

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 to the National Regulatory Authority.

4.9 Overdose

A large overdose of metformin, or concomitant risks, may lead to lactic acidosis, which is a medical emergency and must be treated in hospital; the most effective method to remove lactate and metformin is haemodialysis. Overdose of empagliflozin increases urinary glucose excretion; there is no specific antidote, and in the event of overdose the usual supportive measures should be employed (removal of unabsorbed material from the gastrointestinal tract, clinical monitoring, and institution of supportive treatment) according to the patient's clinical status. Single doses of linagliptin of up to 600 mg were well tolerated; linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs used in diabetes; combinations of oral blood glucose lowering drugs. ATC code: A10BD27.

This medicinal product combines three antihyperglycaemic agents with complementary and distinct mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor; linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor; and metformin, a biguanide.

Empagliflozin

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of SGLT2, the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate. By reducing renal glucose reabsorption, empagliflozin increases urinary glucose excretion (averaging approximately 78 g/day) and thereby lowers plasma glucose; the mechanism is independent of beta-cell function and the insulin pathway, contributing to a low risk of hypoglycaemia. The accompanying natriuresis and osmotic diuresis contribute to a moderate reduction in blood pressure and to weight loss.

Linagliptin

Linagliptin is a selective inhibitor of DPP-4, the enzyme that inactivates the incretin hormones GLP-1 and GIP. By inhibiting DPP-4, linagliptin increases and prolongs active incretin levels, glucose-dependently increasing insulin secretion

and lowering glucagon secretion, thereby improving glucose homeostasis with a low risk of hypoglycaemia.

Metformin

Metformin is a biguanide that decreases hepatic glucose production (by inhibiting gluconeogenesis and glycogenolysis), decreases intestinal glucose absorption, and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. It does not stimulate insulin secretion and therefore does not cause hypoglycaemia when used alone.

5.2 Pharmacokinetic properties

Administration of the combination with food resulted in no change in the overall exposure of empagliflozin or linagliptin; for the metformin prolonged-release component, a high-fat meal increased systemic exposure (AUC) by approximately 70% relative to fasting, without an effect on Cmax, and prolonged Tmax by about 3 hours.

Empagliflozin

Empagliflozin is rapidly absorbed, with peak plasma concentrations at a median of 1.5 hours; steady-state AUC and Cmax were 1,870 nmol·h/L and 259 nmol/L with 10 mg once daily. The apparent volume of distribution is approximately 73.8 L and plasma protein binding is about 86%. It is mainly excreted unchanged, with a minor fraction metabolised by glucuronidation (UGT2B7, UGT1A3, UGT1A8, UGT1A9); the apparent terminal half-life is about 12.4 hours, with elimination in faeces (about 41%) and urine (about 54%).

Linagliptin

The absolute bioavailability of linagliptin is approximately 30%, with peak concentrations at a median of 1.5 hours. Owing to concentration-dependent, saturable binding to DPP-4, plasma pharmacokinetics are non-linear; the effective accumulation half-life is about 12 hours (terminal half-life > 100 hours reflects tight DPP-4 binding). Metabolism is a minor elimination pathway; approximately 85% of a dose is eliminated via the enterohepatic system (about 80%) or urine (about 5%), with renal clearance of about 70 mL/min.

Metformin (prolonged-release)

Following a single oral prolonged-release dose, Tmax is reached at approximately 7 to 8 hours. Metformin is negligibly bound to plasma proteins and partitions into erythrocytes; the apparent volume of distribution averages 654 ± 358 L. Metformin does not undergo hepatic metabolism and is excreted unchanged in the urine; the plasma elimination half-life is approximately 6.2 hours (about 17.6 hours in blood). Renal clearance is approximately 3.5 times creatinine clearance, indicating that tubular secretion is the major route of elimination, and the clearance of metformin decreases with declining renal function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic

development with empagliflozin and linagliptin. In long-term studies, empagliflozin produced findings consistent with its exaggerated pharmacology (urinary glucose loss and electrolyte changes) and renal mineralisation; carcinogenicity findings (male-rat and male-mouse tumours) are considered species-specific and not relevant to humans. Empagliflozin was not teratogenic but caused adverse effects on postnatal renal development, and only at maternally toxic doses caused bent limb bones (rat) and increased embryofetal loss (rabbit). Linagliptin was not teratogenic or carcinogenic at clinically relevant exposures. Metformin, at conventional doses, has not shown genotoxic or carcinogenic potential and has not impaired fertility in animals; it crosses the placenta.

6. Pharmaceutical particulars

6.1 List of excipients

- Microcrystalline cellulose (PH 102)
- Hypromellose (HPMC K100)
- Povidone (K30)
- Colloidal anhydrous silica
- Isopropyl alcohol
- Magnesium stearate
- Mannitol (E421)
- Pregelatinised starch
- Crospovidone (XL 10)
- Lactose monohydrate
- Hydroxypropyl cellulose
- Croscarmellose sodium
- Yellow iron oxide (lake)
- Titanium dioxide (E171)
- Ready-coat film (AQ Yellow)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C. Protect from moisture. Keep out of the reach of children.

6.5 Nature and contents of container

3 × 10 tablets in an Alu/Alu blister (30 tablets), packed in a printed carton together with a package insert.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorisation Holder

Dawa Limited

Baba Dogo Road, Ruaraka, P.O. Box 16633-00620, Nairobi, Kenya.

Manufacturer

Cubit Lifesciences LLP

Plot No. 39-40, Ozone Industrial Park, At. & Post: Kerala-Bhayla, Near Kerala G.I.D.C, Taluka: Bavla, Dist.: Ahmedabad-382220, Gujarat, India.

8. Marketing Authorisation Number

CTD12952

9. Date of first authorisation / renewal of the authorisation

03.07.2026

10. Date of revision of the text

03.07.2026