SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Empaflo-M 1000 film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Empagliflozin .....12.5 mg

Metformin hydrochloride BP .....1000 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet. Dark brownish purple coloured, capsule shaped film coated tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise: in patients insufficiently controlled on maximally tolerated metformin alone; in combination with other medicinal products for diabetes, in patients insufficiently controlled with metformin and these products; or in patients already being treated with empagliflozin and metformin as separate tablets.

4.2 Posology and method of administration

Recommended dose is one tablet twice daily; dosage individualized based on current regimen, effectiveness and tolerability, using recommended daily dose of 10 mg or 25 mg empagliflozin, not exceeding maximum recommended metformin dose.

For patients insufficiently controlled on metformin (alone or with other medicines): starting dose should provide empagliflozin 5 mg twice daily (10 mg daily) with the metformin dose already being taken; may increase to 25 mg total daily dose if tolerated and tighter control needed. Lower sulphonylurea/insulin dose may be considered when used in combination. For

patients switching from separate tablets: same daily doses should be continued.

Missed dose

Take as soon as remembered; do not take a double dose at the same time - skip the missed dose.

Renal impairment

No adjustment for mild impairment. GFR should be assessed before initiation and at least annually (more frequently in high-risk/elderly patients, e.g. every 3-6 months). Posology table: GFR 60-89: metformin max 3000mg/day (dose reduction may be considered), empagliflozin max 25mg/day. GFR 45-59: metformin max 2000mg/day (starting dose at most half max), empagliflozin should not be initiated, adjust/maintain at max 10mg/day. GFR 30-44: metformin max 1000mg/day (starting dose at most half max), empagliflozin not recommended. GFR <30: metformin contraindicated, empagliflozin not recommended. If no adequate combination strength available, individual monocomponents should be used.

Hepatic impairment

Must not be used in patients with hepatic impairment.

Elderly

Use with caution; monitor renal function to prevent metformin-associated lactic acidosis, particularly given increased risk for volume depletion in patients ≥75. Initiation not recommended for patients ≥85 years.

Paediatric population

Safety and efficacy in children/adolescents aged 0-18 years not established; no data available.

Method of administration

Should be taken twice daily with meals to reduce gastrointestinal adverse reactions; tablets swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substances or excipients
- Any type of acute metabolic acidosis (lactic acidosis, diabetic ketoacidosis)

- Diabetic pre-coma
- Severe renal failure (GFR<30 mL/min)
- Acute conditions with potential to alter renal function: dehydration, severe infection, shock
- Diseases causing tissue hypoxia: decompensated heart failure, respiratory failure, recent myocardial infarction, shock
- Hepatic impairment, acute alcohol intoxication, alcoholism

4.4 Special warnings and precautions for use

Lactic acidosis

A very rare but serious metabolic complication, most often occurring at acute worsening of renal function or cardiorespiratory illness/sepsis. In case of dehydration, temporarily discontinue metformin. Risk factors include excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and hypoxia-associated conditions. Characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma.

Diabetic ketoacidosis

Rare cases including life-threatening/fatal cases have been reported with SGLT2 inhibitors including empagliflozin, sometimes with only moderately increased glucose (below 14 mmol/L). Discontinue immediately if suspected/diagnosed; interrupt for major surgery/acute illness with ketone monitoring. Higher-risk patients as described for empagliflozin monotherapy. Not for use in type 1 diabetes.

Administration of iodinated contrast agents / Renal function / Cardiac function / Surgery

Discontinue metformin prior to/at time of imaging, restart no earlier than 48 hours after with stable renal function. GFR should be assessed before treatment and regularly; contraindicated at GFR<30 mL/min. Patients with stable chronic heart failure may use with regular cardiac/renal monitoring; contraindicated in acute/unstable heart failure due to metformin component. Discontinue metformin at time of surgery under general/spinal/epidural anaesthesia; restart no earlier than 48 hours after with stable renal function.

Risk for volume depletion / Elderly / Urinary tract infections / Fournier's gangrene / Lower limb amputations / Hepatic injury / Cardiac failure / Elevated haematocrit

Osmotic diuresis may cause modest blood pressure decrease; caution in at-risk patients. Elderly patients require special attention to volume intake; initiation not recommended ≥85 years. Complicated UTIs (pyelonephritis/urosepsis) reported; consider temporary interruption. Rare but serious Fournier's gangrene reported; discontinue and treat promptly if suspected. Increase in lower limb amputation cases observed with another SGLT2 inhibitor. Hepatic injury cases reported without established causal relationship. Limited experience in NYHA class III-IV. Haematocrit increase observed.

Urine laboratory assessments / 1,5-AG assay interference

Patients will test positive for glucose in urine. 1,5-AG assay unreliable for monitoring glycaemic control in SGLT2 inhibitor users.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of multiple doses of empagliflozin and metformin does not meaningfully alter pharmacokinetics of either substance in healthy subjects. No dedicated interaction studies performed for the fixed-dose combination; statements below reflect individual components.

Empagliflozin

Diuretics may add to diuretic effect, increasing dehydration/hypotension risk. Insulin/insulin secretagogues may increase hypoglycaemia risk. Metabolised via UGT1A3/1A8/1A9/2B7 glucuronidation; substrate of OAT3, OATP1B1/1B3, P-gp, BCRP. Probenecid increased Cmax 26%/AUC 53% (not clinically meaningful); gemfibrozil increased Cmax 15%/AUC 59%; rifampicin increased Cmax 75%/AUC 35% (not clinically meaningful); no clinically relevant effect from metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide, hydrochlorothiazide. Empagliflozin does not inhibit/induce CYP450 or major UGT isoforms; digoxin AUC/Cmax minimally increased (not clinically meaningful).

Metformin

Alcohol increases lactic acidosis risk. OCT1/OCT2 transporters: inhibitors (verapamil, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib,

isavuconazole) and inducers (rifampicin) may alter metformin efficacy/elimination; inhibitors of both (crizotinib, olaparib) may alter both. Iodinated contrast agents require discontinuation as above. NSAIDs, ACE inhibitors, angiotensin II receptor antagonists, and loop diuretics may increase lactic acidosis risk via renal effects - monitor closely. Glucocorticoids, beta-2 agonists and diuretics have intrinsic hyperglycaemic activity requiring monitoring. Insulin/insulin secretagogues may increase hypoglycaemia risk.

4.6 Fertility, pregnancy and lactation

Pregnancy

No data from use of this medicinal product or empagliflozin in pregnant women. Empagliflozin crosses the placenta during late gestation to a very limited extent without harmful effects on early embryonic development, but has shown adverse effects on postnatal development in animal studies. Limited data suggest metformin use is not associated with increased risk of congenital malformations. Insulin is recommended to maintain blood glucose as close to normal as possible during pregnancy planning and pregnancy.

Breast-feeding

Metformin is excreted into human milk with no observed effects in breastfed infants. No human data for empagliflozin; animal data show excretion of both in milk. Should not be used during breast-feeding.

Fertility

No human fertility studies for this product or empagliflozin. Animal studies with the combination do not indicate direct/indirect harmful effects on fertility.

4.7 Effects on ability to drive and use machines

Empagliflozin and Metformin HCl tablet has minor influence on ability to drive and use machines. Patients should take precautions to avoid hypoglycaemia while driving, particularly when combined with a sulphonylurea and/or insulin.

4.8 Undesirable effects

The most commonly reported adverse reactions in clinical trials were hypoglycaemia (in combination with insulin and/or sulphonylurea) and gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, loss

of appetite). No additional adverse reactions identified with empagliflozin as add-on to metformin compared to single components.

Common: Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections; urinary tract infection; thirst; taste disturbance; increased urination; serum lipids increased; pruritus (generalised); rash. Very common: Hypoglycaemia (with sulphonylurea/insulin); gastrointestinal symptoms. Uncommon: Volume depletion; urticaria; blood creatinine increased/GFR decreased; haematocrit increased. Rare: Diabetic ketoacidosis. Very rare: Lactic acidosis; vitamin B12 deficiency; liver function test abnormalities/hepatitis; erythema. Not known: Necrotising fasciitis of the perineum (Fournier's gangrene); angioedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'

4.9 Overdose

Empagliflozin

Single doses up to 800 mg (32x max recommended dose) and multiple doses up to 100 mg (4x max dose) did not show toxicity; no experience above 800 mg.

Metformin

Hypoglycaemia not seen with doses up to 85g, though lactic acidosis has occurred; a medical emergency requiring hospital treatment.

Therapy

Treatment as appropriate to clinical status. Haemodialysis is the most effective method to remove lactate and metformin; removal of empagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs. ATC code: A10BD20.

Mechanism of action

Combines two complementary mechanisms: empagliflozin (SGLT2 inhibitor) reduces renal glucose reabsorption leading to urinary glucose excretion and mild osmotic diuresis; metformin (biguanide) reduces hepatic glucose production, increases peripheral insulin sensitivity, and delays intestinal glucose absorption, with favourable lipid effects.

Clinical efficacy

Assessed in 10,366 patients across 9 double-blind studies of at least 24 weeks. Treatment with empagliflozin plus metformin (with or without pioglitazone, sulfonylurea, DPP-4 inhibitors, insulin) led to clinically relevant improvements in HbA1c, FPG, body weight, and blood pressure. In the EMPA-REG OUTCOME cardiovascular study, empagliflozin (pooled 10/25 mg) as adjunct to standard care reduced cardiovascular death (HR 0.62) and all-cause mortality (HR 0.68) versus placebo, and reduced heart failure hospitalisation risk (HR 0.65) and nephropathy risk (HR 0.61) in patients with established cardiovascular disease.

The UKPDS study established long-term benefits of metformin in overweight patients: significant reductions in absolute risk of diabetes-related complications, diabetes-related mortality, overall mortality, and myocardial infarction versus diet alone.

5.2 Pharmacokinetic properties

Bioequivalence studies demonstrated Empagliflozin/Metformin combination tablets (5/850, 5/1000, 12.5/850, 12.5/1000 mg) are bioequivalent to co-administration of the individual tablets. Food decreased empagliflozin AUC 9%/Cmax 28% and metformin AUC 12%/Cmax 26% (not clinically relevant); recommended to give with food as per metformin recommendation.

Empagliflozin

Rapidly absorbed, median Tmax 1.5h; steady-state AUC/Cmax 1870 nmol.h/L / 259 nmol/L (10mg) and 4740 nmol.h/L / 687 nmol/L (25mg). Apparent Vd 73.8L; 86% protein bound. Metabolised via glucuronidation (UGT2B7, 1A3, 1A8, 1A9). Terminal half-life ~12.4 hours; ~96% of radioactivity eliminated via faeces (41%) or urine (54%).

Metformin

Tmax ~2.5h; absolute bioavailability 50-60%; negligible protein binding; Vd 63-276L; excreted unchanged in urine (renal clearance >400 mL/min); terminal half-life ~6.5 hours.

5.3 Preclinical safety data

Combination

General toxicity studies in rats up to 13 weeks revealed no additional target organs versus either substance alone; hypochloremia was the only adverse finding at high exposure multiples. Embryofetal development study showed no teratogenic effect at high exposure multiples of both components.

Empagliflozin

No special hazard for humans; not genotoxic. Tumours observed in rodents only at high exposure multiples with mechanisms not relevant to humans. No adverse effects on fertility/early embryonic development at sufficient margins; not teratogenic except at maternally toxic doses.

Metformin

No special hazard based on conventional studies; teratogenicity (increased skeletal malformations) observed in rats at 500 mg/kg/day (7x MRHD).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Microcrystalline cellulose pH 102 BP
- Crospovidone BP
- Polyvinylpyrrolidone BP
- Isopropyl alcohol BP
- Low-substituted hydroxypropyl cellulose BP
- Aerosil 200 BP
- Magnesium stearate BP

Film coating materials:

- Hypromellose 6CPS BP
- Propylene glycol BP
- Purified talc BP

- Titanium dioxide BP
- Red iron oxide USP
- Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu-Alu/Aluminium foil blister of 1x10, packed in unit box of 3x10's with literature 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,

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Nairobi-Kenya.

8. MARKETING AUTHORISATION NUMBER(S)

H2021/CTD8557/19915

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20-09-2021

10. DATE OF REVISION OF THE TEXT

February 2021.