DR. REDDY'S LABORATORIES (PTY) LTD.
INGLYFLO 10 and INGLYFLO 25
FILM-COATED TABLETS
APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

INGLYFLO 10; Film-coated tablets

INGLYFLO 25; Film-coated tablets

INGLYFLO IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. INGLYFLO IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES AND NOT INDICATED FOR THE TREATMENT OF ANY OTHER CONDITIONS EXCEPT TYPE 2 DIABETES.

There have been reports of metabolic acidosis, including ketoacidosis which were serious life threatening or fatal in patients taking INGLYFLO.

Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 11 mmol/L. INGLYFLO should be discontinued and the patient should be promptly evaluated and managed accordingly.

Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with INGLYFLO.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g., history of pancreatitis or pancreatic surgery. INGLYFLO is contraindicated in these patients.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INGLYFLO 10: Each film-coated tablet contains 10 mg empagliflozin.

INGLYFLO 25: Each film-coated tablet contains 25 mg empagliflozin.

Excipients with known effect:

INGLYFLO 10: Each film-coated tablet contains sugar: 20,5 mg lactose anhydrous.

INGLYFLO 25: Each film-coated tablet contains sugar: 51,4 mg lactose anhydrous.

INGLYFLO 10 and INGLYFLO 25 contains sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

INGLYFLO 10: Pale yellow coloured, round shaped, film-coated tablets debossed with "ME" on one side and "3" on the other side.

INGLYFLO 25: Pale yellow coloured, round shaped, film-coated tablets debossed with "ME4" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INGLYFLO film-coated tablets are indicated as an adjunct to diet and exercise to improve glycaemic control in adults (aged 18 years and older) with type 2 diabetes mellitus.

Prevention of cardiovascular events:

INGLYFLO is indicated in patients with type 2 diabetes mellitus and high cardiovascular risk* to reduce the risk of:

- cardiovascular death due to myocardial infarction

*e.g. previous myocardial infarction, multi vessel coronary artery disease, previous coronary revitalisation, single vessel coronary disease, at least 50 % narrowing of coronary artery lumen.

INGLYFLO tablets are not recommended for use in combination with other antidiabetic medicines and for treatment of chronic kidney disease and heart failure. However, it is recommended to use another suitable medicine containing empagliflozin for the same.

4.2 Posology and method of administration

Posology

Assess hydration status and renal function before initiating treatment with INGLYFLO. Do not initiate

treatment if the estimated glomerular filtration rate (eGFR) is < 60 mL/min/1,73 m^2 (or creatinine clearance < 60 mL/min) and/or in patients who are volume depleted or acidotic (see section 4.4).

The recommended starting dose of INGLYFLO is 10 mg once daily.

In patients tolerating INGLYFLO 10 once daily and requiring additional glycaemic control, the dose may be increased to 25 mg once daily.

Special populations

Patients with renal insufficiency

No dose adjustment is required for patients with mild renal insufficiency (e.g., eGFR ≥ 60 to < 90 mL/min/1,73 m^2).

INGLYFLO is not recommended for use in patients with moderate to severe renal impairment (defined as eGFR < 60 mL/min/1,73 m^2 by modification of diet in renal disease or creatinine clearance < 60 mL/min by Cockroft-Gault) (see sections 4.3 and 4.4).

Patients with hepatic insufficiency

Dose adjustment may be necessary for patients with severe hepatic impairment.

Elderly patients

No dosage adjustment is recommended based on age if the creatinine clearance is ≥ 60 mL/min.

Therapeutic experience in patients aged 85 years and older is limited. Initiation of INGLYFLO therapy in this population is not recommended (see section 4.4).

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Paediatric population

Safety and effectiveness of INGLYFLO in children under 18 years of age have not been established.

Method of administration

For oral use.

INGLYFLO can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to empagliflozin or any of the excipients listed in section 6.1.
- Treatment of Type 1 diabetes mellitus.
- Treatment of ketoacidosis (see section 4.4).
- Moderate and severe renal impairment (creatinine clearance < 60 mL/min), end-stage renal disease or dialysis (see section 4.4).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/100 mL). It is not known if DKA is more likely to occur with higher doses of empagliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where diabetic ketoacidosis (DKA) is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients.

Measurement of blood ketone levels is preferred to urine.

Treatment with empagliflozin may be restarted when the ketone values are normal, and the condition of the patient has stabilised.

Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta cell function reserve (e.g., type 2

diabetes patients with low C-peptide or latent autoimmune diabetes in adults [LADA] or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT-2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.
INGLYFLO should not be used for treatment of patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased DKA with a frequent occurrence in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to insulin compared to placebo.

Renal impairment

INGLYFLO should not be initiated in patients with an eGFR below 60 mL/min/1,73 m^2 or CrCl < 60 mL/min. In patients tolerating empagliflozin whose eGFR is persistently below 60 mL/min/1,73 m^2 or CrCl < 60 mL/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1,73 m^2 or CrCl persistently below 45 mL/min. Empagliflozin should not be used in patients with end-stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in these patients (see sections 4.2 and 5.2).

Monitoring of renal function

Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. Therefore, assessment of renal function is recommended as follows:

- Prior to INGLYFLO initiation and periodically during treatment, i.e. at least yearly (see sections 4.2, 5.1 and 5.2).
- Prior to initiation of any concomitant medicine that may have a negative impact on renal function.

Hepatic injury

Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established.

Elevated haematocrit

Increase in haematocrit values were observed with empagliflozin treatment (see section 4.8).

Risk for volume depletion

Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure (see section 5.1). Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.

In case of conditions that may lead to fluid loss (e.g., gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.

Elderly patients

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo (see section 4.8). Therefore, special attention should be given to their volume intake in case of co-administered medicines which may lead to volume depletion (e.g., diuretics, ACE inhibitors). Therapeutic experience in patients aged 85 years and older is limited. Initiation of empagliflozin therapy in this population is not recommended (see section 4.2).

Complicated urinary tract infections and genital infections

SGLT2 inhibitors such as INGLYFLO have been associated with an increased risk of urinary tract infection and/or genital infection in both males and females caused by bacteria and/or fungi. Genital fungal infections appear to be more common in females. Balanoposthitis in males may result in phimosis.

Temporary interruption of INGLYFLO should be considered in patients with complicated urinary tract infections.

Urinary tract infections

In a pool of placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo and higher in patients treated with empagliflozin 10 mg (see section 4.8). Patients with a

history of chronic or recurrent urinary tract infection (UTI) were more likely to experience UTI.

Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin.

Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either urogenital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, INGLYFLO should be discontinued, and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Infiltrative disease or Takotsubo cardiomyopathy

Patients with infiltrative disease or with Takotsubo cardiomyopathy have not been specifically studied. Therefore, efficacy in these patients has not been established.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients, it is important to counsel patients on routine preventative foot- care.

Cardiac failure

Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV. In the EMPA-REG OUTCOME study, 10,1 % of the patients were reported with cardiac failure at baseline. The reduction of cardiovascular death in these patients was consistent with the overall study population.

Urine laboratory assessments

Due to its mechanism of action, patients taking INGLYFLO will test positive for glucose in their urine.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

Lactose

INGLYFLO tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take INGLYFLO.

Sodium

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Effects on laboratory tests: Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring of glycaemic control cannot be done by urine glucose monitoring or with a 1,5 AG blood assay, as SGLT2 inhibitors interfere with the assay.

Pharmacokinetic interactions

Lithium

Concomitant use of SGLT2 inhibitors, including empagliflozin, with lithium may decrease blood lithium levels through increased renal lithium elimination. Therefore, serum lithium concentration should be monitored more frequently with empagliflozin initiation or following dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

Effects of other medicines on empagliflozin

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2.

Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26 % increase in peak empagliflozin plasma concentrations (C_{max}) and a 53 % increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.

The effect of UGT induction (e.g., induction by rifampicin or phenytoin) on empagliflozin has not been studied. Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to INGLYFLO is appropriate.

An interaction study with gemfibrozil, an *in vitro* inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C_{max} increased by 15 % and AUC increased by 59 % following co- administration. These changes were not considered to be clinically meaningful.

Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75 % increase in C_{max} and a 35 % increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor, indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin.

Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

Effects of empagliflozin on other medicines

Based on *in vitro* studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms.

Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9 or UGT2B7. Medicine-medicine interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with active substances that are P-gp substrates. Co-administration of digoxin, a P-gp substrate, with empagliflozin resulted in a 6 % increase in AUC and 14 % increase in C_{max} of digoxin. These changes were not considered to be clinically meaningful.

Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1B1, and OATP1B3 in vitro at clinically relevant plasma concentrations and, as such, medicine-medicine interactions with substrates of these uptake transporters are considered unlikely.

Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

No available data.

Pregnancy

There are no data from the use of empagliflozin in pregnant women. Animal studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. However, animal studies have shown adverse effects on postnatal development. INGLYFLO is contraindicated during pregnancy (see section 4.3).

Breastfeeding

No data in humans are available on excretion of empagliflozin into milk. Available toxicological data in animals have shown excretion of empagliflozin in milk. A risk to the new-born/infant cannot be excluded. INGLYFLO is contraindicated during breastfeeding (see section 4.3).

Fertility

No studies on the effect on human fertility have been conducted for INGLYFLO. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

INGLYFLO has minor influence on the ability to drive a vehicle and use machines.

4.8 Undesirable effects

a) Summary of safety profile

The most frequent undesirable effect was hypoglycaemia.

b) Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse effects
Infections and Infestations	Frequent	vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[a], urinary tract infection (including pyelonephritis and urosepsis)[a]
	Frequency unknown	necrotising fasciitis of the perineum (Fournier's gangrene)*
Immune system disorders	Frequency unknown	angioedema
Metabolism and nutrition disorders	Frequent	thirst, weight loss
	Less frequent	diabetic ketoacidosis*, ketoacidosis with atypical presentation (see section 4.4).
Skin and subcutaneous tissue disorders	Frequent	pruritus (generalised), rash
	Less frequent	urticaria
Vascular disorders	Less frequent	volume depletion[a]
Gastrointestinal disorders	Frequent	thirst, constipation
Renal and urinary disorders	Frequent	increased urination[a], glucosuria
	Less frequent	dysuria, ketonuria, tubulointerstitial nephritis
Reproductive system and breast disorders	Less frequent	phimosis
Investigations	Frequent	increased serum lipids[b]
	Less frequent	increased blood creatinine, decreased glomerular filtration

		rate[a], increased haematocrit[c].

[a] See sub-sections below for additional information.

[b] Mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 4,9 % and 5,7 % versus 3,5 %; HDL cholesterol 3,3 % and 3,6 % versus 0,4 %; LDL cholesterol 9,5 % and 10,0 % versus 7,5 %; triglycerides 9,2 % and 9,9 % versus 10,5 %.

[c] Mean changes from baseline in haematocrit were 3,4 % and 3,6 % for empagliflozin 10 mg and 25 mg, respectively, compared to 0,1 % for placebo. In the EMPA-REG Outcome study, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment discontinuation.

[*] See section 4.4.

Description of selected adverse reactions

Major hypoglycaemia (events requiring assistance)

No increase in major hypoglycaemia was observed with empagliflozin compared to placebo as monotherapy.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently in patients treated with empagliflozin (empagliflozin 10 mg: 4,0 %, empagliflozin 25 mg: 3,9 %) compared to placebo (1,0 %). These infections were reported more frequently in females treated with empagliflozin compared to placebo, and the difference in frequency was less pronounced in males. The genital tract infections were mild or moderate in intensity.

Increased urination

Increased urination (including the predefined terms pollakiuria, polyuria, and nocturia) was observed at higher frequencies in patients treated with empagliflozin (empagliflozin 10 mg: 3,5 %, empagliflozin 25 mg: 3,3 %) compared to placebo (1,4 %). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was similar for placebo and empagliflozin (< 1 %).

Urinary tract infection

The overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo (7,0 % and 7,2 %) and higher in empagliflozin 10 mg (8,8 %). Similar

to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity (mild, moderate, severe) of urinary tract infection was similar in patients treated with empagliflozin and placebo.

Urinary tract infection was reported more frequently in females treated with empagliflozin compared to placebo; there was no difference in males.

Volume depletion

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was similar in patients treated with empagliflozin (empagliflozin 10 mg: 0,6 %, empagliflozin 25 mg: 0,4 %) and placebo (0,3 %). The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg (2,3 %) or empagliflozin 25 mg (4,3 %) compared to placebo (2,1 %).

Blood creatinine increased/glomerular filtration rate decreased

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were similar between empagliflozin and placebo (blood creatinine increased: empagliflozin 10 mg 0,6 %, empagliflozin 25 mg 0,1 %, placebo 0,5 %; glomerular filtration rate decreased: empagliflozin 10 mg 0,1 %, empagliflozin 25 mg 0 %, placebo 0,3 %).

Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with empagliflozin were generally transient during continuous treatment or reversible after discontinuation of medicine treatment.

Consistently, in the EMPA-REG OUTCOME study, patients treated with empagliflozin experienced an initial fall in eGFR (mean: 3 mL/min/1,73 m^2). Thereafter, eGFR was maintained during continued treatment.

Mean eGFR returned to baseline after treatment discontinuation suggesting acute haemodynamic changes may play a role in these renal function changes.

Serum lipids increased

Mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 4.9 % and 5.7 % versus 3.5 %; HDL-cholesterol 3.3 % and 3.6 % versus 0.4 %; LDL-cholesterol 9.5 % and 10.0 % versus 7.5 %; triglycerides 9.2 % and 9.9 % versus 10.5 %.

Haematocrit increased

Mean changes from baseline in haematocrit were 3.4 % and 3.6 % for empagliflozin 10 mg and 25 mg, respectively, compared to 0.1 % for placebo. In the EMPA-REG Outcome study, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

For any information about this medicine, please contact the local representative of the Holder of Certificate of Registration: Dr. Reddy's Laboratories (Pty) Ltd. Tel: +27 11 324 2100

4.9 Overdose

Symptoms

The risk and severity of side effects may be increased.

Empagliflozin, as in INGLYFLO, increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful.

There is no experience with doses above 800 mg in humans.

Therapy

In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin, as in INGLYFLO, by haemodialysis has not been studied. Hypoglycaemia should be monitored for, especially when other antidiabetic medication has been co-administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.2 Oral hypoglycaemics

Pharmacotherapeutic group: Medicines used in diabetes. Other blood glucose lowering medicines, excluding insulins.

ATC code: A10BK03

Mechanism of action

Empagliflozin is a reversible, highly potent (IC_{50} of 1,3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5 000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.
In patients with type 2 diabetes, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24-hour dosing interval. Increased urinary glucose excretion was maintained at the end of the 4-week treatment period, averaging approximately 78 g/day. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.
Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-β (HOMA-β) was noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body mass reduction. The glucosuria observed with empagliflozin is accompanied by diuresis which may contribute to sustained and moderate reduction of blood pressure. The glucosuria, natriuresis and osmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with type 2 diabetes. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} of 1,5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1 870 nmol.h/L and 259 nmol/L with empagliflozin 10 mg, and 4 740 nmol.h/L and 687 nmol/L with empagliflozin 25 mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with type 2 diabetes.

Administration of empagliflozin 25 mg after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16 % and C_{max} by approximately 37 % compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution

The apparent steady-state volume of distribution was estimated to be 73,8 L based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C] empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37 % and plasma protein binding was 86 %.

Biotransformation

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-, 3-, and 6-*O*-glucuronide). Systemic exposure of each metabolite was less than 10 % of total medicine-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of

empagliflozin was estimated to be 12,4 hours and apparent oral clearance was 10,6 L/hour. The inter-subject and residual variabilities for empagliflozin oral clearance were 39,1 % and 35,8 %, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22 % accumulation, with respect to plasma AUC, was observed at steady state. Following administration of an oral [14C] empagliflozin solution to healthy volunteers, approximately 96 % of the medicine-related radioactivity was eliminated in faeces (41 %) or urine (54 %). The majority of medicine-related radioactivity recovered in faeces was unchanged parent medicine and approximately half of medicine-related radioactivity excreted in urine was unchanged parent medicine.

Special populations

Renal impairment:

In patients with mild, moderate or severe renal impairment (eGFR < 30 – < 90 mL/min/1,73 m^2) and patients with kidney failure/end- stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18 %, 20 %, 66 %, and 48 %, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20 % higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in medicine exposure.

Hepatic impairment:

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23 %, 47 %, and 75 % and C_{max} by approximately 4 %, 23 %, and 48 %, respectively, compared to subjects with normal hepatic function. Based on pharmacokinetics, dosage adjustment may be necessary in patients with severe hepatic impairment.

Body mass index (BMI):

No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. In this analysis, AUC was estimated to be 5,82 %, 10,4 %, and 17,3 % lower in subjects with BMI of 30, 35 and 45 kg/m2, respectively, compared to subjects with a body mass index of 25 kg/m^2.

Gender:

No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race:

In the population pharmacokinetic analysis, AUC was estimated to be 13,5 % higher in Asians with a body mass index of 25 kg/m^2 compared to non-Asians with a body mass index of 25 kg/m^2.

Elderly patients:

Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Paediatric patients:

Studies characterising the pharmacokinetics of empagliflozin in paediatric patients have not been performed.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose anhydrous

Croscarmellose sodium

Hydroxypropyl cellulose

Isopropyl alcohol

Colloidal silicon dioxide

Magnesium stearate.

Film coating:

Opadry Yellow consisting of:

Hypromellose (E464)

Titanium dioxide (E171)

Propylene glycol (E1520)

Talc (E553b)

Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original packaging until required for use.

6.5 Nature and contents of container

Silver aluminium/PVC/PVdC blister strips containing 10 tablets each and placed in an outer carton. Pack sizes: 10 or 30 tablets.

White opaque, 40 cc high-density polyethylene (HDPE) bottle with 33 mm child-resistant closure. Pack sizes: 30 or 90 tablets.

Not all strengths and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block C, Woodmead North Office Park,

54 Maxwell Drive,

Woodmead,

Sandton,

Gauteng,

2191

8. REGISTRATION NUMBER(S)

INGLYFLO 10: 56/21.2/0284

INGLYFLO 25: 56/21.2/0285

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 May 2024

10. DATE OF REVISION OF TEXT

17 February 2026