1. *NAME OF DRUG PRODUCT*

Empiget (Empagliflozin) Tablets 25mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Empagliflozin..... 25mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream colored, oval shaped, biconvex film-coated tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

EMPIGET (Empagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus as:

Monotherapy
When diet and exercise alone do not provide adequate glycemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy
In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycemic control.

4.2 Posology and Method of Administration

Monotherapy and add-on combination
The recommended starting dose is 10mg empagliflozin once daily with or without food for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. In patients tolerating empagliflozin 10mg once daily who have an eGFR ≥60 ml/min/1.73 m^2 and need tighter glycemic control, the dose can be increased to 25mg once daily. The maximum daily dose is 25mg. When empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycemia.

Special populations

Renal impairment

No dose adjustment is required for patients with an eGFR ≥60 ml/min/1.73 m^2 or CrCl ≥60 ml/min. Empagliflozin should not be initiated in patients with an eGFR <60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60ml/min/1.73 m^2 or CrCl below 60ml/min, the dose of empagliflozin should be adjusted to or maintained at 10mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45ml/min/1.73 m^2 or CrCl persistently below 45ml/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.

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population.

Elderly
No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account. In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.

Pediatric population
The safety and efficacy of empagliflozin in children and adolescents has not yet been established.

4.4 Contraindications

Empagliflozin is contraindicated in:

- Patients with known hypersensitivity to empagliflozin or to any excipient of the product.
- Severe renal impairment, end-stage renal disease, or dialysis.

4.5 Special warnings and special precautions for use

- Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.
- Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairement.
- Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulphonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin.

- Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.
- Empagliflozin increases the risk for urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including empagliflozin. Monitor and treat as appropriate. Discontinuation of empagliflozin may be considered in cases of recurrent urinary tract infections.
- Empagliflozin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (DKA). In patients where 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. In both cases, treatment with empagliflozin may be restarted once the patient's condition has stabilised.
- Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. 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.
- Empagliflozin has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines, in particular when empagliflozin is used in combination with a sulphonylurea and/or insulin.

4.6 Interaction with other medicaments

- Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.
- Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin.
- Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
- Monitoring glycemic control with 1, 5-AG assay is not recommended as measurements of 1, 5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

4.7 Pregnancy and Lactation

Pregnancy

There are no adequate and well-controlled studies of empagliflozin in pregnant women. Empagliflozin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known if empagliflozin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from empagliflozin, a decision should be made whether to discontinue nursing or to discontinue empagliflozin, taking into account the importance of the drug to the mother.

4.8 Effects on ability to drive and use machine

Empagliflozin 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, in particular when Empagliflozin is used in combination with a sulphonylurea and/or insulin.

4.9 Undesirable effects

Very Common

Hypoglycemia (when used with sulphonylurea or insulin).

Common

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection, pruritus (generalised) and increased urination.

Uncommon

Volume depletion, dysuria and blood creatinine increased / glomerular filtration rate decreased.

Rare

Diabetic ketoacidosis.

Overdosage

Symptoms

Multiple daily doses of up to 100mg empagliflozin (equivalent to 4 times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume.

Treatment

In the event of an overdose with empagliflozin, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and

institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose and thereby increases urinary glucose excretion.

5.2 Pharmacokinetic properties

Absorption

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 1870nmol.h and 259nmol/L with empagliflozin 10mg and 4740nmol.h and 687nmol/L with empagliflozin 25mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. Administration of empagliflozin 25mg 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.

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, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Metabolism

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 drug-related material. The primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho- glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6L/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 [^{14}C]-empagliflozin solution, approximately 96% of the drug-related radioactivity was eliminated in feces (41%) or urine (54%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Special Population

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. 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 drug exposure.

Hepatic Impairment

In 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.

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.

Geriatric patients

Empagliflozin is expected to have diminished efficacy in elderly patients with renal impairment. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10mg, and empagliflozin 25mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% respectively.

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.

In long term toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of empagliflozin. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on

the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Empagliflozin is not genotoxic.

In a 2 year carcinogenicity study, empagliflozin did not increase the incidence of tumours in female rats up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72- times the maximal clinical AUC exposure to empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26-times the maximal clinical exposure to empagliflozin. Interstitial cell tumours in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to approximately 18-times the maximal clinical exposure to empagliflozin. Both tumours are common in rats and are unlikely to be relevant to humans.

Empagliflozin did not increase the incidence of tumours in female mice at doses up to 1000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to empagliflozin. The mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumours are considered not relevant to humans.

At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit.

In pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear.

In a juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug-free recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Pharmatose DCL-11, Lactose Monohydrate, Microcrystalline Cellulose (Avicel PH-102), Colloidal Anhydrous Silica (Aerosil 200), Klucel EXF Pharm (HPC), Croscarmellose Sodium, Magnesium Stearate, Pharmacoat 606 (HPMC 6 CPS), Macrogols (P.E.G 6000), Titanium dioxide, Ferric Oxide Yellow, Purified Talc and Purified Water.

6.2 Incompatibilities

None

6.3 Shelf-life

2 Years
The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

Do not store above 30°C
Protect from sunlight and moisture.

6.5 Nature and contents of container

Empiget (Empagliflozin) Tablets 25mg are available in Alu-Alu blister packs of 2 X 7 (14's) tablets in a unit carton along with a package insert.

6.6 Instructions for use/handling

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

7. MARKETING AUTHORISATION HOLDER

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

8. PRODUCT REGISTRATION NUMBER

006197-EX

9. DATE OF PRODUCT REGISTRATION ISSUED

March 15, 2017

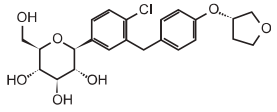
295mm

Empiget™

[Empagliflozin]

10mg, 25mg Film-coated Tablets

DESCRIPTION
Empiget (Empagliflozin) tablets contain empagliflozin, an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2). The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C- [4-chloro-3-[[4-[(3S)-tetrahydro- 3furanyl]oxy]phenyl] methyl]phenyl]-, (1S). Its molecular formula is $C_{23}H_{27}ClO_7$ and the structural formula is:



Empagliflozin

QUALITATIVE AND QUANTITATIVE COMPOSITION
Empiget (Empagliflozin) is available for oral combination as:

Empiget Film-coated Tablets 10mg
Each film-coated tablet contains:
Empagliflozin...10mg
Each Tablet contains Lactose monohydrate equivalent to 41.04mg lactose anhydrous.
Excipients...qs

Empiget Film-coated Tablets 25mg
Each film-coated tablet contains:
Empagliflozin...25mg
Each Tablet contains Lactose monohydrate equivalent to 102.06mg lactose anhydrous.
Excipients...qs

Empiget Tablets 10mg is available as Cream colored, round shaped, biconvex film coated tablet engraved "GP" on one side and plain from other side.

Empiget Tablets 25mg is available as Cream colored, oval shaped, biconvex film coated tablet plain on both sides.

CLINICAL PHARMACOLOGY
Mechanism of Action
Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose and thereby increases urinary glucose excretion.

Pharmacokinetics
Absorption
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 1870nmol.h and 259nmol/L with empagliflozin 10mg and 4740nmol.h and 687nmol/L with empagliflozin 25mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. Administration of empagliflozin 25mg 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.

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, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Metabolism
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 drug-related material. The primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6L/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 [^{14}C]-empagliflozin solution, approximately 96% of the drug-related radioactivity was eliminated in feces (41%) or urine (54%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Special Population
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. 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 drug exposure.

Hepatic Impairment
In 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.

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.

Geriatric patients
Empagliflozin is expected to have diminished efficacy in elderly patients with renal impairment. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10mg, and empagliflozin 25mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% respectively.

THERAPEUTIC INDICATIONS
Empiget (Empagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus as:

Monotherapy
When diet and exercise alone do not provide adequate glycemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy
In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycemic control.

DOSAGE & ADMINISTRATION
Monotherapy and add-on combination therapy

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population.

Elderly
No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account. In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.

Pediatric population
The safety and efficacy of empagliflozin in children and adolescents has not yet been established.

ADVERSE REACTIONS
Very Common
Hypoglycemia (when used with sulphonylurea or insulin).

Common
Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection, pruritus (generalised) and increased urination.

Uncommon
Volume depletion, dysuria and blood creatinine increased / glomerular filtration rate decreased.

Rare
Diabetic ketoacidosis.

CONTRAINDICATIONS
Empagliflozin is contraindicated in:
- Patients with known hypersensitivity to empagliflozin or to any excipient of the product.
- Severe renal impairment, end-stage renal disease, or dialysis.

PRECAUTIONS
- This tablets contain lactose. Patient with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.
- Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairement.
- Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulphonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin.
- Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.
- Empagliflozin increases the risk for urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including empagliflozin. Monitor and treat as appropriate. Discontinuation of empagliflozin may be considered in cases of recurrent urinary tract infections.
- Empagliflozin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (DKA). In patients where 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. In both cases, treatment with empagliflozin may be restarted once the patient's condition has stabilised.
- Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. 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.
- Empagliflozin has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycemia while driving and using machines, in particular when empagliflozin is used in combination with a sulphonylurea and/or insulin.

Pregnancy
There are no adequate and well-controlled studies of empagliflozin in pregnant women. Empagliflozin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known if empagliflozin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from empagliflozin, a decision should be made whether to discontinue nursing or to discontinue empagliflozin, taking into account the importance of the drug to the mother.

DRUG INTERACTIONS
- Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion. Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.
- Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as it increases urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
- Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

OVERDOSAGE
Symptoms
Multiple daily doses of up to 100mg empagliflozin (equivalent to 4 times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume.

Treatment
In the event of an overdose with empagliflozin, employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

HOW SUPPLIED
Empiget (Empagliflozin) Film-coated Tablets 10mg are available in pack of 14's, 28's and 30's.
Empiget (Empagliflozin) Film-coated Tablets 25mg are available in pack of 14's, 28's and 30's.

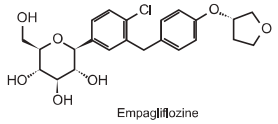
Keep out of reach of children

Empiget™

[Empagliflozine]

10mg, 25mg Comprimés Pelliculés

LA DESCRIPTION
Les comprimés Empiget (Empagliflozine) contiennent de l'empagliflozine, un inhibiteur actif par voie orale du co-transporteur sodium-glucose 2 (SGLT2). Le nom chimique de l'empagliflozine est D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)- tetrahydro-3furanyl] oxy]phényl]méthyl]phényl]-, (1S). Sa formule moléculaire est $C_{23}H_{27}ClO_7$ da formule moléculaire est:



Empagliflozine

COMPOSITION QUALITATIVE ET QUANTITATIVE
Empiget (Empagliflozine) est disponible sous forme de comprimés oraux:

Empiget Comprimés Pelliculés 10mg
Chaque comprimé pelliculé contient:
Empagliflozine...10mg
Chaque comprimé contient du lactose monohydraté équivalent à 41,04 mg de lactose anhydre.

Empiget Comprimés Pelliculés 25mg
Chaque comprimé pelliculé contient:
Empagliflozine...25mg
Chaque comprimé contient du lactose monohydraté équivalent à 102,06 mg de lactose anhydre.

Empiget Tablets 10mg se vend sous forme de comprimés pelliculés de couleur crème, de forme ronde et biconvexe, gravés "GP" sur une côte et non gravés sur l'autre.

Empiget Tablets 25mg se vend sous la forme d'un comprimé pelliculé biconvexe de couleur crème, de forme ovale, non gravés des deux côtés.

PHARMACOLOGIE CLINIQUE
Mécanisme d'action
Le co-transporteur sodium-glucose 2 (SGLT2) est le transporteur prédominant responsable de la réabsorption du glucose du filtrat glomérulaire dans la sang. Empagliflozine est un inhibiteur du SGLT2. En inhibant le SGLT2, Empagliflozine réduit la réabsorption rénale du glucose filtré et diminue le seuil rénal pour le glucose, augmentant ainsi l'excrétion urinaire du glucose.

Pharmacocinétique
Absorption
Après administration orale, l'empagliflozine a été rapidement absorbée et les concentrations plasmatiques maximales ont été atteintes avec un t_{max} médian de 1,5 heure après l'administration. Par la suite, les concentrations plasmatiques ont diminué de manière biphasique, avec une phase de distribution rapide et une phase finale relativement lente. L'ASC et la C_{max} plasmatiques moyennes à l'état d'équilibre étaient de 1870nmol.h et 259nmol/L avec l'empagliflozine 10mg et de 4740nmol.h et 259nmol/L avec l'empagliflozine 10mg, 4740nmol.h et 687nmol/L avec l'empagliflozine 25mg une fois par jour. L'exposition systémique à l'empagliflozine a augmenté de manière proportionnelle à la dose. L'administration d'empagliflozine 25 mg après un repas riche en graisses et en calories a entraîné une augmentation de la dose légèrement plus faible ; l'ASC a diminué d'environ 16 % et la C_{max} d'environ 37 % par rapport à l'état de jeûne.

Distribution
Le volume de distribution apparent à l'état d'équilibre a été estimé à 73,8 L sur la base de l'analyse pharmacocinétique de la population. Après administration d'une solution orale d'[^{14}C]-empagliflozine, la répartition dans les globules rouges était d'environ 37 % et la liaison aux protéines plasmatiques était de 86 %.

Métabolisme
Aucun métabolite majeur de l'empagliflozine n'a été détecté dans le plasma humain et les métabolites les plus abondants étaient trois glucuronides conjugués (2-, 3- et 6-O glucuronide). L'exposition systémique de chaque métabolite représentait moins de 10 % de l'ensemble des substances associées au médicament. La principale voie de métabolisation de l'empagliflozine chez les humains est la glucuronidation par les uridines 5'-diphospho-glucuronosyltransférases UGT2B7, UGT1A3, UGT1A8 et UGT1A9.

Excrétion
La demi-vie d'élimination terminale apparente de l'empagliflozine a été estimée à 12,4 heures et la clairance orale apparente était de 10,6 L/heure. Les variabilités inter-sujets et résiduelles pour la clairance orale de l'empagliflozine étaient respectivement de 39,1 % et 35,8 %. Lors de l'administration d'une dose quotidienne unique, les concentrations plasmatiques d'empagliflozine à l'état d'équilibre ont été atteintes dès la cinquième dose. Conformément à la demi-vie, jusqu'à 22 %, par rapport à l'ASC plasmatique, a été observée à l'état d'équilibre. Après administration d'une solution orale d'[^{14}C]-empagliflozine, environ 96 % de la radioactivité liée au médicament a été éliminée dans les fèces (41 %) ou dans l'urine (54 %). La majorité de la radioactivité liée au médicament retrouvée dans les fèces était du médicament mère inchangé et environ la moitié de la radioactivité liée au médicament excrétée dans l'urine était du médicament source inchangé.

Population spéciale
Insuffisance rénale
Chez les patients présentant une insuffisance rénale moyenne, légère ou sévère (DFGe <30 - <90 ml/min/1,73 m²) et chez les patients présentant une insuffisance rénale ou une maladie rénale terminale, l'ASC de l'empagliflozine a augmenté d'environ 18 %, 20 %, 66 % et 48 %, respectivement. Les niveaux de pic plasmatique de l'empagliflozine étaient similaires chez les sujets présentant une insuffisance rénale modérée et une insuffisance rénale/RSU par rapport aux patients présentant une fonction rénale normale. Les niveaux plasmatiques maximaux d'empagliflozine étaient environ 20 % plus élevés chez les sujets atteints d'insuffisance rénale légère et sévère que chez les sujets ayant une fonction rénale normale. L'analyse pharmacocinétique de population a montré que la clairance orale apparente de l'empagliflozine diminuait avec la baisse du DFGe, entraînant une augmentation de la dose d'empagliflozine.

Insuffisance hépatique
En cas d'insuffisance hépatique légère, modérée et sévère selon la classification de Child-Pugh, l'ASC de l'Empagliflozine a augmenté d'environ 23 %, 47 % et 75 % et la C_{max} d'environ 4 %, 23 % et 48 %, respectivement.

Race
Dans l'analyse pharmacocinétique de la population, on a estimé que l'ASC était 13,5 % plus élevée chez les Asiatiques ayant un indice de masse corporelle de 25 kg/m² que chez les non-asiatiques ayant un indice de masse corporelle de 25 kg/m².

Patients âgés
L'efficacité de l'Empagliflozine devrait être réduite chez les patients âgés souffrant d'insuffisance rénale. Le risque d'effets indésirables liés à la réduction du volume sanguin a augmenté chez les patients âgés de 75 ans et plus de 2,1 %, 2,3 % et 4,4 % pour le placebo, l'Empagliflozine 10 mg et l'Empagliflozine 25 mg. Le risque d'infections urinaires a augmenté chez les patients âgés de 75 ans et plus, atteignant respectivement 10,5 %, 15,7 % et 15,1 %.

INDICATIONS THÉRAPEUTIQUES
Empiget (Empagliflozine) est recommendé comme adjuvant au régime alimentaire et à l'exercice physique pour améliorer le contrôle de la glycémie chez les adultes atteints de diabète sucré de type 2:

Monothérapie
Lorsque le régime alimentaire et l'exercice physique ne suffisent pas à assurer un contrôle glycémique adéquat chez les patients pour lesquels l'utilisation de la metformine est considérée comme inappropriée en raison d'une intolérance.

Traitement combiné additionnel
En association avec d'autres médicaments hypoglycémiants, y compris l'insuline, lorsque ceux-ci, associés à un régime alimentaire et à de l'exercice physique, ne permettent pas un contrôle adéquat de la glycémie.

DOSAGE ET ADMINISTRATION
Monothérapie et thérapie combinée complémentaire

Insuffisance hépatique
Aucun ajustement du dosage n'est nécessaire chez les patients qui souffrent d'insuffisance hépatique. L'exposition d'empagliflozine accroît chez les patients présentant une insuffisance hépatique sévère. L'expérience thérapeutique chez les patients atteints d'insuffisance hépatique sévère est limitée et son utilisation n'est donc pas recommandée dans le cas de cette catégorie.
Âgé
Aucun ajustement du dosage n'est recommandé en fonction de l'âge. Chez les patients de 75 ans et plus, un risque accru de déplétion volémique doit être pris en compte. Chez les patients âgés de 85 ans et plus, le début du traitement avec 'empagliflozine n'est pas recommandé en raison de l'expérience thérapeutique limitée.
Catégorie pédiatrique
La sécurité et l'efficacité de l'empagliflozine chez les enfants et les adolescents n'ont pas encore été établies à travers les testes.

EFFETS INDÉSIRABLES
Très fréquents
Hypoglycémie (lorsqu'il est utilisé ensemble avec une sulfonylurée ou de l'insuline).

Fréquent
Candidose vaginale, vulvovaginite, balanite et autres infections génitales, infection des voies urinaires, prurit (généralisé) et augmentation de la miction.

Peu fréquent
Déplétion volémique, dysurie et augmentation de la créatinine sanguine / diminution du débit de filtration glomérulaire.

Rare
Acidocétose diabétique.

CONTRE-INDICATIONS
L'empagliflozine est contre-indiquée dans les cas suivants:
- Patients présentant une hypersensibilité connue à l'empagliflozine ou à l'un des ingrédients du produit.
- Insuffisance rénale sévère, insuffisance rénale terminale ou dialyse.

PRÉCAUTIONS
- Ces comprimés contiennent du lactose. Les patients présentant des problèmes héréditaires très rares d'intolérance au galactose, de déficit total en lactase ou de malabsorption du glucose et du galactose ne doivent pas prendre ce médicament.
- Empagliflozine provoque une contraction du volume intravasculaire. Une hypotension symptomatique peut survenir après administration de l'empagliflozine, en particulier chez les patients souffrant d'insuffisance rénale, les personnes âgées, les patients ayant une pression artérielle systolique réduite et les patients sous diurétiques.
- Empagliflozine augmente la créatinine sérique et diminue le DFGe. Le risque d'altération de la fonction rénale dans le cas de traitement avec Empagliflozine est accru chez les patients âgés et les patients présentant une insuffisance rénale modérée.
- L'insuline et les sécrétagogues de l'insuline sont connus pour provoquer des hypoglycémies. Le risque d'hypoglycémie est accru lorsque l'empagliflozine est utilisée en association avec des sécrétagogues de l'insuline (par exemple, une sulfonylurée) ou de l'insuline. Par conséquent, une dose plus réduite du sécrétagogue de l'insuline ou de l'insuline peut être nécessaire pour réduire le risque d'hypoglycémie en cas d'association avec l'Empagliflozine.
- Empagliflozine augmente le risque d'infections mycosiques génitales. Les patients ayant des antécédents d'infections mycosiques génitales chroniques ou récurrentes étaient plus susceptibles de développer des infections génitales mycosiques. Surveillez et traitez comme il convient.
- Empagliflozine augmente le risque d'infections des voies urinaires, y compris l'urosepsis et la pyélonéphrite nécessitant une hospitalisation chez les patients recevant des inhibiteurs du SGLT2, y compris l'empagliflozine. Surveiller et traiter comme il convient. Une interruption de l'empagliflozine peut être envisagée en cas d'infections urinaires récurrentes.
- Empagliflozine ne doit pas être utilisé chez les patients atteints de diabète de type 1 ou pour le traitement de l'acidocétose diabétique (ACD). Chez les patients chez qui une ACD est suspectée ou diagnostiquée, le traitement avec Empagliflozine doit être immédiatement interrompu. Le traitement doit être interrompu chez les patients hospitalisés pour des interventions chirurgicales majeures ou des maladies graves aiguës. Dans les deux cas, le traitement avec Empagliflozine peut être repris une fois que l'état du patient s'est stabilisé.
- Selon le mode d'action des inhibiteurs du SGLT2, la diurèse osmotique accompagnant la glucosurie thérapeutique peut entraîner une baisse modérée de la pression artérielle. Par conséquent, il convient de faire preuve de prudence chez les patients pour lesquels une baisse de la pression artérielle induite par l'Empagliflozine pourrait présenter un risque, tels que les patients présentant une maladie cardiovasculaire connue, les patients sous traitement antihypertenseur ayant des antécédents d'hypotension ou les patients âgés de 75 ans et plus.
- Empagliflozine a une influence mineure sur l'aptitude à conduire et à utiliser des machines. Il convient de conseiller aux patients de prendre des précautions pour éviter l'hypoglycémie lorsqu'ils conduisent ou utilisent des machines, en particulier lorsque l'Empagliflozine est utilisée en association avec une sulfonylurée et/ou de l'insuline.

Grossesse
Il n'y a pas d'études adéquates et bien testées concernant l'effet du traitement avec Empagliflozine chez les femmes enceintes. Empagliflozine ne doit être utilisée pendant la grossesse que si le bénéfice potentiel justifie le risque potentiel pour le fœtus.

Mère nourricière
On ne sait pas si Empagliflozine est sécrétée dans le lait maternel. Étant donné que de nombreux médicaments sont sécrétés dans le lait maternel et que Empagliflozine peut entraîner des effets indésirables graves chez les nourrissons, il convient de décider d'interrompre l'allaitement ou d'arrêter le traitement avec Empagliflozine, en tenant compte de l'importance du médicament pour la mère.

INTERACTIONS MÉDICAMENTEUSES
- L'administration conjointe d'Empagliflozine et de diurétiques a entraîné une augmentation du volume d'urine et de la fréquence des mictions, ce qui pourrait accroître le risque de déplétion volumique. Empagliflozine peut renforcer l'effet diurétique des diurétiques thiazidiques et des diurétiques de l'anse et augmenter le risque de déshydratation et d'hypotension.

- La surveillance de l'équilibre glycémique par des tests de glycémie urinaire n'est pas recommandée chez les patients prenant des inhibiteurs du SGLT2, car ils augmentent l'excrétion urinaire du glucose et conduisent à des tests de glycémie urinaire positifs. Utilisez d'autres méthodes pour surveiller l'équilibre glycémique.

- La surveillance du contrôle glycémique par le dosage du 1,5-AG n'est pas recommandée car les mesures du 1,5-AG ne sont pas fiables pour évaluer le contrôle glycémique chez les patients prenant des inhibiteurs du SGLT2. Utilisez d'autres méthodes pour surveiller le contrôle glycémique.

SURDOSAGE
Symptômes
Des doses quotidiennes multiples allant jusqu'à 100 mg d'Empagliflozine (équivalant à 4 fois la dose quotidienne la plus élevée recommandée) chez des patients atteints de diabète de type 2 n'ont pas montré de toxicité. Empagliflozine a augmenté l'excrétion urinaire du glucose, ce qui a entraîné une augmentation du volume de l'urine.
Traitement
En cas de surdosage à l'Empagliflozine, il convient d'appliquer les mesures de soutien habituelles (par exemple, éliminer les substances non absorbées du tractus gastro-intestinal, mettre en place une surveillance clinique et instaurer un traitement de soutien) en fonction de l'état clinique du patient. L'élimination d'Empagliflozine par hémodialyse n'a pas été testée.

STOCKAGE
Ne pas conserver au-dessus de 30°C.
Protéger de la lumière solaire et de l'humidité.
La date de péremption fait référence au produit correctement stocké aux conditions requises.
Tout produit médicinal non utilisé ou déchet doit être détruit en conformité avec les réglementations locales.

COMMENT FOURNIE
Empiget (Empagliflozine) Comprimés Pelliculés 10mg sont disponibles en pack des années 14, 28 et 30.
Empiget (Empagliflozine) Comprimés Pelliculés 25mg sont disponibles en pack des années

295mm