Bosch

For Medical Professional only

# Boschempa™ Tablets
(Empagliflozin)

# بوش ایمپا ٹیبلیٹس
(ایمپاگلائی فلوزِن)

**DESCRIPTION:**
Boschempa tablets for oral use contain empagliflozin, an 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-3 furanyl]oxy] phenyl]methyl]phenyl]-, (1S). Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91.

**COMPOSITION:**
**Boschempa 10mg Tablet**
**Each film coated tablet contains :**
Empagliflozin M.S. ..... 10mg
(Product Specs.: Innovator's)

**Boschempa 25mg Tablet**
**Each film coated tablet contains :**
Empagliflozin M.S. ..... 25mg
(Product Specs.: Innovator's)

**CLINICAL PHARMACOLOGY:**
**Pharmacodynamic Properties:**
Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK03

**Mechanism of Action:**
Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2), the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions such as lowering both pre-and afterload of the heart and downregulating sympathetic activity.

**Pharmacokinetic Properties**
**Absorption:**
The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

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 a population pharmacokinetic analysis. Following administration of an oral [$^{14}$C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

**Metabolism:**
No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, 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.

**Elimination:**
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [$^{14}$C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). 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.

**SPECIFIC POPULATIONS**
**Renal Insufficiency**
In patients with type 2 diabetes mellitus with mild, moderate and severe renal impairment and patients on dialysis due to kidney failure, AUC of

empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and patients on dialysis due to kidney failure compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

**Hepatic Insufficiency**
In patients with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and Cmax increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

**Pediatrics:**
The observed pharmacokinetic and pharmacodynamic responses in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus were consistent with those found in adult.

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

**THERAPEUTIC INDICATIONS:**
Boschempa is indicated:
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.
- To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.
- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- As monotherapy when metformin is considered inappropriate due to intolerance.
- As an add-on combination therapy in addition to other medicinal products for the treatment of diabetes.

**DOSAGE AND ADMINISTRATION:**
- The recommended dose of Boschempa is 10 mg once daily in the morning, taken with or without food.
- For additional glycemic control, the dose may be increased to 25 mg in patients tolerating empagliflozin.
- Use for glycemic control is not recommended in patients with an eGFR less than 30 mL/min/1.73 $m^2$.
- Data are insufficient to provide a dosing recommendation in patients;
  - Who have type 2 diabetes and established cardiovascular disease with an eGFR less than 30 mL/min/1.73 $m^2$, or
  - Who have heart failure with an eGFR less than 20 mL/min/1.73 $m^2$
- Empagliflozin is contraindicated in patients on dialysis.

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

**Renal impairment:**
In patients with type 2 diabetes mellitus, the glycaemic efficacy of empagliflozin is dependent on renal function. For cardiovascular risk reduction as add on to standard of care, a dose of 10 mg empagliflozin once daily should be used in patients with an eGFR below 60 ml/min/1.73 $m^2$. Because the glycaemic lowering efficacy of empagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered.

**Dose adjustment recommendations:**

| Indication | eGFR [ml/min/1.73 $m^2$] or CrCL [ml/min] | Total daily dose |
|---|---|---|
| Type 2 diabetes mellitus | ≥60 | Initiate with 10 mg empagliflozin.<br>In patients tolerating 10 mg empagliflozin and requiring additional glycaemic control, the dose can be increased to 25 mg empagliflozin. |
| | 45 to <60 | Initiate with 10 mg empagliflozin.<br>Continue with 10 mg empagliflozin in patients already taking Boschempa. |
| | 30 to <45[a] | Initiate with 10 mg empagliflozin.<br>Continue with 10 mg empagliflozin in patients already taking Boschempa. |
| | <30 | Empagliflozin is not recommended. |
| Heart failure (with or without type 2 diabetes mellitus) | ≥20 | Recommended daily dose is 10 mg empagliflozin. |
| | <20 | Empagliflozin is not recommended. |

For treatment of heart failure in patients with or without type 2 diabetes mellitus, empagliflozin 10 mg may be initiated or continued down to an eGFR of 20 ml/min/1.73 $m^2$ or CrCl of 20 ml/min. Empagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis.

**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.

**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.

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

**CONTRAINDICATIONS:**
Hypersensitivity to empagliflozin or any of the excipients and patients on dialysis.

**WARNINGS AND PRECAUTIONS:**
**Ketoacidosis**
Rare cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes mellitus treated with 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/dl). It is not known if ketoacidosis is more likely to occur with higher doses of empagliflozin.

The risk of 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 ketoacidosis 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 patient's condition 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 ketoacidosis 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 ketoacidosis while on SGLT-2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved. Boschempa should not be used for treatment of patients with type 1 diabetes.

**Renal impairment**
For the indication of type 2 diabetes mellitus, in patients with an eGFR below 60 ml/min/1.73 $m^2$ or CrCl <60 ml/min the daily dose of empagliflozin is limited to 10 mg. Empagliflozin is not recommended when eGFR is below 30 ml/min/1.73 $m^2$ or CrCl below 30 ml/min.

For the indication of heart failure, Boschempa is not recommended in patients with eGFR <20 ml/min/1.73 $m^2$. Empagliflozin should not be used in patients with ESRD or in patients on dialysis.

**Assessment of renal function is recommended as follows:**
- Prior to empagliflozin initiation and periodically during treatment, i.e. at least yearly.
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

**Risk for volume depletion**
Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying 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.

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**
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. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products 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.

**Complicated urinary tract infections**
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)**
Cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients with diabetes mellitus 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 uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Boschempa should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

**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.

**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**
Haematocrit increase was observed with empagliflozin treatment

**Chronic kidney disease**
There is experience with empagliflozin for the treatment of diabetes in patients with chronic kidney disease (eGFR ≥30 mL/min/1.73 $m^2$) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin.

**Urine laboratory assessments**
Due to its mechanism of action, patients taking Boschempa will test positive for glucose in their urine.

**Lactose**
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

**DRUG INTERACTIONS:**

**Diuretics**

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**

Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin.

**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.

**ADVERSE EFFECTS:**

**Very Common:**

Hypoglycaemia (when used with sulphonylurea or insulin), volume depletion.

**Common:**

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection, urinary tract infection (including pyelonephritis and urosepsis), thirst, constipation, pruritus (generalised), rash, increased urination, serum lipids increased.

**Uncommon:**

Urticaria, angioedema, dysuria, blood creatinine increased/ glomerular filtration rate decreased, haematocrit increased.

**Rare:**

Necrotising fasciitis of the perineum (fournier's gangrene), diabetic ketoacidosis.

**USE IN 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.

**Lactation:**

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.

**OVERDOSE:**

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.

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.

**SHELF LIFE**

2 years

**INSTRUCTIONS:**

Protect from heat, sunlight and moisture, Store between 15°C - 30°C.

The expiration date refers to the product correctly stored at the required conditions.

Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.

To be sold on prescription of a registered medical practitioner only.

"Product Contains Lactose"

**PRESENTATION:**

**Boschempa 10mg tablets:**

Each Cold Form & Cold Seal pack contains 14's tablets.

**Boschempa 25mg tablets:**

Each Cold Form & Cold Seal pack contains 14's tablets.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

**ہدایات :**

دھوپ، گرمی اور نمی سے محفوظ ۱۵۔۳۰ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان میں رکھیں۔

بچوں کی پہنچ سے دُور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔

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ISO 9001:2015 Certified Company