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Review

A complete review of empagliflozin: Most specific and potent SGLT2 inhibitor used for the treatment of type 2 diabetes mellitus

Gita Chawla*, Krishna Kr Chaudhary

Department of Pharmaceutical Chemistry, School of Pharmaceutical Education and Research, Jamia Hamdard (Deemed to be University), Hamdard Nagar, New Delhi, 110 062, India

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the latest class of drugs to be introduced for the treatment of type 2 diabetes mellitus (T2DM). They reduce hyperglycemia by increasing urinary glucose excretion and exert favorable effects beyond glucose control with consistent body weight, blood pressure, and serum uric acid reductions.

Empagliflozin is a potent SGLT2 inhibitor used to improve glycemic control in adults with T2DM. It has the highest SGLT2 specificity among all the clinically used or currently tested SGLT2 inhibitors. Low risk of hypoglycemia, absence of weight gain and demonstrated cardiovascular risk reduction support its consideration as a first line medication in addition to metformin for patients with T2DM and cardiovascular disease. Mostly reported adverse events are genital mycotic infections, while urinary tract infections and events linked to volume depletion are rather rare. This review covers the complete information on empagliflozin including the history of its development, synthesis, pharmacology and different methods which have been reported for its analysis.

1. Introduction

Type 2 diabetes mellitus (T2DM) has become a global pandemic. The age-standardized prevalence of diabetes in adults has increased in most countries since 1980 and along with population growth and ageing, this has led to a near quadrupling of the number of adults with diabetes worldwide [1]. It is now estimated that nearly 387 million people have diabetes globally. Numbers in developing countries are increasing due to the changes in rates of obesity and inactivity. Deaths from diabetes are projected to increase 50% worldwide by 2025. Eighty percent of these deaths will occur in low and middle income countries. T2DM is a complex and progressive disease. Once thought of as only a disease of insulin resistance, it is now believed that there are at least eight pathologic processes that lead to type 2 diabetes. These include abnormal β-cell insulin secretion, excessive α-cell glucagon production, abnormal incretin effect, insulin resistance at the peripheral tissues, increased hepatic glucose production, increased lipolysis, neurotransmitter dysfunction, and abnormal renal handling of hyperglycemia [2,3]. Hypertension, which is strongly associated with the presence of albuminuria, is an important predictor of both cardiovascular and renal events in patients with T2DM [4].

Age is another important factor influencing the burden of diabetic nephropathy. Recent analyses have shown that the prevalence of diabetic kidney disease and of end stage renal disease (ESRD) is consistently highest in older patients [5]. A recent analysis highlighted the strong link between T2DM and chronic kidney disease (CKD) with age. With 43.5% of adult patients with T2DM are identified as having CKD, and prevalence increasing to 61.0% in those aged 65 years or older [6].

In patients with type 2 diabetes, higher levels of hyperglycemia are associated with increasing risk of vascular events. Each 1% increase in glycosylated hemoglobin (HbA1c) is associated with as much as 38% increased risk of mortality [7].

Elevated hemoglobin A1c (HbA1c) values correlate with microvascular and macrovascular complications. Thus, patients with T2DM are at an increased risk of developing macrovascular events. Macrovascular complications and mortality are best clinical trial endpoints for evaluating the efficacy of antidiabetic drugs.

* Corresponding author.
E-mail address: gchawla@jamiahamdard.ac.in (G. Chawla).

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Although more than nine different classes of oral pharmacological agents and a variety of insulin and noninsulin injection products are available for the treatment of T2D, 50% of patients still fail to meet recommended goals for diabetes care [8,9].

The maintenance of normal glucose homeostasis requires a complex, highly integrated interaction among the liver, muscle, adipocytes, pancreas and neuroendocrine system. Recent studies have showed that the kidneys also play a central role in glucose homeostasis by reabsorbing all the filtered glucose, an adaptive mechanism that ensures sufficient energy is available during fasting periods [10]. This mechanism becomes maladaptive in diabetes. Hyperglycemia augments the expression and activity of the sodium–glucose cotransporter (SGLT2) in the proximal tubule of the kidney. As a result, glucose reabsorption may be increased by as much as 20% in individuals with poorly controlled diabetes. SGLT2 is a low-affinity, high-capacity glucose transport protein that reabsorbs 90% of filtered glucose, while the high-affinity, low-capacity SGLT1 transporter reabsorbs the remaining 10%. SGLT2 represents a novel target for the treatment of diabetes. In animal studies, SGLT2 inhibition reduces plasma glucose levels, resulting in improved β-cell function and enhanced insulin sensitivity in liver and muscle. Human studies have confirmed the efficacy of SLGT2 inhibitors in improving glucose control and reducing the A1c. Since, the mechanism of SGLT2 inhibition is independent of circulating insulin levels or insulin sensitivity, these agents can be combined with all other antidiabetic classes, including exogenous insulin. Although the long-term efficacy and safety of SGLT2 inhibitors remain under study, the class represents a novel therapeutic approach with potential for the treatment of both type 2 and 1 diabetes. The first antidiabetic drug that demonstrated a reduction in mortality in the treatment of T2DM was empagliflozin which is a SGLT2 inhibitor [11].

There are currently three SGLT2 inhibitors available in the US. Canagliflozin was approved by the US Food and Drug Administration (FDA) in March 2013 (FDA news release 2013), dapagliflozin in January 2014, and empagliflozin in August 2014 [12].

All of these agents are potent competitive inhibitors of the SGLT2 protein, but dapagliflozin and empagliflozin are highly selective for SGLT2, while canagliflozin has dual blockade of SGLT1 and SGLT2. Of the three commercially available SGLT2 inhibitors, empagliflozin has the highest selectivity for SGLT2 (2500-fold) compared to SGLT1 [13].

Three additional drugs within this class are available in Japan (ipragliflozin, luseogliflozin, and tofogliflozin) and at least two are under current investigation (ertugliflozin, remogliflozin). Ertugliflozin was approved in the United States under the brand name Steglatro in December 2017 [14]. Remogliflozin etabonate discontinued in clinical trials [15]. Sergliflozin etabonate discontinued after Phase II trials [15]. A combined SGLT1 and 2 inhibitor, sotagliflozin, was also in clinical trials [16]. Sotagliflozin is a dual SGLT1/SGLT2 inhibitor in phase III trials till March 2019 under the brand name Zynquista. It was developed by Lexicon pharmaceuticals and was reported that if approved, sotagliflozin would be the first oral treatment in combination with insulin to treat type 1 diabetes mellitus [17]. The FDA in March 2019 issued a complete response letter regarding a new drug application for oral sotagliflozin, a first-in-class dual SGLT1 and SGLT2 inhibitor for adult with type 1 diabetes, according a press release from Sanofi and Lexicon.

Empagliflozin is a selective inhibitor of SGLT2, producing dose-dependent urinary glucose excretion increase in healthy volunteers, with up to 90 g of glucose excreted per day. It can be administered orally, and studies of people with renal or hepatic impairment indicated empagliflozin needed no dose adjustment based on pharmacokinetics. In Phase II trials in patients with type 2 diabetes, empagliflozin provided improvements in glycosylated hemoglobin (HbA1c) and other measures of glycemic control when given as monotherapy or add-on to metformin. It also causes reductions in weight and systolic blood pressure. As add-on to basal insulin, empagliflozin not only improved HbA1c levels but also reduced insulin doses. Phase III studies have also reported a good safety profile along with significant improvements in HbA1c, weight and blood pressure, with no increased risk of hypoglycemia versus placebo. Empagliflozin has shown a good efficacy and safety profile from clinical trials when given as monotherapy, and as an add-on therapy to other glucose-lowering agents [18].

In obese, difficult-to-treat patients with T2DM inadequately controlled on high Multiple Dose Insulin (MDI) doses, empagliflozin improved glycemic control and reduced weight without increasing the risk of hypoglycemia and with lower insulin requirements [19]. Clinical trials have shown that in addition to reducing HbA1c, SGLT2 inhibitors reduce body weight, systolic BP and serum uric acid, therefore have the potential to reduce cardiovascular risk in patients with T2DM [20].

Empagliflozin has the highest SGLT2 specificity among all the clinically used or currently tested SGLT2 inhibitors. Most of the pharmacological effects of SGLT2 inhibitors have the potential to reduce the development and progression of heart failure. Whether this receptor specificity or the previously mentioned CaMKII activity is truly relevant and explains the benefits seen in T2DM, future studies will tell. However, numerous reports are there to confirm that empagliflozin reduces the cardiovascular mortality and morbidityin patients with T2DM with associated cardiovascular disease and CKD. Despite diminishing glucose-lowering efficacy with declining renal function, improved clinical outcomes with empagliflozin were consistent across subgroups of patients by baseline renal function or albuminuria [21–24].

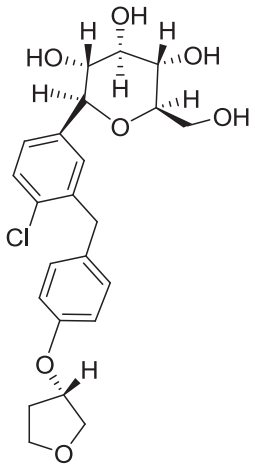
Experiments showed that empagliflozin is a potent, competitive SGLT-2 inhibitor with high selectivity over SGLT-1, 4, 5 and 6, and has potential as a treatment for type 2 diabetes. Empagliflozin showed >2500-fold selectivity for hSGLT-2 over hSGLT-1. The selectivity over SGL1 is highly desirable. SGLT-1 has an important role in normal intestinal glucose absorption, and thus its inhibition may lead to diarrhoea and severe dehydration, symptoms observed in people with inherited mutations in the SGLT-1gene. An inhibitor with high specificity for SGLT-2 over SGLT-1 may have better gastrointestinal tolerability properties than one with low specificity [25].

Considering the above facts which prove the benefits of empagliflozin over other SGLT-2 inhibitors, this review has been presented covering its complete profile including detailed chemistry and pharmacological aspects.

2. Description [26,27].

IUPAC name of empagliflozin is (2S,3R,4R,5S,6R)-2-[4-chloro-3-[[4-[(3S)-oxolan-3-yl]oxyphenyl]methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol.

Synonyms of empagliflozin are-(1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol;(1S)-1,5-Anhydro-1-C-{4-chloro-3-[(4-{[(3S)-oxolan-3-yl]oxy}phenyl)methyl]phenyl}-D-glucitol;(1S)-1,5-Anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-D-glucitol;D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]M ethyl]phenyl]-, (1S).



chemical structure of empagliflozin

Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91.

Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

3. History and development

Phlorizin was the first SGLT inhibitor discovered [28]. The molecule itself was known since 1835 and is a naturally occurring compound isolated from the bark of pear, apple, cherry, and other fruit trees [29,30].

This compound was superseded by better and more selective synthetic analogs like canagliflozin, dapagliflozin and empagliflozin. Empagliflozin, a newer SGLT2 inhibitor in current clinical use, has improved potency, longer half-life, and better oral availability compared with phlorizin [31].

On June, 2013 Boehringer Ingelihm and Eliylilly company announced the result of 52-week phase III trial investigating the addition of empigliflozin on existing oral-glucose lowering therapy in type 2 diabetes patients. The results of the study demonstrated a significant decrease in HA1c (average blood glucose) on 24 week and reduction in body weight. A systemic review and meta-analysis were done **on April 28, 2014** to detect the efficacy and safety of empagliflozin. It includes 10 studies with 6203 participants and the result showed a mean change in haemoglobin A1c (0.62% for empagliflozin 10 mg) and (0.66% for empagliflozin 25 mg). It was also associated with body weight loss and favorable effect on blood pressure.

On August 1, 2014 the FDA approved the application of new drug empagliflozin to treat type 2 diabetes, Empagliflozin is a SGLT2 inhibitor, work by increasing the amount of glucose exerted in urine, can be used by itself as an addition to diet & exercise, or with other drugs for type 2 diabetes. On December 2, 2016 FDA approved this drug to reduce cardiovascular death in adults with T2D. This approval was given after a study of post market clinical trial of more than 7000 patients with type 2 diabetes and cardiovascular disease.

The application of empagliflozin was based on the results of phase III clinical trial programme, comprised of 10 multinational clinical trials over 14,500 people with type 2 diabetes.

Empagliflozin hold promise as an important addition to other antidiabetic drugs as treatment option for type 2 diabetes [32–35].

4. Synthesis

Wang et al. [36] developed and reported a concise, robust process for the production of empagliflozin on a metric ton scale. The synthesis is based on a highly β-selective $AlCl_3$-promoted silane reduction of a methyl β-glycopyranoside. The one-stage process involves four chemical transformations starting from 5-halo-2-chlorobenzoic acids without isolation of intermediates and precise control over the purity profile of the final drug substance.

Hrapchak et al. [37] reported the synthesis of carbon-13 and carbon-14 labeled empagliflozin. They prepared carbon-13 labeled empagliflozin in five steps and in 34% overall chemical yield starting from the commercially available α-D-glucose-[13C6]. For the radiosynthesis, the carbon-14 atom was introduced in three different positions of empagliflozin. In the first synthesis, carbon-14 D-(+)-gluconic acid δ-lactone was used according to the literature to prepare carbon-14 specifically labeled empagliflozin in carbon-1 of the sugar moiety. This four step-synthesis gave the desired material in 19% overall radiochemical yield and with a specific activity of 57.5 mCi/mmol and a radiochemical purity of 99.2%. Carbon-14 labeled empagliflozin with the radioactive atom in the benzylic position was obtained in eight steps and in 7% overall radiochemical yield with a specific activity of 54.3 mCi/mmol and a radiochemical purity of 98.9%. In the last synthesis carbon-14 uniformly labeled phenol was used to give [14C] empagliflozin in eight steps and in 18% overall radiochemical yield with a specific activity of 53.4 mCi/mmol and a radiochemical purity of 98.6%. Labeled empagliflozin was indispensable in DMPK and other studies.

One more method for empagliflozin synthesis was patented in 2014 which is based on reduction [38].

5. Pharmacology

5.1. Mechanism of action

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 its renal threshold and thereby increases urinary glucose excretion.

Empagliflozin, increases urinary excretion of glucose by markedly reducing the renal tubular threshold for glycosuria. This leads to excretion of 60–100 g/day of glucose, improving glucose control with low risk of hypoglycemia, and results in loss of 240–400 kCal/day into the urine with associated weight reduction. In addition, a decrease in blood pressure is seen due to osmotic diuresis of glucose and natriuresis of co-transported sodium [39,40].

5.2. Pharmacological actions

SGLT2-inhibitos function not only as antidiabetics for normalizing blood glucose, but also have diuretic and hypotensive actions and resolve salt-sensitive hypertension, which plays an important role in diabetes. Therefore, SGLT2-inhibitos strongly prevent heart and renal failure [41,42].

The mechanism by which empagliflozin reduces BP has yet to be fully elucidated but may be related to improved glucose control, weight loss, volume contraction due to osmotic diuresis, and improved arterial stiffness. 10 and 25 mg empagliflozin oral dose were well tolerated and led to clinically meaningful improvements in systolic blood pressure and diastolic blood pressure in patients with type 2 diabetes and hypertension, in addition to significant reductions in HbA1c and body weight [43].

Empagliflozin showed remarkable reductions in cardiovascular/all-cause mortality and in hospitalization for heart failure in patients with previous cardiovascular disease. This effect was attributed to a diuretic (haemodynamic) rather than metabolic (antiatherogenic) effect. Positive renal outcomes were also shown with empagliflozin [44,45]. In the recent EMPA-REG OUTCOME trial, empagliflozin was shown to improve cardiovascular outcomes in patients with T2DM and established cardiovascular risk where it reduced Heart failure (HF) hospitalizations and cardiovascular death, with a consistent benefit among patients both with and without baseline HF [46].

Like the other SGLT2 inhibitors, empagliflozin has a low propensity to cause hypoglycemia and it is associated with some additional non-glycemic beneficial effects including lowering

BP and body weight and favorably altering body fat distribution [47]. Combination studies in animals demonstrated that beneficial metabolic effects of empagliflozin may also manifest when added to other types of anti-hyperglycemic treatments including linagliptin, pioglitazone and metformin. While some anti-hyperglycemic drugs lead to weight gain, empagliflozin treatment was associated with reduced body weight in normoglycemic obese and non-obese animals despite an increased food intake, largely due to a loss of adipose tissue; on the other hand, empagliflozin preserved body weight in models of type 1 diabetes [48].

Empagliflozin as add-on to metformin was well tolerated and provided additional benefits beyond glucose lowering, such as weight loss and reduction of blood pressure [49]. The beneficial effects of empagliflozin on blood pressure, body weight, and HDL-cholesterol may result in improved cardiovascular and metabolic health, in contrast to several other anti-hyperglycemic medications such as rosiglitazone, pioglitazone, sulfonylureas, and saxagliptin which have been associated with an increased risk for atherosclerotic CVD [50,51] and/or heart failure [52–54].

Empagliflozin/linagliptin (Glyxambi) is a once-daily fixed dose product that is approved in the USA as an adjunct to diet and exercise in adults with T2DM when treatment with both empagliflozin and linagliptin is appropriate. Glyxambi® combines 10 mg or 25 mg empagliflozin with 5 mg linagliptin, with different, complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes. Empagliflozin removes glucose through the urine by blocking blood glucose re-absorption in the kidney, and linagliptin exerts glucose-lowering activity by increasing hormones that stimulate the pancreas to produce more insulin and decreasing the levels of glucagon in the circulation. It is a dipeptidyl peptidase-4 (DPP-4) inhibitor). In addition, this combination therapy modestly reduces body weight and blood pressure without significant safety issues. Fixed-dose combination of Empagliflozin/linagliptin generally improves glycaemic control more than its individual components, when used as an initial therapy or as an add-on to metformin [55,56].

Type 2 diabetes is characterized by at least eight pathophysiological abnormalities. The combination of linagliptin plus empagliflozin improves at least five of these pathophysiological disturbances: increased incretin effect, enhanced insulin secretion, decreased glucagon secretion, suppression of the elevated rate of hepatic glucose production (HGP) and reduction of the elevated threshold for glucose spillage into the urine, leading to decreased reabsorption of glucose by the diabetic kidney. The combination of linagliptin plus empagliflozin is effective in further lowering HbA1c values beyond those observed with either monotherapy. Combination therapy with linagliptin plus empagliflozin may be especially useful in patients who are intolerant to metformin therapy or in those who are on metformin (with or without other oral agents) and who need an extra 1.0–1.5% HbA1c reduction to get to their glycemic goal [57].

5.3. Pharmacodynamics

5.3.1. Urinary glucose excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 g per day with 10 mg empagliflozin and 78 g per day with 25 mg empagliflozin once daily. Dose-proportional exposure of empagliflozin over 8 days resulted in urinary glucose excretion ranging from 77.9 g with the 10 mg dose to 89.8 g with the 100 mg dose [58].

5.3.2. Urinary volume

In a 5-day study, mean 24-h urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment [58].

5.3.3. Cardiac electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Like other SGLT2 inhibitors, empagliflozin lowers serum uric acid levels, probably through an effect on the urate transporter, solute carrier family 2 (facilitated glucose transporter), member 9 (SLC2A9), which is expressed in the proximal convoluted tubule and is involved in the renal handling of urate [59].

5.4. Pharmacokinetics

5.4.1. Absorption

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with T2DM and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 h post-dose with 78% bioavailability. 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 Cmax were 1870 nmol h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. 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.

Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and Cmax decreased 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 [60].

5.4.2. 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 [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2% [61].

5.4.3. Metabolism

In the pre-clinical species, oxidative metabolism of

empagliflozin was the primary metabolism pathway [62], but in humans empagliflozin is mainly metabolized by glucuronidation by the uridine 5′-diphospho-glucuronosyltransferase (UGT) isoforms UGT1A3, UGT1A8, UGT1A9 and UGT2B7 to three main glucuronide conjugates (2-O-, 3- O-, and 6-O-glucuronide), which are each present in human plasma at <10% of total drug related exposure and are thought to be inactive. 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. *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 [63].

5.4.4. Elimination

The mean terminal half-life ranged from 5.6 to 13.1 h in single rising dose studies, and from 10.3 to 18.8 h in multiple-dose studies [64]. 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 [14C]-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. In humans, both renal (~54%, about half as unchanged parent drug) and fecal (~41%, mostly unchanged parent drug) excretion are important elimination routes in contrast to most observations in the non-clinical species in which biliary/fecal elimination predominates [65].

5.5. Indications [39].

Empagliflozin is indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- To reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Limitations of Use: Empagliflozin is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

5.6. Dosage and administration [39,66].

5.6.1. Recommended dosage

Empagliflozin is started as 10 mg in the morning, and the dose may be increased to 25 mg if tolerated. In patients with volume depletion, correcting this condition prior to initiation of empagliflozin is recommended.

5.6.2. Patients with renal impairment

Assessment of renal function is recommended prior to initiation of empagliflozin therapy and periodically thereafter. Empagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m2. No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m2. Empagliflozin should be discontinued if eGFR is less than 45 mL/min/1.73 m.2

5.7. Side effects and contraindications [39].

The following important side effects are associated with empagliflozin:

- hypotension
- ketoacidosis
- acute kidney injury and impairment in renal function
- urosepsis and pyelonephritis
- hypoglycemia with concomitant use with insulin and insulin secretagogues
- genital mycotic infections
- increased low-density lipoprotein cholesterol (LDL-C)

The following are important contraindications:

- history of serious hypersensitivity reaction to empagliflozin.
- severe renal impairment, end-stage renal disease, or dialysis.

The polyuria resulting from extra glucose in the urine may produce dehydration with postural hypotension, especially in the elderly and patients on diuretics. This effect may be of particular concern in hot countries during the summer time [67]. Glycosuria predisposes patients to urinary and genital tract infections, especially females. At two years of treatment, SGLT2 inhibitors increased the risk of urinary tract and genital tract infections with an odds ratio of 1.477 and 4.196, respectively [68]. Cases of euglycaemic diabetic ketoacidosis have been reported with the use of SGLT2 inhbitors [69].

The most commonly reported adverse effects for empaglifozin were urinary tract infections, female genital mycotic infections, and dyslipidemia. Empagliflozin causes osmotic diuresis therefore, adverse reactions related to volume depletion were also reported (decreased systolic blood pressure, dehydration, hypotension, orthostatic hypotension, hypovolemia, and syncope). Impaired renal function and hypoglycemia were also reported [70]. Recently, there has been a growing concern over an increased risk for developing diabetic ketoacidosis related to use of SGLT2 inhibitors (including empagliflozin) in the literature and media. A recent search of the FDA Adverse Event Reporting System (FAERS) database identified 20 case of ketoacidosis in patients treated with SGLT2 inhibitors from March 2013 to June 2014 [71].

SGLT2 inhibitors are thought to increase serum phosphate concentrations with the potential to adversely affect bone metabolism [72].

SGLT2 inhibitors significantly increase the rate of genital yeast infections with a relative risk (RR) of 3.9 ($P < 0.001$) in a meta-analysis, and a modest increase in urinary tract infections (RR ¼ 1.23, P ¼ 0.02) [73]. The FDA recently released a warning regarding the risk of diabetic ketoacidosis and SGLT-2 inhibitors, and also has concerns regarding breast and bladder cancers which await further data on safety [74].

5.8. Drug interactions

5.8.1. Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion [39].

5.8.2. Insulin or insulin secretagogues

Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia [39].

5.8.3. Positive urine glucose test

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. Alternative methods to monitor glycemic control is recommended.

Coadministration of empagliflozin with sitagliptin had no clinically relevant effect on the pharmacokinetics of either drug [75] and a similar study with linagliptin also showed no clinically meaningful interaction [76].

Likewise, there was no significant pharmacokinetic interaction between empagliflozin and metformin [77], and no clinically relevant interaction with pioglitazone [78].

6. Availability [79,80].

Empagliflozin (BI 10773, Jardiance®, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) is an orally available, potent and highly selective inhibitor of the SGLT2. It was approved in the U.S. and by the European Medicines Agency (EMA) in 2014 and is available as 10 and 25 mg tablets.

It is also available as a combination product with metformin (Synjardy®) and in the U.S. as a combination with the DPP-4 inhibitor, linagliptin (Glyxambi®).

6.1. Combination products containing empagliflozin

1. Empagliflozin/linagliptin systemic

   Brand names: Glyxambi
   Drug class (es): antidiabetic combinations
   Empagliflozin/linagliptin systemic is used in the treatment of diabetes, type 2

2. Empagliflozin/metformin systemic

   Brand names: Synjardy, Synjardy XR
   Drug class (es): antidiabetic combinations
   Empagliflozin/metformin systemic is used in the treatment of diabetes, type 2

7. Analytical aspects

1. A Reverse Phase High Performance Liquid Chromatography (RP-HPLC) method was developed and validated for the determination of Empagliflozin in API. Better separation of the drug was achieved on Intersil column(150 × 40mm, 5 μm) with the mobile phase consisted of mixture of 0.01 M acetate buffer, methanol in ratio of (30:70v/v) at flow rate of 2 ml/min, with detection at 260 nm using PDA detector. The Precision was estimated by employing repeatability; intra-day and inter-day studies and the results were calculated as %RSD values. By studying validation parameters it was concluded that the method was linear, accurate, precise, robust and rapid for the determination of Empagliflozin in API. Hence the method can be successfully applied for the estimation of Empagliflozin in API [81].
2. A stability indicating RP-HPLC method for the analysis of empagliflozin in its API was developed and validated. The proposed method utilizes Hypersil BDS column. Mobile phase 0.1% OPA: Acetonitrile in the ratio of 70:30 and flow rate was maintained at 1 ml/min, detection wave length was 233 nm, and column temperature was set to 30 °C. The developed method was successfully validated for different validation parameters as per ICH guidelines. The stability of the drug was determined by studying the degradation of the drug under acidic, alkaline, peroxide, neutral, heat and UV conditions. The method was found to be linear, precise, accurate and robust. The degradation studies reveal the stability of the drug. The proposed method can be safely and successfully used for the estimation of empagliflozin API in routine analysis [82].
3. A method was developed for the estimation of empagliflozin by RP-HPLC technique. Chromatographic conditions used are stationary phase Hypersil BDS 150 mm x 4.6 mm, 5μ, Mobile phase 0.1% OPA: Acetonitrile in the ratio of 70:30 and flow rate was maintained at 1 ml/min, detection wave length was 233 nm, column temperature was set to 30 °C and diluent was mobile phase. Degradation studies of empagliflozin were done, in all conditions purity threshold was more than purity angle and within the acceptable range [83].
4. A RP-HPLC method was developed for simultaneous determination of the binary mixture of metformin (MET) and empagliflozin in dosage forms. The method uses a mobile phase consisting of phosphate buffer, acetonitrile, methanol (15:80:5 v/v/v), an octadecyl silica C-18 column (4.6 mm × 250 mm, 5 μ particle size) in isocratic mode, detection wavelength of 227 nm, and a flow rate of 1 mL/min. The method was fast, accurate, precise, and sensitive hence it can be employed for routine quality control of tablets containing both drugs in quality control laboratories and pharmaceutical industries [84].
5. A rapid RPHPLC method has been developed and validated for the determination of linagliptin and empagliflozin in tablet dosage form. Isocratic chromatography has been developed on a ODS column (250 × 4.6 mm, 5μ) with a mobile phase consists of buffer and Acetonitrile (45:50) with the flow rate of 1 ml/min with PDA detector at 245 nm. Chromatography parameters were validated as per ICH guidelines and can be applied for routine quantitative analysis of drugs in combined tablet dosage form [85].
6. The first UPLC method was developed for simultaneous determination of empagliflozin, linagliptin and metformin hydrochloride in their different combinations as pharmaceutical dosage forms. Chromatographic separation was achieved on a Symmetry Acclaim TM RSLC 120 C18 column (100 mm × 2.1 mm, 2.2 μm) applying an isocratic elution based on potassium dihydrogen phosphate buffer pH (4) - methanol (50:50, v/v) as a mobile phase. All the variables were studied to optimize the chromatographic conditions. The optimized method was validated and proved to be suitable for the quality control of the mentioned drugs in their different pharmaceutical dosage forms. The developed UPLC method can be conveniently used by quality control laboratories with the advantages of using simple mobile phase, saving time and decreased cost by using less solvent in UPLC [86].
7. Simple, sensitive and accurate UV and two visible spectrophotometric methods were developed for the analysis of empagliflozin in pharmaceutical formulations. Method M1 based on the UV absorption of drug in UV region that shows absorption maxima at 247 nm. Method M2 and M3 based on the oxidative coupling reaction of drug with 1, 10 phenanthroline and potassium ferricyanide that shows maximum absorbance at 438 nm and 782 nm for method M2 and M3 respectively. The methods were validated as per ICH guidelines. The proposed methods have been applied for the estimation of empagliflozin in tablets. The developed method was simple, accurate, reliable and economical. The proposed method is specific without and interference of excepients and hence can be used for the routine analysis of empagliflozin in bulk and in pharmaceutical formulation [87].

8. Future prospects

The combination of a dipeptidyl peptidase-4 (DPP-4) inhibitor and a SGLT2 inhibitor is attractive because their complementary modes of action contribute to improve blood glucose control in patients with T2D without deteriorating the safety/tolerance profile of each compound (on the contrary, a reduction in some adverse events may be expected). Fixed-dose combinations (FDCs) formulations combining saxagliptin plus dapagliflozin and linagliptin plus empagliflozin are already commercialized and others combinations are currently investigated for the management of T2D. Although the precise positioning of a DPP-4 inhibitor and SGLT2 inhibitor combination should be better delineated by further studies, this approach appears to be a new option for the management of patients with T2D, with a good efficacy/safety ratio but at a higher cost [88].

9. Conclusion

Empagliflozin lowers glycosylated hemoglobin as monotherapy or add-on to existing anti-hyperglycemic therapies among patients with T2DM, with consistent observations of associated weight reduction and blood pressure lowering. More recently, empagliflozin was proven superior to placebo for reduction of major adverse cardiovascular risk among patients with T2DM and established CVD. Empagliflozin has a favorable pharmacokinetic and metabolic profile so that it is suitable for once daily oral dosing and has no major drug interactions. Overall, empagliflozin represents a new and attractive oral medication for most patients with T2DM that will result in improvement of glycemic control with the additional advantages of reduction of body weight and BP. Along with the other SGLT2 inhibitors, empagliflozin is not yet approved for the treatment of type 1 diabetes, partly owing to concern for risk of diabetic ketoacidosis. Due to its mechanism of action, caution is advised among patients with renal impairment, the elderly, and those with low blood pressure or taking diuretics.

Oral once-daily empagliflozin monotherapy or add-on therapy to other antihyperglycaemics, including insulin, was an effective and well tolerated treatment in adult patients with type 2 diabetes. With its insulin-independent mechanism of action and convenient administration regimen, empagliflozin monotherapy or combination therapy with other antidiabetic drugs, including insulin, provides a useful addition to the therapeutic options for the management of type 2 diabetes.

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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