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Diabetes & its Complications

Adverse Reactions to the Use of Forxiga in Patients with Type 2 Diabetes Mellitus. Comparison with Currently Used Drugs

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ABSTRACT

Type 2 diabetes mellitus (T2DM)is a very common chronic disease, accounting for approximately 85–95% of all diabetes cases. In recent years, the incidence has increased significantly, particularly among younger individuals, which appears to be largely associated with behavioral and social factors such as low physical inactivity, obesity, and unhealthy dietary habits. T2DM is characterized by a progressive deterioration of pancreatic β-cell function and increasing insulin resistance. This condition leads to a higher risk of developing microvascular complications (affecting eyes, kidneys, and nerves) as well as macrovascular complications, significantly impacting patients' quality of life. Pharmacological management of this condition has exspanded in recent years with the introduction of new classes of drugs, including sodium-glucose co-transporter type 2 (SGLT2) inhibitors, which act by promoting urinary glucose elimination.

Dapagliflozin (Forxiga), is one of the most studied and widely used SGLT2 inhibitors in clinical practice. In addition to its glucose-lowering effect, Forxiga provides additional cardiovascular and renal benefits, independently of glycemic control. However, the drug presents adverse effects such as urogenital infections and more rarely, severe adverse reactions, such as diabetic ketoacidosis, which can severely compromise patient health.

The objective of this review is to analyze the adverse reactions associated with the use of Forxiga in patients with T2DM, and to examine how evidence emerging from clinical studies has influenced the evolution of its indications and prescribing practices.

***Methods:** This review integrates clinical, pharmacological, and pharmacovigilance evidence on dapagliflozin using a narrative synthesis approach. Peer reviewed articles, randomized controlled trials, mechanistic studies, and regulatory documents from EMA, AIFA, and other international agencies were examined. Sources include clinical outcome trials evaluating cardiovascular and renal endpoints, analyses of SGLT2 inhibition, and post marketing pharmacovigilance data derived from spontaneous reporting systems and post authorization safety studies. Data were extracted to describe the drug's mechanism of action, therapeutic effects, safety profile, and regulatory evolution. No statistical pooling or meta analytic techniques were applied, as the objective was to provide a comprehensive clinical and pharmacovigilance overview consistent with the scope of a narrative review.*

Keywords
Dapagliflozin, SGLT2 inhibition, Renal glucose reabsorption, Glycosuria, Metabolic modulation, Ketone body utilization, myocardial energetics, Intraglomerular pressure, Diabetic ketoacidosis, Fournier's gangrene, Pharmacovigilance, Chronic kidney disease, Heart failure, Type 2 diabetes mellitus.

Introduction
Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease, classified by the World Health Organization (WHO) as one of the leading causes of morbidity and mortality worldwide. It is characterized by a state of chronic hyperglycemia resulting from a combination of peripheral insulin resistance and progressive dysfunction of pancreatic β cells, which impairs the maintenance of glycemic homeostasis, leading to a persistent increase in blood

glucose levels [1].

Long-term uncontrolled hyperglycemia increases the risk of microvascular complications (retinopathy, nephropathy, and diabetic neuropathy) and macrovascular complications (ischemic heart disease, stroke, and peripheral arterial disease), with a significant impact on quality of life and healthcare costs. The etiopathogenesis of T2DM is multifactorial and involves interactions between genetic predisposition and environmental factors. Major modifiable risk factors include obesity, particularly visceral adiposity, low physical activity, and an unbalanced dietary habits [1].

Insulin secretion in response to glucose follows a biphasic pattern. The first phase consists of a rapid release of a small pool of insulin granules that are already ready for exocytosis and located near the plasma membrane of β cells. This is followed by a second, more gradual and sustained phase, during which newly formed insulin granules are mobilized from intracellular stores and continuously secreted in response to persistent hyperglycemic stimulus [2].

When blood glucose levels increase, pancreatic β cells take up glucose through facilitated diffusion, mainly via the GLUT2 (Glucose Transporter Type 2), which is highly expressed in these cells. Once inside the cell, glucose is metabolized through glycolysis and the Krebs cycle, leading to an increase in the ATP/ADP ratio. This increase induces the closure of ATP-sensitive potassium channels (K_ATP), causing depolarization of the plasma membrane. The resulting depolarization opens voltage-dependent calcium channels, allowing an influx of calcium ions (Ca^{2+}) into the cytoplasm. The increase in intracellular calcium concentration represents the key signal that triggers the exocytosis of insulin-containing granules, enabling the release of the hormone into the bloodstream.

Once secreted, about 50% of insulin is inactivated and degraded by the liver during its first portal passage. The remaining 50% reaches target tissues (liver, skeletal muscle, and adipose tissue), where it exerts its biological effects by binding to specific insulin receptors on the cell membrane. The binding of insulin to its receptor stimulates the intrinsic tyrosine kinase activity of the receptor itself, leading to its autophosphorylation on tyrosine residues. This event initiates a signal transduction cascade that regulates multiple intracellular metabolic processes, including glucose uptake, glycogen synthesis, and modulation of gene expression [2].

In pathological conditions, such as type 2 diabetes, where circulating glucose concentration is chronically elevated, the described mechanism undergoes significant alterations. Pancreatic β-cells initially increase their secretory activity in response to hyperglycemia, but their functionality progressively declines: they are unable to meet metabolic demand, resulting in compromised insulin production [1,2].

Pharmacological Treatment Options For T2dm

For the treatment of patients with type 2 diabetes mellitus, several pharmacological options are available, including:

- Metformin;
- Sulfonylureas;
- Glinides;
- Glitazones (or Thiazolidinediones);
- DPP-4 enzyme inhibitors;
- Renal glucose transporter SGLT-2 inhibitors

Metformin: Mechanism of Action and Adverse Effects

Metformin is a drug belonging to the biguanide class and currently represents the first-line treatment for patients with type 2 diabetes mellitus, as recommended by major international guidelines (ADA, EASD). Introduced in the mid-20th century, it was the first antidiabetic drug to demonstrate significant clinical benefits in terms of glycemic control and reduction of cardiovascular mortality in diabetic patients. Although the mechanism of action of metformin is not fully clarified, preclinical and clinical studies have identified several metabolic effects, including [3]:

- Inhibition of hepatic gluconeogenesis and glycogenolysis, reducing endogenous glucose production;
- Increased peripheral glucose utilization, particularly in skeletal muscle and adipose tissue, through improved insulin sensitivity;
- Reduced intestinal glucose absorption, contributing to postprandial glycemic control.

Metformin acts as an insulin-sensitizing agent and does not directly stimulate insulin secretion, which explains its low risk of hypoglycemia.

Adverse Reactions and tolerability

Despite its favorable efficacy profile, metformin is frequently associated with adverse reactions, which may limit adherence to therapy, especially during the early stages of treatment. The most common adverse effects involve the gastrointestinal system and include:

- Nausea;
- Vomiting;
- Diarrhea;
- Abdominal pain;
- Loss of appetite (anorexia).

These symptoms occur in a significant proportion of patients, particularly during the first weeks of treatment, and tend to decrease with prolonged use. Extended-release formulations may improve gastrointestinal tolerability. A rare but potentially fatal adverse reaction associated with metformin is lactic acidosis, an acute metabolic complication characterized by the accumulation of lactic acid in the blood, leading to severe metabolic acidosis. Considering this risk, specific recommendations have been issued for the safe use of metformin [3].

- Assess renal function before starting therapy, by estimating the glomerular filtration rate (eGFR);

- Periodically monitor eGFR during treatment, with particular attention to elderly patients, who are more susceptible to rapid decline in renal function;
- Temporarily discontinue therapy in patients undergoing diagnostic procedures with iodinated contrast agents, as these substances may cause acute worsening of renal function: renal function should be reassessed 48 hours after the procedure before resuming drug administration.

Discontinuation of metformin is also strongly recommended in cases of severe hepatic or cardiac insufficiency.

Sulfonylureas: Mechanism of action, therapeutic advantages, and adverse effects

Sulfonylureas, including glibenclamide, glimepiride, and gliclazide, represent a class of oral hypoglycemic agents used in the treatment of type 2 diabetes mellitus. Their mechanism of action consists of stimulating pancreatic β cells, to increase endogenous insulin secretion. For these drugs to be effective, the presence of adequate residual pancreatic function is required [4].

A relevant therapeutic advantage is the generally once-daily dosing, which can improve adherence to therapy compared with other antidiabetic agents, such as metformin. However, sulfonylureas are associated with several adverse effects, both in acute and chronic.

Among the acute adverse reactions are:

- Hypoglycemia, which may be severe, since insulin secretion is stimulated independently of plasma glucose levels;
- Weight gain, due to the anabolic effect of insulin, which promotes fat accumulation in adipocytes.

Long term, continuous use of sulfonylureas may lead to a progressive reduction in pancreatic β cell function and number, as continuous stimulation, may induce functional exhaustion, potentially accelerating progression toward insulin dependence. Another critical aspect concerns the wide range of drug–drug interactions associated with this therapeutic class. Sulfonylureas can interact with numerous other drugs, modifying their efficacy or increasing the risk of hypoglycemia. This makes careful clinical and pharmacological evaluation necessary before prescribing them, especially in polymedicated patients [4].

Glinides: pharmacological characteristics, mechanism of action, and adverse effects

Glinides, a class of oral hypoglycemic drugs, include two main active substances: nateglinide and repaglinide. In Italy, however, the only currently available drug belonging to this category is repaglinide. The mechanism of action of glinides is similar to that of sulfonylureas, as they stimulate pancreatic β-cells to release insulin. However, compared with sulfonylureas, glinides have a faster onset and a shorter duration of action, making them particularly effective in controlling postprandial glycemia. Repaglinide must be administered orally three times a day, in correspondence with main meals. This dosing frequency may represent a limitation in terms of therapeutic adherence, especially when compared with once-daily treatment regimens.

The main adverse events associated with the use of glinides include:

- Weight gain,
- Hypoglycemia, which can be severe, especially if the drug is taken without adequate food intake or in combination with other hypoglycemic agents [5].

Glitazones (Thiazolidinediones): Mechanism of action, clinical uses, and adverse effects

Glitazones, or thiazolidinediones, are insulin-sensitizing drugs. In Italy, the only active substance currently on the market is pioglitazone. Their mechanism of action involves activating PPAR-γ receptors in peripheral tissues, particularly skeletal muscle and adipose tissue. PPAR-γ is a nuclear receptor that regulates genes involved in glucose and lipid metabolism, and its activation leads to enhanced insulin sensitivity, with an effect that is generally more pronounced than that achieved with metformin. In addition to improving insulin sensitivity, glitazones increase HDL cholesterol levels and reduce blood pressure, potentially contributing to a more favorable cardiovascular profile.

However, the use of pioglitazone is associated with several adverse effects, including:

- Increased body weight;
- Fluid retention, which may worsen pre-existing heart failure conditions, representing a relative contraindication [6].

Gliptins (DPP-4 inhibitors): pharmacological characteristics and safety

Gliptins, or dipeptidyl peptidase-4 (DPP-4) inhibitors, represent a class of oral hypoglycemic agents including several molecules, such as sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin.

These drugs are administered orally, generally once or twice daily, and share a common mechanism of action: inhibition of the DPP-4 enzyme, which is responsible for the degradation of incretin mimetics (GLP-1 and GIP). These hormones stimulate insulin secretion in response to food intake. Inhibiting DPP-4 prolongs incretin activity, resulting in increased insulin secretion in a glucose-dependent manner. Consequently gliptins do not cause hypoglycemia, since the insulinotropic effect occurs only in the presence of high blood glucose levels.

Additional advantages of gliptins include:

- Absence of weight gain;
- Low risk of drug interactions, a particularly useful feature in polymedicated patients [7].

Sodium-glucose co-transporter type 2 (SGLT-2) inhibitors

SGLT-2 inhibitors represent an innovative class of oral hypoglycemic drugs. These agents act by reducing renal glucose reabsorption, promoting its elimination through the urine. Their effect is independent of insulin secretion, making them particularly useful in patients with reduced β-cell function [8].

The main SGLT-2 inhibitors currently on the market are:
- Canagliflozin,
- Empagliflozin,
- Dapagliflozin, which will be examined in detail in the following sections.

Dapagliflozin (Forxiga)
Forxiga is a medicinal product whose active substance is dapagliflozin. Specifically, each tablet contains dapagliflozin propanediol monohydrate, equivalent to 5 mg or 10 mg of dapagliflozin. The 10 mg tablets formulation contains 50 mg of anhydrous lactose as an excipient [9].

Pharmacokinetic properties of Dapagliflozin
Absorption: Dapagliflozin is rapidly absorbed after oral administration. Under fasting conditions, maximum plasma concentration (Cmax) is reached in approximately 2 hours. Oral bioavailability after a 10 mg dose is 78%.

Distribution: Dapagliflozin shows high plasma protein binding (approximately 91%). The mean volume of distribution at steady state is about 118 liters, indicating extensive tissue distribution [9].

Biotransformation
Dapagliflozin undergoes extensive metabolism, mainly in the liver and kidneys, primarily via the enzyme uridine diphosphate-glucuronosyltransferase 1A9 (UGT1A9). The main metabolite is dapagliflozin 3-O-glucuronide, which is pharmacologically inactive [9].

Elimination
The mean terminal plasma half-life is approximately 13 hours, supporting once-daily administration. Elimination occurs mainly via the urine and, to a lesser extent via the feces:
- About 15% of the dose is excreted unchanged in feces,
- About 2% is excreted unchanged in urine.

In the presence of renal impairment, dapagliflozin clearance is reduced, potentially leading to accumulation and an increased risk of adverse events [9].

Pharmacodynamic properties of Dapagliflozin
Dapagliflozin is a highly selective and potent inhibitor of sodium-glucose co-transporter type 2 (SGLT2), with an inhibition constant (Ki) of 0.55 nmol/L. The drug shows more than 1,400-fold selectivity for SGLT2 compared to SGLT1, the latter being mainly expressed in the intestine and responsible for enteric glucose absorption. Inhibition of SGLT2 by reduces glucose reabsorption in the proximal convoluted tubule, promoting urinary glucose excretion (glycosuria). Furthermore, dapagliflozin increases sodium delivery to the distal tubule, enhancing tubuloglomerular feedback and reducing intraglomerular pressure [8,9].

Dapagliflozin can be used as monotherapy or in combination with other hypoglycemic agents, including insulin. Clinical studies have shown that, compared with placebo, dapagliflozin monotherapy reduces glycated hemoglobin (HbA1c) by 0.66–1.45% over 24 weeks with associated weight loss of 1.0–2.73%. In dual therapy with metformin, glycated hemoglobin (HbA1c) reduction reached 0.8% over 102 weeks [9].

Extraglycemic therapeutic effects of dapagliflozin
In addition to its proven efficacy in glycemic control, dapagliflozin has demonstrated several additional clinical benefits, including:

Reduction in Body Weight
One of the most evident favorable effects of dapagliflozin treatment is a reduction in body weight typically around 2 kg. This effect is initially due to osmotic diuresis induced by glycosuria, leading to loss of extracellular fluids in the early phase of therapy. Over time, fluid loss is associated with a gradual reduction in visceral fat compared to adipose tissue [9.10].

Effects on Blood Pressure
Several studies have demonstrated an antihypertensive effect of dapagliflozin, with reductions in both systolic and diastolic blood pressure typically observed within 1–2 weeks of treatment initiation. The underlying mechanisms appear to be multifactorial and include:
- Osmotic diuretic secondary to glycosuria;
- Natriuresis;
- Reduction in plasma volume;
- A likely improvement in endothelial function.

This latter effect contributes to the overall cardiovascular benefit observed in clinical trials, including the DECLARE-TIMI 58 study, which has significantly influenced the use of dapagliflozin in patients with cardiovascular diseases and heart failure [9,10].

Adverse reactions observed with the use of Forxiga
Numerous clinical studies conducted on Forxiga (dapagliflozin) in patients with type 2 diabetes mellitus have assessed bot hits efficacy and its tolerability, including the occurrence of adverse reactions that may require treatment discontinuation.

The reported adverse reactions include the following:

Necrotizing fasciitis of Fournier (Fournier's gangrene)
This is a rare but potentially life-threatening acute infection, affecting the soft tissues of the genital and perineal region, characterized by rapid progression and requiring prompt medical intervention. Fournier's gangrene was first described by Baurienne in 1764 and later clinically characterized by Jean-Alfred Fournier in 1883. It is caused by a polymicrobial infection, involving both aerobic and anaerobic bacteria. The most frequently

isolated pathogens include: *Escherichia coli, Pseudomonas spp., Enterococcus spp., Staphylococcus spp., Streptococcus spp., Proteus spp., Acinetobacter spp., Bacteroides spp., Klebsiella pneumoniae.* Despite its rarity, the severity of this condition has led regulatory authorities to require a specific warning in package leaflets [11].

Diabetic ketoacidosis

Diabetic ketoacidosis is a possible adverse reaction associated with therapy with SGLT2 inhibitors, including dapagliflozin (Forxiga), in patients with T2DM. It is a potentially serious condition that may occur even with normal or only mildly elevated blood glucose levels (euglycemic DKA) [11,12].

Ketoacidosis results from reduced insulin availability, leading the body to use lipids as an alternative energy source. In this context, fatty acids (particularly triglycerides) are oxidized in the liver via β-oxidation, resulting in the production of ketone bodies (acetoacetate, β-hydroxybutyrate, acetone). The accumulation of these compounds in the bloodstream lowers blood pH, leading to metabolic acidosis.

SGLT2 inhibitors lower blood glucose by increasing urinary glucose excretion, resulting in reduced insulin secretion by pancreatic β-cells. The decrease in circulating insulin levels reduces antilipolytic activity, thereby promoting lipolysis and increasing free fatty acids, which serve as substrates for hepatic ketogenesis.

Additionally, it has been observed that SGLT2 inhibitors may increase glucagon levels. Although a direct effect on pancreatic α-cells secretion has not been demonstrated, it is hypothesized that the increase in glucagon is indirectly induced by reduced insulin levels. In conditions of depleted hepatic glycogen stores, glucagon stimulates lipolysis in adipocytes, further contributing to ketone body production.

Another mechanism by which SGLT2 inhibitors may exacerbate ketoacidosis is the increased renal reabsorption of ketone bodies, increasing their plasma concentration.

In light of the above, early recognition of the clinical signs of a ketoacidotic state is essential, even in the absence of hyperglycemia [13,14].

Urinary and Genital Infections

Urinary tract infections (UTIs) and genital mycotic infections, especially candidiasis, are among the most frequently reported adverse events during dapagliflozin therapy. These complications are directly related to the drug's mechanism of action, which promotes glycosuria. The increased glucose concentration in the urinary tract creates a favorable environment for bacterial and fungal proliferation, predisposing to genitourinary infections. Women with diabetes are particularly susceptible to urinary tract infections compared with men, due to anatomical factors: the shorter female urethra and its proximity to the vaginal and anal openings facilitate bacterial colonization [14].

Local factors may further increase infection risk, including reduced presence of lactobacilli (essential for maintaining vaginal flora balance) and elevated vaginal pH, both of which are predisposing factors for pathogenic overgrowth [12].

Monitoring and follow-up

To maintain a favorable risk/benefit ratio, ensuring therapeutic efficacy and minimizing the occurrence of significant adverse events, clinical and regulatory strategies must be implemented by the prescribers.

These interventions operate on multiple levels. First, careful selection of patients eligible for dapagliflozin therapy is essential.

Factors to be evaluated include:
- Advanced age,
- Concomitant use of diuretics (which may increase the risk of dehydration and hypotension),
- A clinical history of recurrent urinary or genital infections.

A second essential component of risk management is patient education. Informing patients about potential adverse reactions and symptoms to monitor is crucial for early diagnosis and for reducing the severity of complications [15].

Pharmacovigilance investigations

The frequency and nature of adverse reactions observed in patients with T2DM treated with Forxiga are summarized in the Summary of Product Characteristics (see Table 1).This table includes adverse reactions identified in more than 15,000 patients treated with dapagliflozin. An initial safety assessment was conducted in a predefined pooled analysis of 13 short-term studies (24 weeks), in which 2,360 patients received dapagliflozin 10 mg and 2,295 patients received placebo. Reported adverse reactions were identified in placebo-controlled clinical trials and post-marketing surveillance. None were dose-dependent. Adverse reactions were classified according to frequency and system organ class:
- Very common (≥1/10)
- Common (≥1/100, <1/10)
- Uncommon (≥1/1,000, <1/100)
- Rare (≥1/10,000, <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

From Table 1 it can be observed that hypoglycemia is a very common adverse reaction . Evidence from the DECLARE-TIMI58 and DAPA-HF studies indicates that dapagliflozin alone does not induce hypoglycemia. However, hypoglycemia has been reported when dapagliflozin is used in combination with other agents such as insulin, in cases of metformin intolerance or when diet and physical exercise alone do not provide adequate glycemic control [10,15,16].

Table 1: Frequency of adverse reaction reports.

System Organ Class	Very common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)	Very rare (<1/10,000)
Infections	—	Urinary tract infection; Genital infections	Fungal infections	—	Necrotizing fasciitis of the perineum
Metabolism and nutrition disorders	Hypoglycaemia	—	Volume depletion; Increased thirst	Diabetic ketoacidosis	—
Nervous system disorders	—	Dizziness	—	—	—
Gastrointestinal disorders	—	—	Constipation; Dry mouth	—	—
Skin and subcutaneous tissue disorders	—	Rash	—	—	Angioedema
Musculoskeletal and connective tissue disorders	—	Back pain	—	—	—
Renal and urinary disorders	—	Dysuria; Polyuria	Nocturia	—	—
Reproductive system and breast disorders	—	—	Pruritus in the genital area	—	—
Investigations	—	Increased haematocrit; Initial reduction in creatinine clearance; Dyslipidaemia	Increased creatinine; Increased urea; Reduction in body weight	—	—

Reporting difficulties and biases affecting data evaluation

The reporting of adverse reactions occurring after a drug is placed on the market plays a fundamental role in protecting public health. This process enables health authorities to promptly identify any risks associated with the use of the drug and to adopt the necessary minimization measures. However, despite specific directives issued by regulatory authorities such as AIFA to promote active pharmacovigilance, reporting by healthcare professionals remains insufficient. In type 2 diabetes mellitus, clinical complexity often makes it difficult to distinguish adverse events caused by the drug from symptoms related to the disease itself. An emblematic example is diabetic ketoacidosis. This condition may present with common symptoms such as nausea and vomiting, but also with more nonspecific manifestations such as dehydration and xerostomia (dry mouth), which may be attributed either to the disease or to drug use. It is therefore essential that healthcare professionals maintain a high level of clinical vigilance, paying attention even to milder or ambiguous signs. Continuous and accurate analysis of clinical and laboratory data is an indispensable tool for correctly assessing the patient's clinical picture. Furthermore, considering that Forxiga is authorized by the EMA specifically for the treatment of type 2 diabetes mellitus, although its applicability has progressively expanded, it is essential to carefully monitor any cases of abuse, misuse, or off-label prescription. Such non-compliant uses may expose patients to inadequately evaluated risks and compromise the drug's efficacy and safety [13,15].

Among the categories for which the use of the drug is currently not recommended or requires particular caution are pediatric patients below the approved age range, very elderly subjects over 75 years of age, and pregnant or breastfeeding women.

Regarding use in pregnancy, sufficient clinical data in humans are not available. However, studies conducted in animals (particularly rats) have shown toxicity during fetal renal development. Consequently, treatment must be discontinued as soon as pregnancy is confirmed.

During breastfeeding, the use of the drug is also not recommended, as it cannot be definitively excluded that dapagliflozin is excreted in breast milk, with the risk of potential risk of adverse reactions in the newborn.

Based on studies conducted to date, no clinically relevant differences have been observed among populations belonging to different ethnic groups [15].

Monitoring and evaluation of adverse events

The Summary of Product Characteristics (SmPC) indicates that, before starting therapy with Forxiga, patients should undergo a complete clinical evaluation.

Since the glycemic efficacy of the drug largely depends on renal function, Forxiga should not be administered in patients with severe renal impairment according to the approved labeling, and renal function should be monitored during treatment.

The drug should be used with caution in patients at risk of a dapagliflozin-induced drop in blood pressure, such as those receiving antihypertensive therapy or with a history of hypotension.

In the presence of conditions that may cause volume depletion, for example gastrointestinal disorders, careful monitoring of volume status is recommended. During the first medical visit, the following assessments should be performed:

- Blood pressure measurement;
- Laboratory tests, including:
  Complete blood count (to assess hematocrit),
  Electrolyte measurement (sodium, potassium, chloride).

If the patient develops clinical signs of volume depletion, temporary discontinuation of Forxiga is recommended until general conditions have stabilized [15].

Management of adverse events

Following the review conducted by the Pharmacovigilance Risk Assessment Committee (PRAC), the EMA recommended updating the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) to include diabetic ketoacidosis as a rare but serious undesirable effect. Patients receiving these drugs must be adequately informed about early signs and symptoms.

Patients receiving these drugs must be adequately informed about early signs and symptoms, including:

- Weight decreased,
- Nausea/Vomiting,
- Abdominal Pain,
- Polydipsia
- Tachypnoea,
- Confusional state,
- Somnolence,
- Fatigue,
- Breath odour,
- Dysgeusia,
- Body odour

If any of these symptoms occur, it is essential that patients immediately contact a doctor or go to the nearest emergency department. In cases of suspected or confirmed diabetic ketoacidosis, treatment with the drug must be stopped immediately and must not be restarted unless an alternative cause of the ketoacidosis is identified, adequately treated and resolved. Furthermore, the EMA has recommended temporarily discontinuing dapagliflozin (Forxiga) therapy in patients undergoing major surgery or who are hospitalized. In August 2018, the U.S. Food and Drug Administration (FDA) issued an official warning regarding the possible risk of Fournier's gangrene associated with the use of SGLT2 inhibitors [13,17].

This communication was based on reports of 12 cases occurring in diabetic patients treated with these drugs. All 12 patients were hospitalized and required major surgical interventions, some of which were highly mutilating. Post-operative complications also occurred and, in one case, the patient died. Although rare, the severity of these outcomes led regulatory authorities to require the inclusion of a specific warning in the SmPC and Patient Information Leaflet (PIL).

Despite the various recommendations regarding possible adverse reactions, the benefits associated with the use of Forxiga continue to outweigh the potential risks in the treatment of type 2 diabetes mellitus.

In line with this, subsequent PRAC evaluations on the therapeutic benefit of Forxiga for indications other than type 2 diabetes mellitus were forwarded to the Committee for Medicinal Products for Human Use (CHMP), which in turn submitted the documentation to the European Commission [4]. The latter authorized the extension of the therapeutic indication of Forxiga, recognizing it as a drug indicated for [15]:

Type 2 diabetes mellitus

Forxiga is indicated in adults and in children from aged 10 years of age for the treatment of insufficiently controlled type 2 diabetes mellitus, in addition to diet and physical exercise:

- As monotherapy, in cases where metformin is considered inappropriate due to intolerance;
- In combination with other medicinal products for type 2 diabetes.

Heart failure

Forxiga is indicated in adults for the treatment of symptomatic chronic heart failure, irrespective of ejection fraction. The extension of this indication is supported by the results of the phase III DAPA-HF study, published in the *New England Journal of Medicine*, which showed a significant clinical benefit in terms of reduction of cardiovascular events. Dapagliflozin is the first SGLT2 inhibitor to demonstrate a statistically significant reduction in the risk of cardiovascular death or worsening heart failure events (including hospitalization for heart failure, hHF) compared with placebo. Both components of the primary composite endpoint contributed substantially to the observed therapeutic effect, indicating a favorable impact on both mortality and cardiovascular morbidity in patients with chronic heart failure [18].

Chronic Kidney Disease

Approval for this indication is based on the results of the phase III DAPA-CKD study, which demonstrated that dapagliflozin reduces the risk of progression to end-stage renal failure in patients with chronic kidney disease, irrespective of the presence of type 2 diabetes mellitus.

During the initial phase of therapy, an acute decline in glomerular filtration rate (eGFR) was observed, a phenomenon expected with SGLT2 inhibitors. This initial reduction is not considered clinically concerning, as it does not compromise long-term benefits.

In particular, in patients with type 2 diabetes mellitus, poor glycemic control (high HbA1c) and elevated urinary albumin/creatinine ratio (UACR), treatment with dapagliflozin resulted in a significant reduction in the long-term rate of eGFR decline, thereby helping to slow the progression of kidney disease [19].

Conclusions

The analysis of the safety profile of dapagliflozin in patients with type 2 diabetes mellitus has highlighted a non-negligible risk of adverse drug reactions (ADRs), although in most cases these are mild or moderate. Urogenital infections, particularly fungal infections, represent the most frequently reported adverse reactions, in line with the drug's mechanism of action, which promotes glycosuria, creating a favorable environment for microbial proliferation. More serious adverse reactions, although rare, have also been reported, including diabetic ketoacidosis and Fournier's gangrene, potentially life-threatening conditions that require careful clinical monitoring.. Despite these risks, data from clinical studies indicate that the overall risk/benefit profile of dapagliflozin remains favorable, especially in appropriately selected and monitored patients.

The therapeutic benefits observed include [10,18,19]:

- A significant reduction in blood glucose levels;
- An improvement in cardiovascular outcomes;
- A slowing of the progression of chronic kidney disease, including diabetic nephropathy.

These positive effects outweigh potential adverse reactions, especially when treatment is initiated and monitored in accordance with clinical guidelines and regulatory authorities recommendations. In 2015, when the cardiovascular and renal benefits were not yet known, AIFA introduced restrictions on the use of Forxiga through a Therapeutic Plan to ensure controlled and monitored prescribing. Reimbursement of this drug was limited to adult patients with type 2 diabetes mellitus, under the specific clinical conditions:

- As monotherapy, in patients intolerant to metformin, in whom the use of other hypoglycemic agents was contraindicated or not appropriate;
- In combination with metformin, when the use of a different hypoglycemic agent was contraindicated or not appropriate;
- In combination with insulin, with or without metformin.

In the following years, the results of numerous clinical studies progressively expanded the therapeutic indications of Forxiga, demonstrating its efficacy not only in type 2 diabetes mellitus but also in symptomatic chronic heart failure. Based on this evidence, AIFA issued Determination 80/2024, extending reimbursement by the National Health Service to the new therapeutic indication of chronic heart failure [20].

"Heart failure: Forxiga is indicated in adults for the treatment of symptomatic chronic heart failure"

At the same time, a web-based Therapeutic Plan was introduced to monitor the use of the drug for this new indication, integrated into the AIFA Registry platform and structured into sections dedicated to patient registration, clinical eligibility, prescription, reassessment, and treatment discontinuation. Completion of the Therapeutic Plan and issuance of the first prescription, remained the exclusive responsibility of specialists working in authorized centers.

A significant turning point in the clinical use of Forxiga occurred in 2025, with the publication of the AIFA Determination Pres/927/2025. This provision marked a new phase in the management of the drug, providing for a renegotiation of reimbursement conditions in light of the clinical benefits observed not only in patients with type 2 diabetes mellitus and chronic heart failure, but also in those with chronic kidney disease. The most relevant impact of this determination was the removal of the requirement for prescription through an evaluation form and the consequent closure of web-based Therapeutic Plans. This expanded prescribing possibilities, extending them also to general practitioners and significantly improving patient access to treatment [21].

In conclusion, pharmacovigilance is assuming an increasingly central role, representing not only an essential instrument for the early identification of safety signals but also a key component in optimizating therapeutic management. Post-marketing data are fundamental for updating clinical guidelines, improving patient selection and promptly identifying rare or unexpected adverse reactions, thus supporting the safe and effective use of the drug in routine clinical practice [22].

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