Int. J. Sci. R. Tech., 2026 3(5)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Saxagliptin In Type 2 Diabetes Mellitus : Pharmacology, Clinical Efficacy, Safety, And Future Perspectives

M. Prasada Rao*, Y. Narasimha Rao, S. Rajini, SK. Apsana

M.A.M College of Pharmacy, Andhrapradesh

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and impaired β-cell function. Saxagliptin is an oral antidiabetic drug belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class. It improves glycemic control by increasing endogenous incretin hormone levels, thereby enhancing glucose-dependent insulin secretion and reducing glucagon release. Saxagliptin is effective as both monotherapy and combination therapy with other antidiabetic agents, including metformin, sulfonylureas, and insulin. Clinical studies have demonstrated significant reductions in fasting blood glucose and HbA1c levels with a low risk of hypoglycemia and no significant weight gain. The drug is generally well tolerated, although adverse effects such as upper respiratory tract infections, headache, pancreatitis, hypersensitivity reactions, and arthralgia have been reported. Overall, saxagliptin is a safe and effective treatment option for the management of type 2 diabetes mellitus.

Keywords: Saxagliptin, Type 2 Diabetes Mellitus, DPP-4 Inhibitors, Incretin Hormones, GLP-1, Glycemic Control, Antidiabetic Agents.

INTRODUCTION

Saxagliptin is an oral antidiabetic medication belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class, used in the management of type 2 diabetes mellitus. It exerts its therapeutic effect by inhibiting the DPP-4 enzyme, thereby enhancing incretin hormone activity, which improves glycemic control. The drug was initially developed by . In 2007, entered into a collaboration with Bristol Myers Squibb to co-develop saxagliptin and jointly oversee its commercialization and marketing. Saxagliptin is indicated as monotherapy or in combination with other antidiabetic agents for the management of type 2 diabetes mellitus. While it effectively improves glycemic control, current evidence suggests that it does not significantly reduce the risk of major cardiovascular events such as myocardial infarction or stroke. Clinical studies have reported an increased incidence of hospitalization for heart failure among patients receiving saxagliptin (3.5%) compared with those receiving placebo (2.8%)[1,2,3].

Similar to other dipeptidyl peptidase-4 (DPP-4) inhibitors, saxagliptin demonstrates a moderate glycated hemoglobin (HbA1c)–lowering effect, carries a low risk of hypoglycemia, and is generally weight-neutral. In a 24-week clinical trial involving patients with type 2 diabetes mellitus, saxagliptin significantly improved mean HbA1c levels compared with placebo. Furthermore, combination therapy with saxagliptin and metformin produced greater reductions in HbA1c than either saxagliptin or metformin administered as monotherapy.

In another study involving 768 patients with inadequately controlled type 2 diabetes, the addition of saxagliptin to sulfonylurea therapy resulted in significantly greater improvements in fasting blood glucose levels compared with simply increasing the dose of glibenclamide. These findings support the efficacy of saxagliptin as an adjunctive therapy in patients requiring enhanced glycemic control[4,5].

1.2. Pathophysiology of Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by insulin resistance and impaired pancreatic β-cell function. Insulin resistance develops as a result of

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

factors such as visceral obesity, lipotoxicity, and defects in intracellular insulin signaling pathways, leading to reduced glucose uptake by peripheral tissues. Initially, pancreatic β-cells compensate by increasing insulin secretion; however, over time, progressive β-cell dysfunction and loss result in inadequate insulin production and eventual insulin deficiency.

In addition to insulin resistance and β-cell dysfunction, abnormalities in the secretion and action of incretin hormones contribute significantly to the pathogenesis of T2DM. The principal incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted by the gastrointestinal tract in response to nutrient intake and play a crucial role in maintaining glucose homeostasis[6].

GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon release, and delays gastric emptying, thereby reducing postprandial glucose excursions. In patients with T2DM, impaired incretin activity results in inadequate suppression of glucagon secretion during meals. Consequently, excessive hepatic glycogenolysis and gluconeogenesis occur, leading to increased hepatic glucose production and postprandial hyperglycemia.

The recognition of the incretin effect and its role in glucose regulation has facilitated the development of novel therapeutic approaches for T2DM management. These include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, which enhance incretin activity and improve glycemic control[7,8].

1.3. Rationale for DPP-4 Inhibitors in Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance, β-cell dysfunction, and impaired incretin hormone activity. The global prevalence of T2DM continues to rise, making effective glycemic management essential to reduce diabetes-related morbidity and mortality. Despite the availability of multiple therapeutic options, achieving and maintaining optimal glycemic control remains challenging for many patients.

Incretin hormones, primarily glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), play a critical role in glucose homeostasis by enhancing glucose-dependent insulin secretion. In patients with T2DM, diminished incretin activity contributes to hyperglycemia. These hormones are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in a short biological half-life[9,10].

DPP-4 inhibitors were developed to prevent the enzymatic degradation of GLP-1 and GIP, thereby prolonging their activity and enhancing endogenous incretin effects. This leads to increased insulin secretion, suppression of glucagon release, reduced hepatic glucose production, and improved glycemic control. Saxagliptin is a selective DPP-4 inhibitor that has demonstrated efficacy in reducing both fasting and postprandial blood glucose levels when used as monotherapy or in combination with other antidiabetic agents such as metformin, sulfonylureas, and thiazolidinediones.

Compared with traditional antidiabetic therapies, DPP-4 inhibitors offer several advantages, including a low risk of hypoglycemia, weight neutrality, and a favorable tolerability profile. These characteristics make saxagliptin a valuable therapeutic option in the management of patients with T2DM[11,12].

1.4. Dosage and Administration of Saxagliptin

The recommended dosage of saxagliptin for the management of type 2 diabetes mellitus is 2.5 mg or 5 mg administered orally once daily, with or without food. Tablets should be swallowed whole and must not be split, crushed, or chewed.

Dosage in Renal Impairment

No dosage adjustment is required for patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min). However, in patients with moderate to severe renal impairment or end-stage renal disease (ESRD) requiring hemodialysis (CrCl ≤50 mL/min), the recommended dose is 2.5 mg once daily. For patients undergoing hemodialysis, saxagliptin should be administered after the dialysis session. The safety and efficacy of saxagliptin have not been established in patients receiving peritoneal dialysis.

Assessment of renal function is recommended before initiating therapy and periodically during treatment, as dosage adjustments are based on renal function. Renal function may be estimated using serum creatinine-based equations such as the Cockcroft–Gault or Modification of Diet in Renal Disease (MDRD) formula[13,14].

Dosage Adjustment with Strong CYP3A4/5 Inhibitors

When saxagliptin is co-administered with potent cytochrome P450 3A4/5 (CYP3A4/5) inhibitors, including ketoconazole, itraconazole, clarithromycin, ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, nefazodone, or telithromycin, the recommended dosage is 2.5 mg once daily due to increased systemic exposure to saxagliptin.

Use with Insulin Secretagogues or Insulin

When saxagliptin is used in combination with insulin secretagogues, such as sulfonylureas, or with insulin therapy, a reduction in the dose of the concomitant agent may be necessary to minimize the risk of hypoglycemia.

Dosage Forms and Strengths

Saxagliptin is available as 5 mg film-coated tablets, which are pink, round, and biconvex in shape.

The tablets are imprinted with “5” on one side and “4215” on the reverse side in blue ink[15,16].

1.2. Warnings and Precautions of Saxagliptin

1. **Pancreatitis**

Post marketing surveillance has identified cases of acute pancreatitis in patients receiving saxagliptin. Patients should be closely monitored for signs and symptoms suggestive of pancreatitis, including persistent severe abdominal pain that may radiate to the back. If pancreatitis is suspected, saxagliptin should be discontinued immediately and appropriate clinical management initiated. The risk of pancreatitis in patients with a prior history of the condition remains uncertain[17].

2. **Hypoglycemia with Concomitant Use of Sulfonylureas or Insulin**

The use of saxagliptin in combination with insulin secretagogues, such as sulfonylureas, or with insulin may increase the risk of hypoglycemia. Clinical studies have demonstrated a higher incidence of confirmed hypoglycemic events when saxagliptin is administered alongside these agents compared with placebo. Therefore, dose reduction of the sulfonylurea or insulin may be necessary to minimize the risk of hypoglycemia.

3. **Hypersensitivity Reactions**

Serious hypersensitivity reactions, including anaphylaxis, angioedema, and severe exfoliative skin disorders, have been reported following saxagliptin therapy. These reactions generally occur within the first three months of treatment and may develop even after the initial dose. If a hypersensitivity reaction is suspected, saxagliptin should be discontinued immediately and appropriate alternative therapy considered. Caution is advised in patients with a history of angioedema associated with other DPP-4 inhibitors.

4. **Severe and Disabling Arthralgia**

Cases of severe and disabling joint pain have been reported in patients receiving DPP-4 inhibitors, including saxagliptin. Symptom onset may occur from a few days to several years after initiation of therapy. Symptoms typically resolve upon discontinuation of the medication; however, recurrence has been observed following re-exposure to the same or another DPP-4 inhibitor. Healthcare professionals should consider DPP-4 inhibitors as a potential cause of severe arthralgia and discontinue treatment when appropriate.

5. **Macro vascular Outcomes**

To date, no clinical trials have conclusively demonstrated that saxagliptin or any other antidiabetic agent reduces the risk of major macro vascular complications, such as myocardial infarction, stroke, or cardiovascular mortality. Therefore, the effect of saxagliptin on long-term macro vascular outcomes remains unestablished[18].

1.3. Clinical Pharmacology of Saxagliptin

Mechanism of Action

Saxagliptin is a selective, competitive inhibitor of dipeptidyl peptidase-4 (DPP-4), an enzyme responsible for the rapid degradation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). By inhibiting DPP-4 activity, saxagliptin prolongs the action of endogenous incretins, resulting in increased glucose-dependent insulin secretion and reduced glucagon release. Consequently, hepatic glucose production decreases, leading to reductions in both fasting and postprandial blood glucose levels in patients with type 2 diabetes mellitus (T2DM)[19].

Pharmacodynamics

In patients with T2DM, saxagliptin effectively inhibits DPP-4 enzyme activity for approximately 24 hours following administration. This inhibition produces a two- to three-fold increase in circulating active GLP-1 and GIP concentrations, enhances glucose-dependent insulin secretion, and suppresses glucagon release. These effects contribute to improved glycemic control by lowering fasting plasma glucose and reducing postprandial glucose excursions.

Cardiac Electrophysiology

Clinical studies have demonstrated that saxagliptin does not cause clinically significant prolongation of the QTc interval or alterations in heart rate, even at doses substantially higher than the maximum recommended therapeutic dose. These findings indicate a favorable cardiac safety profile[20,21].

1.4. Pharmacokinetics

Absorption

Saxagliptin is rapidly absorbed following oral administration, with peak plasma concentrations achieved approximately 2 hours after dosing, while its active metabolite reaches peak levels within 4 hours. Administration with food has minimal impact on drug absorption; therefore, saxagliptin may be administered with or without meals.

Distribution

Both saxagliptin and its active metabolite exhibit negligible plasma protein binding, suggesting a low likelihood of clinically significant drug displacement interactions and minimal influence of disease-related changes in plasma protein concentrations.

Metabolism

Saxagliptin undergoes extensive hepatic metabolism primarily via cytochrome P450 isoenzymes CYP3A4 and CYP3A5. Its major metabolite, 5-hydroxysaxagliptin, retains pharmacological activity, although it possesses approximately half the potency of the parent compound.

Excretion

Elimination of saxagliptin occurs through both renal and hepatic pathways. A substantial proportion of the administered dose is excreted in the urine as unchanged drug, active metabolite, and other metabolites. The renal clearance of saxagliptin exceeds the glomerular filtration rate, indicating the involvement of active renal tubular secretion in its elimination[22].

1.5. Adverse Effects of Saxagliptin

Saxagliptin is generally well tolerated; however, several adverse effects have been reported during clinical trials and post marketing surveillance.

Hypersensitivity Reactions

Serious hypersensitivity reactions may occur and include:

- Angioedema (swelling of the face, lips, tongue, throat, or other body areas)
- Anaphylactic reactions
- Urticaria (hives)
- Skin rash, pruritus, exfoliation, or skin peeling
- Difficulty swallowing or breathing

Patients who develop signs of hypersensitivity should discontinue treatment immediately and seek appropriate medical attention.

Severe Arthralgia

Dipeptidyl peptidase-4 (DPP-4) inhibitors, including saxagliptin, have been associated with severe and disabling joint pain. Symptoms may occur shortly

after treatment initiation or after prolonged use and generally resolve following discontinuation of therapy[23].

Common Adverse Effects

Frequently reported adverse effects of saxagliptin include:

- Upper respiratory tract infections
- Urinary tract infections
- Headache
- Nasopharyngitis Hypoglycemia

The risk of hypoglycemia is generally low when saxagliptin is used as monotherapy. However, the incidence increases when it is administered in combination with insulin or insulin secretagogues such as sulfonylureas. Common symptoms of hypoglycemia include:

- Tremors or shaking
- Excessive hunger
- Sweating
- Headache
- Palpitations or rapid heartbeat
- Visual disturbances
- Dizziness and confusion

Dose adjustment of concomitant antidiabetic medications may be required to minimize this risk.

Peripheral Edema

Patients receiving saxagliptin in combination with thiazolidinediones may experience worsening peripheral edema, characterized by fluid retention and swelling of the hands, feet, or ankles.

Mood Changes

Mood alterations have been reported infrequently and should be monitored, particularly in patients with a history of psychiatric disorders[24].

1.6. Drug Interactions of Saxagliptin

Saxagliptin is primarily metabolized by the cytochrome P450 enzymes CYP3A4 and CYP3A5. Therefore, concomitant administration with drugs that affect these enzymes may alter the pharmacokinetics and therapeutic efficacy of saxagliptin.

Interaction with Strong CYP3A4/5 Inhibitors

Strong CYP3A4/5 inhibitors can increase plasma concentrations of saxagliptin, potentially enhancing its pharmacological effects and adverse reactions. Examples include:

- Ketoconazole
- Itraconazole
- Clarithromycin
- Ritonavir
- Atazanavir
- Indinavir
- Nelfinavir
- Saquinavir
- Telithromycin
- Nefazodone

When saxagliptin is co-administered with these agents, the recommended dose is reduced to 2.5 mg once daily.

Interaction with CYP3A4/5 Inducers

Potent CYP3A4/5 inducers may decrease the plasma concentration of saxagliptin, potentially reducing its therapeutic effectiveness. Examples include:

- Rifampicin (rifampin)
- Carbamazepine
- Phenytoin
- Phenobarbital
- Dexamethasone

Patients receiving these medications should be monitored closely for adequate glycemic control.

Interaction with Insulin and Sulfonylureas

Concomitant use of saxagliptin with insulin or insulin secretagogues, such as sulfonylureas, may increase the risk of hypoglycemia. Dose reduction of the insulin or sulfonylurea may be required to minimize this risk.

Interaction with Other Antidiabetic Agents

Saxagliptin can be safely used in combination with metformin, thiazolidinediones, and other commonly prescribed antidiabetic medications. However, patients should be monitored for additive glucose-lowering effects and adverse reactions.

Clinical Significance

Although saxagliptin has a relatively low potential for drug interactions, caution is advised when prescribing it with medications that strongly influence CYP3A4/5 activity or with agents known to increase the risk of hypoglycemia. Appropriate dose adjustments and clinical monitoring are recommended to ensure safety and therapeutic efficacy[25].

CONCLUSION

Saxagliptin is an effective oral antidiabetic agent belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class, indicated for the management of type 2 diabetes mellitus. By inhibiting DPP-4 activity, saxagliptin enhances endogenous incretin hormone levels, resulting in improved glucose-dependent insulin secretion, suppression of glucagon release, and better glycemic control. Clinical studies have demonstrated its efficacy in reducing both fasting and postprandial blood glucose levels, either as monotherapy or in combination with other antidiabetic agents such as metformin, sulfonylureas, and thiazolidinediones. Saxagliptin is generally well tolerated and offers advantages including a low risk of hypoglycemia, weight neutrality, and convenient once-daily administration. However, clinicians should remain vigilant regarding potential adverse effects, including pancreatitis, hypersensitivity reactions, severe arthralgia, and an increased risk of hypoglycemia when used concomitantly with insulin or sulfonylureas. Dose adjustments may be necessary in patients with renal impairment and in those receiving strong CYP3A4/5 inhibitors. saxagliptin represents a valuable therapeutic option for patients with type 2 diabetes mellitus, particularly when individualized treatment strategies are required to achieve optimal glycemic control. Continued clinical monitoring and appropriate patient selection are essential to maximize therapeutic benefits while minimizing potential risks.

REFERENCES

1. Shubrook J, Colucci R, Guo A, Schwartz F. Saxagliptin: A selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. Clin Med Insights Endocrinol Diabetes. 2011;4:1-12. Doi:10.4137/CMED.S5114.
2. U.S. Food and Drug Administration (FDA). Onglyza (saxagliptin) tablets prescribing information. Silver Spring, MD: FDA; 2015.
3. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2025;48(Suppl 1):S1–S350.
4. DeFronzo RA. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773–795.
5. Gallwitz B. Clinical use of DPP-4 inhibitors. Front Endocrinol (Lausanne). 2019;10:389.
6. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: A critical review of head-to-head trials. Diabetes Metab. 2012;38(2):89–101.
7. Drucker DJ, Nauck MA. The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368(9548):1696–1705.
8. Holst JJ, Vilsbøll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. Mol Cell Endocrinol. 2009;297(1–2):127–136.
9. Ahrén B. DPP-4 inhibitors. Best Pract Res Clin Endocrinol Metab. 2007;21(4):517–533.
10. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels, Belgium: International Diabetes Federation; 2021.
11. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Curr Med Res Opin. 2009;25(10):2401–2411.
12. DeFronzo RA, Hissa MN, Garber AJ, Luiz Gross J, Yuyan Duan R, Ravichandran S, et al. The efficacy and safety of saxagliptin when added to

metformin therapy in patients with inadequately controlled type 2 diabetes. Diabetes Care. 2009;32(9):1649–1655.
13. Chacra AR, Tan GH, Ravichandran S, List J, Chen R, Foley JE. Saxagliptin added to a submaximal dose of sulfonylurea improves glycemic control compared with uptitration of sulfonylurea in patients with type 2 diabetes. Int J Clin Pract. 2009;63(9):1395–1406.
14. Hollander P, Li J, Allen E, Chen R. Saxagliptin added to a thiazolidinedione improves glycemic control in patients with type 2 diabetes and inadequate control on thiazolidinedione alone. J Clin Endocrinol Metab. 2009;94(12):4810–4819.
15. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–1326.
16. Scheen AJ. Pharmacokinetics and clinical use of saxagliptin in patients with type 2 diabetes mellitus. Clin Pharmacokinet. 2010;49(9):573–588.
17. Neumiller JJ. Differential chemistry (structure), mechanism of action, and pharmacology of GLP-1 receptor agonists and DPP-4 inhibitors. J Am Pharm Assoc. 2009;49(Suppl 1):S16–S29.
18. Ahrén B, Foley JE. Improved glucose regulation in type 2 diabetic patients with DPP-4 inhibitors: Focus on saxagliptin. Diabetes Obes Metab. 2010;12(7):553–566.
19. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. Diabetes Obes Metab. 2018;20(Suppl 1):5–21.
20. Holst JJ. The physiology of glucagon-like peptide-1. Physiol Rev. 2007;87(4):1409–1439.
21. Gallwitz B. Emerging DPP-4 inhibitors: Focus on saxagliptin for type 2 diabetes. Diabetes Metab Syndr Obes. 2010;3:1–9.
22. Bailey CJ, Day C. DPP-4 inhibitors: New agents for the treatment of type 2 diabetes. Diabet Med. 2009;26(9):889–896.
23. Drucker DJ. Enhancing incretin action for the treatment of type 2 diabetes. Diabetes Care. 2003;26(10):2929–2940.
24. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm. Diabetes Care. 2009;32(1):193–203.
25. American Diabetes Association. Pharmacologic approaches to glycemic treatment. Diabetes Care. 2024;47(Suppl 1):S158–S178.

HOW TO CITE: M. Prasada Rao*, Y. Narasimha Rao, S. Rajini, SK. Apsana, Saxagliptin In Type 2 Diabetes Mellitus : Pharmacology, Clinical Efficacy, Safety, And Future Perspectives, Int. J. Sci. R. Tech., 2026, 3 (6), 778-784. https://doi.org/10.5281/zenodo.20659506