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Combination Drug: Dapagliflozin + Sitagliptin + Metformin

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I. Objective:

This Research paper basically very essential for Knowledge and study aimed to evaluate the bioequivalence of a fixed-dose combination (FDC) therapy containing extended-release Metformin (Metformin XR), Dapagliflozin, and Sitagliptin for the treatment of Type 2 Diabetes Mellitus (T2D). SGLTD-TRIO 500 is a combination medication formulated to manage Type 2 Diabetes Mellitus (T2DM) effectively. It integrates three active ingredients—Dapagliflozin, Sitagliptin, and Metformin Hydrochloride (Extended Release)—each contributing distinct mechanisms to optimize blood glucose control. The primary goal was to compare the absorption rate and extent of the FDC with two reference formulations in healthy adult males under fed conditions as well as over view.[1][6]

The FDC formulation was assessed against:

- Sitagliptin 100 mg tablets.
- A combination of Dapagliflozin 10 mg and Metformin 1000 mg extended-release tablets.

By analyzing pharmacokinetic parameters, including maximum plasma concentration (Cmax) and area under the curve (AUC), the study determined whether the FDC exhibited similar bioavailability to the reference products. Establishing bioequivalence is essential for ensuring therapeutic efficacy and safety in clinical practice.

II. Methods:

This study was designed as an open-label, randomized, cross-over trial involving 24 healthy male participants. The objective was to assess the bioequivalence of a fixed-dose combination (FDC) therapy containing extended release Metformin (Metformin XR), Dapagliflozin, and Sitagliptin by comparing it to two reference products. Each participant received a single dose of both the test FDC and the reference formulations in a randomized sequence. Blood samples were collected over a 72-hour period to analyze key pharmacokinetic (PK) parameters, including:[self]

- Maximum plasma concentration (Cmax)
- Area under the concentration-time curve (AUC0-t and AUC0-inf)
- Time to reach maximum concentration (Tmax)
- Elimination rate constant (Kel)
- Percentage of extrapolated AUC (AUC_% Extrap_obs)
- Half-life (t1/2)
- BASIC STUDY

Bioequivalence was assessed based on the 90% confidence intervals (CIs) of the geometric mean ratios for AUC0-t and Cmax, which had to fall within the predefined regulatory acceptance range of 80.00%–125.00%. Additionally, safety and tolerability were evaluated throughout the study to monitor any adverse effects or concerns related to the FDC formulation.

III. Results:

This paper Pharmacokinetic analysis was conducted on 22 subjects after excluding two participants due to protocol deviations. The results demonstrated that the geometric mean ratios (GMRs) for the fixed-dose combination (FDC), when compared to the reference products, fell within the predefined bioequivalence range of 80.00%–125.00%. This confirms that the absorption profiles of the FDC and the reference formulations were comparable. The mean plasma concentration-time curves for Dapagliflozin, Sitagliptin, and Metformin XR were nearly identical between the FDC and reference products, indicating consistent drug release and absorption.

Furthermore, there were no significant differences observed in key pharmacokinetic parameters such as Tmax (time to reach maximum concentration) and t1/2 (elimination half-life), further supporting the bioequivalence of the FDC.

IV. Introduction:

SGLTD-TRIO 500 is a combination medication formulated to manage Type 2 Diabetes Mellitus (T2DM) effectively. It integrates three active ingredients—Dapagliflozin, Sitagliptin, and Metformin Hydrochloride (Extended Release)—each contributing distinct mechanisms to optimize blood glucose control. Dapagliflozin is an oral Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitor used primarily in the management of Type 2 Diabetes Mellitus (T2DM). It aids in lowering blood glucose levels by inhibiting glucose reabsorption in the kidneys, leading to its excretion through urine. This mechanism helps improve glycemic control while also offering additional benefits such as weight reduction and cardiovascular protection. The fixed-dose combination (FDC) of dapagliflozin (10 mg), sitagliptin (100 mg), and metformin XR (1000 mg) was developed by Exemed Pharmaceuticals, Gujarat, India. The study compared its pharmacokinetic (PK) profile and safety against two reference products:

1. Januvia (Sitagliptin 100 mg Tablets)
2. Xigduo XR (Dapagliflozin 10 mg + Metformin XR 1000 mg Tablets)

A randomized, open-label, two-period crossover study was conducted to determine the bioequivalence of the formulations in healthy adult males under fed conditions.

• Pharmacokinetics & Bioequivalence:

The single-dose administration of Januvia®, Xigduo® XR, and the test FDC formulation demonstrated similar PK parameters in fed states. The geometric mean ratios (GMRs) for Cmax, AUC0-t, and AUC0-inf fell within the 90% confidence interval range (80.00%–125.00%), confirming bioequivalence. The mean plasma concentration-time curves for dapagliflozin, sitagliptin, and metformin XR were nearly identical between the test and reference products, ensuring comparable absorption and drug release.

• Safety & Tolerability:

The study enrolled 24 healthy male participants, out of which 22 completed both study phases. A seven-day washout period was maintained between doses. Subject 007 was discontinued at check-in during Period II, but overall, the clinical study spanned 12 days without any major complications. No serious adverse events were reported, and all subjects remained clinically stable throughout the trial. The post-study laboratory evaluations confirmed that the investigational products were safe and well-tolerated at the administered doses.

V. Keywords:

Dapagliflozin, Sitagliptin, Metformin, Diabetes, Hyperglycemia, Combination, Therapy, Glycemic, Inhibitor, Treatment, ETC.

VI. Literature Of Research:

- **JABBOUR SA, HARDY E, SUGG J, PARIKH S, STUDY 10 GROUP:** Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study.
- **MATHIEU C, RANETTI AE, LI D, ET AL**: Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes.
- **ROSENSTOCK J, HANSEN L, ZEE P, ET AL:** Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin.

VII. Mechanism Of Action:

Dapagliflozin selectively inhibits **SGLT2**, a protein responsible for glucose reabsorption in the renal proximal tubules. By blocking this process, it increases glucose excretion, thereby reducing blood sugar levels. This action is independent of insulin, making it effective even in insulin-resistant individuals. Additionally, dapagliflozin promotes sodium excretion, contributing to mild blood pressure reduction.

Therapeutic Indications:

It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Posology And Method Of Administration:
Sitagliptin:
Pancreatitis:

There have been een postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin. After initiation of Sitagliptin, patients should be observed carefully for signs. and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.

Heart Failure:

Consider the risks and benefits of Sitagliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history tory of renal impairment, and o observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Sitagliptin.[2]

Assessment Of Renal Function:

There have been postmarketing reports subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin. Consideration can be given to cautiously reinitiating Sitagliptin if another etiology is deemed likely to have precipitated the acute worsening of renal function. Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.[3]

Hypersensitivity Reactions:

There have been post marketing reports of serious hypersensitivity reactions in patients treated with Sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with Sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes. Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Sitagliptin.[25]

Severe And Disabling Arthralgia:

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years.

Bullous Pemphigoid:

Post marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. Tell patients to report development of blisters or erosions while receiving Sitagliptin. If bullous pemphigoid is suspected, Sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Dapagliflozin:
Volume Depletion:

Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypoterision or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including Dapagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension.[23]

Ketoacidosis In Patients With Diabetes Mellitus:

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including Dapagliflozin. Fatal cases of ketoacidosis have been reported in patients taking Dapagliflozin. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.[22]Before initiating Dapagliflozin, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing Dapagliflozin for at least 3 days prior to surgery.[2]

Urosepsis And Pyelonephritis:

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including Dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.[3]

Insulin And Insulin Secretagogues:

Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with dapagliflozin.

Necrotizing Fasciitis Of The Perineum (Fournier's Gangrene):

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including Dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Patients treated with Dapagliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Dapagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections:

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.

Metformin:

Lactic Acidosis:

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with Metformin and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypo-perlusion and hypoxemia Lactic acidosisi characterized by elevated blood lactate concentrations (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels 5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride approximately 0.03 cases/1000 patient years, with approximately 0.015 fatal cases/1000 patient-years. In more than 20,000 patient years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primanly in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypo-perfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypo-perfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking Metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, Metformin should be promptly withheld in the presence of any condition associated with hypoxemia dehydration, or sepsis.

Monitoring Of Renal Function:

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore, Metformin ER is contraindicated in patients with renal impairment. Before initiation of Metformin ER and at least annually thereafter, renal function should be assessed and verified as normal Metformin treatment should not be initiated in patients 280 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. Metformin therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Hypoxic States:

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on Metformin therapy, the drug should be promptly discontinued.

Alcohol Intake:

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving Metformin.

Impaired Hepatic Function:

Because impaired hepatic function has been associated with some cases of lactic acidosis Metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B12 Levels:

In controlled, 29-week clinical trials of immediate release metformin, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

Hypoglycemia:

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.[2][4]7]

Macrovascular Outcomes:

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Metformin or any other oral anti-diabetic drug.

VIII. Drug Interactions:

Digoxin:

Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or Sitagliptin is recommended Insulin Secretagogues or Insulin:Co-administration of Sitagliptin with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secrelagogue or insulin to reduce the risk of hypoglycemia,[2]

Dapagliflozin:

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. Use alternative methods to monitor glycemic control

Interference With 1,5-Anhydroglucitol (1,5-Ag) Assay:

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliabile in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.[8]

Metformin:

Carbonic Anhydrase Inhibitors Topiramate or other carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide, or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Lise these drugs with caution in patients treated with metformin, as the risk of lactic acidosis may increase.[9]

Cationic Drugs:

Cationic drugs (eg, amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems.[5]

Drugs Affecting Glycemic Control:

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered to a patient receiving Metformin. the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Metformin, the patient should be observed closely for hypoglycemia.

IX. Use In Special Populations:

Sitagliptin:

Pregnancy:

There are no adequate data from the use of Sitagliptin in pregnant women. Studies in animals have sown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, Sitagliptin should not be used during pregnancy

Lactation:

It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk Sitagliptin should not be used during breast-feeding.

Geriatric Use:

dose adjustment is necessary based on age. Because sitagliptin is substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients.

Renal Impairment:

Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. Lower dosages are recommended in patients with eGFR less than 45 mL/min/1.73 m2 (moderate and severe renal impairment, as well as in ESRD patients requiring dialysis.

Dapagliflozin:

Pregnancy Risk Summary:

Based on animal data showing adverse renal effects, Dapagliflozin is not recommended during the second and third trimesters of pregnancy.

Lactation:

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of Dapagliflozin is not recommended while breastfeeding. Pediatric Safety and effectiveness of Dapagliflozin in pediatric patients under 18 years of age have not been established.

Geriatric Use:

No dapagliflozin dosage change is recommended based on age.

Renal Impairment:

No dose adjustment is required based on renal function. It is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate (eGFR) < 15mL/min/1.73m². In patients with type 2 diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced when eGFR is < 45 mL/min/1.73m² and is likely absent in patients with severe renal impairment. Therefore, if eGFR falls below 45 mL/min/1.73m², additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus.

Hepatic Impairment:

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

Metformin:

Pregnancy:

Teratogenic Effects: Pregnancy Category B Metformin HCI should not be used during pregnancy unless clearly needed. Labor and Delivery The safety and effectiveness of Metformin used during labor and delivery has not been evaluated in human studies Nursing Mothers Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Thus, the potential for hypoglycemia in nursing infants after Metformin HCl Oral Solution may exist.[10]

Geriatric Use:

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function, Regular assessment of renal function is necessary.

X. Description Of Selected Adverse Reactions:

In addition to the drug-related adverse experiences described above, adverse experiences reported regardless of causal relationship to medication and occurring in at least 5% and more commonly in patients treated with sitagliptin included upper raspiratory tract infection and nasopharyngitis. Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with sitagliptin (not reaching the 5% level, but occurring with an incidence of > 0.5% higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity. Some adverse reactions were observed more frequently in studies of combination use of sitagliptin with other anti-diabetic medicinal products than in studies of sitagliptin monotherapy. These included hypoglycaemia (frequency very common with the combination of sulphonylurea and metformin), influenza (common with insulin (with or without metformin)), nausea and vomiting (common with metformin), flatulence (common with metformin or pioglitazone), constipation (common with the combination of sulphenylurea and matformin), peripheral oedema (common with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhoea (uncommon with metformin), and dry mouth (uncommon with insulin (with or without metformin)).[17][19]

XI. Paediatric Population:

In clinical trials with sitagliptin in paediatric patients with type 2 diabetes mellitus aged 10 to17 years, the profile of adverse reactions was comparable to that observed in adults. TECOS Cardiovascular Safety Study. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and 50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA,, and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo. In the intention-to-treat population, among patients who were using insulin and/or a sultonylurea at baseline, the incidence of severe hypoglycaemia was 2.7% in sitagliptin-treated patients and 2.5% in placebo-treated patients, among patients who were not using insulin or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0% in sitagliptin-treated patients and 0.7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients.[22]

XII. Dapagliflozin:

The following important adverse reactions are described below and elsewhere in the labeling:

A] Volume Depletion:

- Ketoacidosis in Patients with Diabetes Mellitus
- Urosepsis and Pyelonephritis
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital Mycotic Infections.

B] Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drog cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice Dapagliflozin has been evaluated in clinical trials in patients with type 2 diabetes mellitus and in patients with heart failure. The overal safety profile of Dapagliflozin was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.[25]

C] Postmarketing Experience:

Additional adverse reactions have been identified during post approval use of Dapagliflozin in patients with diabetes melitus. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency of establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

XIII. Metformin:

Clinical Trials Experience:

Because clinical trials are conducted under widely varying condmons, adverse reactipa rates observed in the clinical trials of a n cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. In clinical trials conducted in the U.S., over 1000 patients with type 2 diabetes mellitus have been treated with Metformin 1500-2000 mg/day in active-controlled and placebo-controlled studies with the 500 mg dosage form In the 24-week monotherapy trial comparing Metformin to immediate-release metformin, serious adverse reactions were reported in 3.6% (19/528) of the Metformin -treated patients compared to 2.9% (5/174) of the patients treated with immediate-release metformin in the add-on to sulfonylurea study, patients receiving background glyburide therapy were randomized to receive add-on treatment of either one of three different regimens of Metformin or placebo. In total, 431 patients received Metformin and glyburide and 144 patients received placebo and glyburide. A serious adverse reaction was reported in 2.1% (9/431) of the Metformin and glyburide-treated patients compared to 1.4% (2/144) of the placebo and glyburide-treated patients. When the data from the monotherapy and add-on to sulfonylurea clinical trials were combined, the most frequently (incidence ≥ 0.5%) reported serious adverse reactions classified by system organ class were gastrointestinal disorders (1.0% of Metformin-treated patients compared to 0% of patients not treated with Metformin) and cardiac disorders (0.4% of Metformin-treated patients compared to 0.5% of patients not treated with Metformin). Only 2 serious adverse reactions (unstable angina (n-2) and pancreatitis (n-2)) were reported in more than one Metformin -treated patient. In 0.7% of patients treated with Metformin and glyburide, diarrhea was responsible for discontinuation of study medication compared to no patients in the placebo and glyburide group.

XIV. Laboratory Tests:

• Vitamin B12 Concentrations:

Metformin may lower serum vitamin B12 concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on Metformin and any apparent abnormalities should be appropriately investigated and managed.

XV. Overdose:

Sitagliptin:

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as dictated by the patient's clinical status. Sitagliptin is modestly dialyzable.

Dapagliflozin:

It is reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

Metformin:

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

XVI. Pharmacological Properties:

Mechanism Of Action:

• Sitagliptin:

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes mellitus by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are

increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also towers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.[24][26]

XVII. Pharmacodynamic Properties:

Sitagliptin:

General:

In patients with type 2 diabetes mellitus, administration of sitagliptin led to Inhibition of DPP-4 enzyme activity for a 24 four period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.[11]

Cardiac Electrophysiology:

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose. the maximum increase in the placebo-corrected mean change in QTc from baseline was observed at 3 hours post dose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose. In patients with type 2 diabetes mellitus administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.[22]

Pharmacokinetic Properties:

Sitagliptin:

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM-hr, Cmax was 950 nM, and apparent terminal half-life (t1/2) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.[24]

Absorption:

After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median Tmax) occurring 1 to 4 hours postdose. The absolute bioavailability of sitagliptin is approximately 87%.

Effect Of Food:

Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

Distribution:

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Metabolism:

Following a [140] sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Elimination:

Following administration of an oral [14C] sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of P-glycoprotein (P-gp), which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin.

Pharmacodynamic Properties:

Dapagliflozin:

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity.

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin. Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day at Week 12. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume. After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.

Cardiac Electrophysiology Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15-times the recommended maximum dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50-times the recommended maximum dose) of dapagliflozin in healthy subjects.

Pharmacokinetic Properties:

• Dapagliflozin:

Absorption:

Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Distribution:

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metabolism:

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-0-glucuronide, which is an inactive metabolite. Dapagliflozin 3-0-glucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination:

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [140]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively.

In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.[22]

Pharmacodynamic Properties:

• Metformin:

Metformin is a biguanide that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in patients with type 2 diabetes or in healthy subjects except in special circumstances, and does not cause hyperinsulinemia. With metformin therapy. insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.[4]

Absorption And Bioavailability:

Following a single oral dose of 1000 mg (2x500 mg tablets) Metformin after a meal, the time to reach maximum plasma metformin concentration (Tmax) is achieved at approximately 7-8 hours. In both single and multiple-dose studies in healthy subjects, once daily 1000 mg (2x500 mg tablets) dosing provides equivalent systemic exposure, as measured by area-under-the-curve (AUC), and up to 35% higher Cmax, of metformin relative to the immediate release given as 500 mg twice daily. Metformin tablets must be administered immediately after a meal to maximize therapeutic benefit.[1]

Single oral doses of Metformin from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and Cmax. fat and high-fat meals increased the systemic exposure (as measured by AUC) from Metformin tablets by about low -38 % and 73%, respectively, relative to fasting. Both meals prolonged metformin Tmax by approximately 3 hours but Cmax was not affected. In a two-way, single-dose crossover study in healthy volunteers, the 1000 mg tablet was found to be bioequivalent to two 500 mg tablets under fed conditions based on equivalent Cmax and AUCs for the two formulations.[6]

Distribution:

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg immediate-release metformin hydrochloride averaged 654 358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 pg/ml. During controlled clinical triats, which served as the basis of approval for metformin, maximum metformin plasma levels did not exceed 5µg/mL, even at maximum doses.[5]

Metabolism:

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans), nor biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.[7]

Elimination:

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination hall-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.[12]

XVIII. Nonclinical Toxicology:

Sitagliptin:

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. In a pre-/postnatal development study performed in rats sitagliptin showed no adverse effects. Reproductive toxicity studies showed a slight treatment-related increased incidence of toetal rib malformations.[21]

Dapagliflozin:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.[19]

Metformin:

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

XIX. Description:

• Sitagliptin: Sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase4 (DPP-4) enzyme. Sitagliptin phosphate monohydrate is described chemically as 7-1(3R)-3-amino-1-oxo-4-(2.4.5-Trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate:

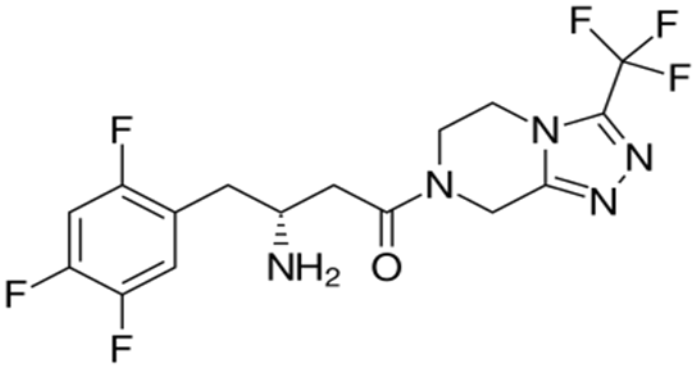

Figure 1: Structure Of Sitagliptin

• Dapagliflozin: Described chemically as D-glucitol, 1.5-anhydro-1-C-14-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-. (15)-compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is C21H25CI06-C3H802-H20 and the molecular weight is 502.98. The structural formula is:

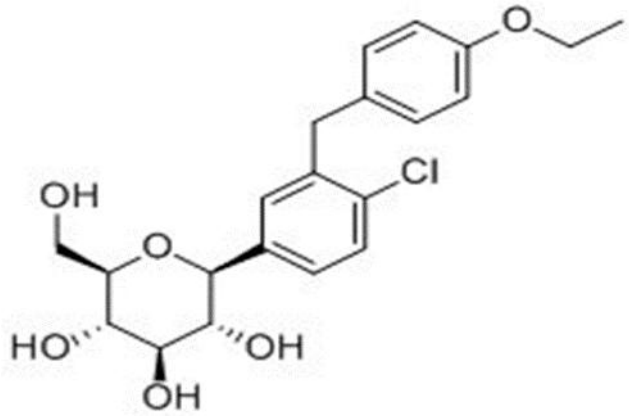

Figure 2: Structure Of Dapagliflozin

• Metformin Hydrochloride: Metformin hydrochloride extended release tablet is an oral antihyperglycemic medication used in the management of type 2 diabetes Metformin hydrochloride (N. Ndimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula of metformin hydrochloride (metformin HCI) is as shown:

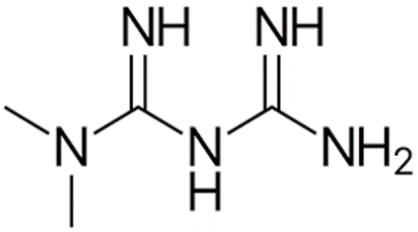

Figure 3: Structure Of Metformin Hydrochloride

XX. Conclusion:

This Research paper basically very essential for Knowledge and study aimed to evaluate the bioequivalence of a fixed-dose combination (FDC) therapy containing extended-release Metformin (Metformin XR), Dapagliflozin, and Sitagliptin for the treatment of Type 2 Diabetes Mellitus (T2D). The study successfully established that the fixed-dose combination (FDC) of Dapagliflozin, Sitagliptin, and Metformin XR is bioequivalent to the reference products in healthy adult males under fed conditions. The comparable absorption profiles and pharmacokinetic parameters confirm that the FDC provides similar efficacy and therapeutic outcomes as the individual components administered separately. These findings support the clinical utility of the FDC as an effective treatment option for improving glycemic control in adults with Type 2 Diabetes Mellitus (T2DM). The convenience of a single-pill combination enhances patient adherence and simplifies diabetes management, making it a promising approach, particularly in the Indian healthcare setting, where optimizing treatment compliance is crucial. By integrating multiple mechanisms of action, this FDC offers a comprehensive solution for diabetes management, reinforcing the benefits of combination therapy in achieving better metabolic control and reducing the long-term complications of T2D. The study confirmed that the Dapagliflozin (10 mg) / Sitagliptin (100 mg) / Metformin XR (1000 mg) FDC tablets are bioequivalent to their corresponding reference products. The pharmacokinetic parameters met regulatory bioequivalence criteria, demonstrating that the FDC formulation provides similar absorption and efficacy as the individual drugs administered separately. Additionally, the safety profile of the FDC was consistent with the known safety profiles of dapagliflozin, sitagliptin, and metformin. The combination was well-tolerated, with no serious adverse effects reported, reinforcing its suitability for long-term use in diabetes management.nThis study suggests that the triple FDC therapy could serve as a viable alternative to the conventional stepwise treatment approach for Type 2 Diabetes Mellitus (T2DM). By incorporating three complementary mechanisms of action in a single tablet, the FDC may enhance treatment adherence, simplify diabetes management, and improve glycemic control. For patients requiring multiple glucose-lowering agents, this fixed-dose combination could offer a more convenient and effective therapeutic option, helping to achieve better glycemic outcomes while reducing pill burden and improving overall treatment compliance.[RESEARCH]

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