WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 5, 1921-1929. Review Article ISSN 2277– 7105

EVOGLIPTIN TARTRATE A NEW DRUG OF DPP-4 INHIBITOR: AN OVERVIEW

Kinjal Thakkar*, Khushbu Patel, U. B. Patel and Dr. C. N. Patel

*Department of Pharmaceutical Quality Assurance, Gujarat Technological University, Ahmedabad, Gujarat, Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India.

Article Received on
19 March 2021,

Revised on 08 April 2021,
Accepted on 29 April 2021

DOI: 10.20959/wjpr20215-20452

***Corresponding Author**
Kinjal Thakkar
Department of Pharmaceutical Quality Assurance, Gujarat Technological University, Ahmedabad, Gujarat, Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India.

ABSTRACT

DPP4 inhibitors (DPP4i) are a modern class of diabetes medications that retain incretin hormones while increasing postprandial insulin secretion. Gliptins also known as DPP-IV inhibitors is a class of antidiabetic drug. DPP-IV inhibitor like Evogliptin tartrate chemically known as (3R)-4-[(3R)-3-amino- 4-(2,4,5-trifluorophenyl) butanoyl]-3-[(2-methylpropan-2-yl) oxymethyl] piperazin-2-one;(2R,3R)-2,3-dihydroxybutanedioic acid is used as a monotherapy. This article explains about chemistry, pharmacology, safety information and drug-drug interaction of Evogliptin tartrate.

KEYWORDS: Type 2 diabetes, DPP-4 inhibitors, Classification of antidiabetics, Drug interaction.

INTRODUCTION

Diabetes mellitus

Diabetes mellitus is a metabolic disease that causes high blood sugar in the blood. Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time.[1]

Pancreas secrets hormone called insulin which metabolizes glucose that we obtain from food that converts into energy. In people with type-II diabetes mellitus either pancreas does not produce enough insulin or pancreas produces insulin but cells don't use it this is also called insulin resistance.[2,5]

When a cell becomes insulin resistance, it requires more insulin to convert glucose into energy and it leads to hyperglycaemia or raised blood sugar. For the treatment of diabetes mellitus type II proper diet and exercise are essential along with drug. [Fig. 1]

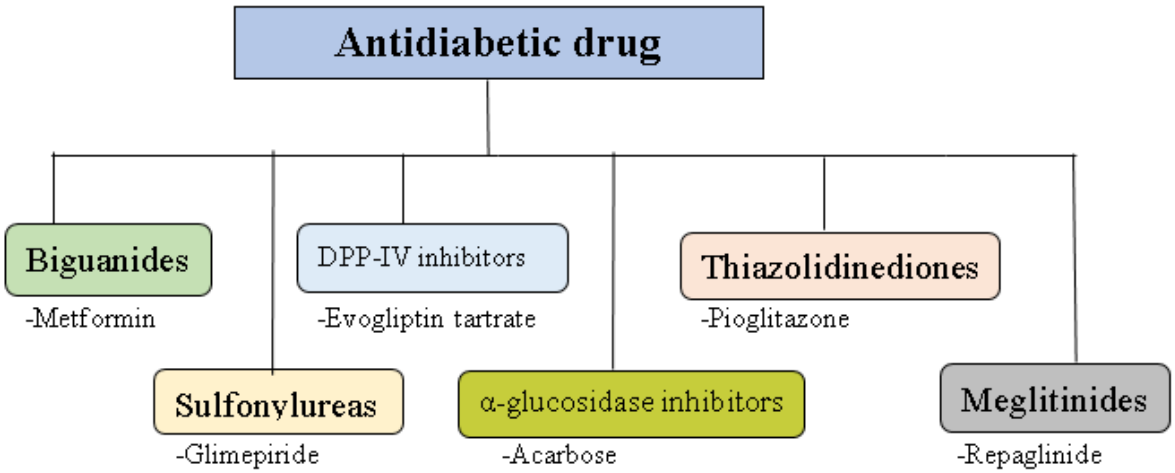

Fig 1: Classification of Antidiabetic Drug.

DPP-IV inhibitors

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are new class of oral diabetes drugs. Gliptins, also known as DPP-IV, are commonly used for patient with type-II diabetes who haven't reacted well to sulphonylureas and metformin. Dipeptidyl peptidase-IV inhibitors can help with weight loss and blood glucose control, but they've also been linked to an increased risk of pancreatitis.

They work by blocking the action of DPP-IV, an enzyme which destroys incretins (a group of gastrointestinal hormones). Incretins aids in the stimulation of insulin production when it is required (e.g., after eating) and the reduction of glucagon production by the liver when it is not required (e.g., during digestion).

They also decrease appetite & delay digestion. So, by defending incretins from damage, DPP-IV inhibitor helps to control blood glucose levels.[3] They do not cause hypoglycaemia unless they are combined with other therapies that cause hypoglycaemia.[4,6] After metformin and sulphonylureas, DPP-IV inhibitors can be used as a second or third-line treatment for patients with type-II diabetes, as a substitute to thiazolidinediones.[3,4]

Example of DDP-IV inhibitors are Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin, Gemigliptin, Anagliptin, Teneligliptin, Alogliptin, Trelagliptin, Omarigliptin, Evogliptin

Evogliptin tartrate

Evogliptin tartrate is a selective DPP-IV (dipeptidyl peptidase-4) inhibitor & it is prescribed in diabetes mellitus. It is also used as anti-atherosclerosis drug when it targets arterial inflammation.[4]

Evogliptin is a β-amino amide derivative.[7] Dong-A ST which is a south Korean pharmaceutical company has developed evogliptin. In South Korea, evogliptin is approved for use. Evogliptin is derived from the words "Evo-lution" and "Gliptin," and it refers to an advanced type of gliptin that has the highest points of known DPP-IV inhibitors.[8]

Evogliptin has a low risk of interaction with other co-administered medications, which can make it easier for patients to take several medications for chronic disease.[8]

History of Evogliptin

- In September 2014, Stage I clinical trials in Type-II diabetes mellitus (in volunteers) were conducted in the U.K (PO) [7]
- Stage-III clinical trials in Type-II diabetes mellitus were conducted on 31st july,2014 in South Korea (PO).[7]
- On July,2014, Dong-A ST began enrolling patients in a phase I study in South Korea for patients with 01 renal failure.[7]

- **22 oct 2018** approved by **CDSCO**.[9]

Mechanism of action

Evogliptin is a dipeptidyl peptidase IV inhibitor that is both competitive and reversible. This enzyme slows the breakdown of GLP-1(Glucagon like peptide) and GIPs. GLP- 1 & GIP stimulate the release of insulin while inhibiting the release of glucagon from beta cell of pancreas. [Fig. 2] The repressive activity of evogliptin compared to Sitagliptin is about 10-fold, also When compared to DPP8/9, evogliptin has a 6,000-fold higher selectivity for DPP-IV.[10]

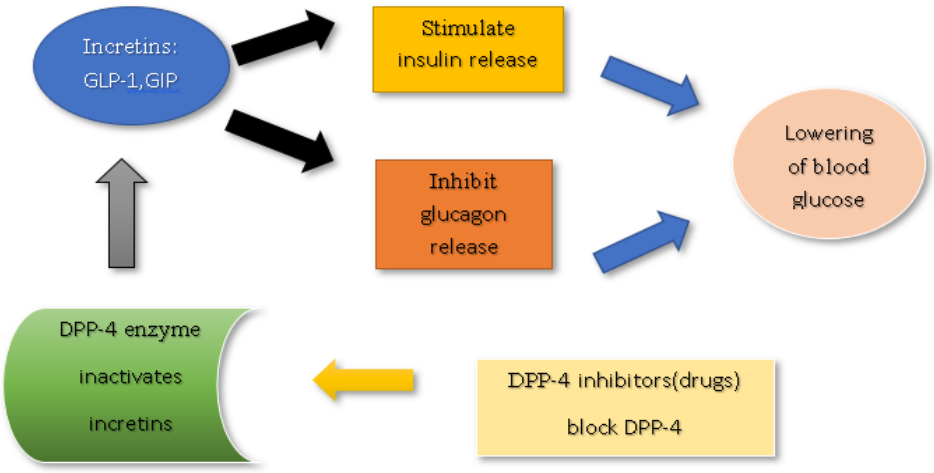

Fig 2: Mechanism of DPP-4 inhibitors.

Chemistry of Evogliptin tartrate is (3*R*)-4-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-[(2-methylpropan-2-yl)oxymethyl]piperazin-2-one;(2*R*,3*R*)-2,3-dihydroxybutanedioic acid.[9] [Fig. 3] Its Chemical formula is $C_{23}H_{32}F_3N_3O_9$. Evogliptin is a hybrid peptide, which is a type of organic compound.[10] These are compounds that contain at least two distinct groups of amino acids (alpha, beta, gamma & delta) connected by peptide bonds.[13] It is a novel molecule with molecular weight 551.5 g/mol[12] The Partition co-efficient (log p) is 1.17 while Dissociation Constant(pka) is 13.69 (Strongest Acidic), -8.78 (Strongest basic)[13] The appearance is white to off white solid and the melting point is 208-212°C.[11]

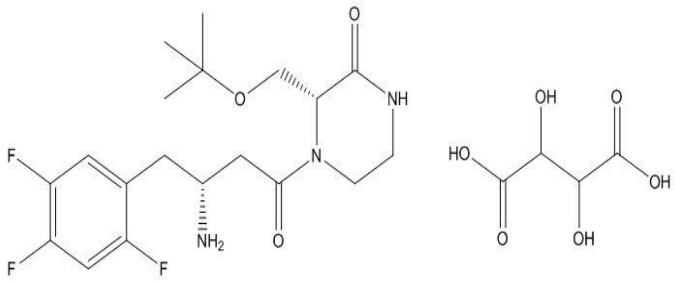

Fig 3: Structure of Evogliptin tartrate.

Pharmacology

Pharmacokinetics

Absorption

- After single oral administration bioavailability of evogliptin is more than 50%. The absorption of evogliptin is unaffected by its administration with food.

- At doses of 1.25–60 mg, the time to achieve maximum concentration (t C $_{max}$) was 3–5.5 hours in healthy patients after a single oral administration of evogliptin.
- In healthy volunteers the maximum plasma concentration (C $_{max}$) After single oral administration of evogliptin was 5.6 ± 1.3 µg/l at dose of 5 mg. C $_{max}$ and the area under the curve "concentration-time" (AUC $_{last}$) increases as the dose is increased.
- By the third day of administration, a stable state had been achieved after repeated oral administrations of evogliptin at doses of 5 mg, 10 mg, and 20 mg once daily.
- After the drug administration, C_{max} of evogliptin was observed in 4-5 hours after reaching the steady state.

Distribution

- Distribution of evogliptin among plasma and whole blood is almost the similar, about 46% of evogliptin binds to plasma proteins.
- Evogliptin is rapidly distributed in body tissues (excluding heart tissue and mesentery) according to Non-clinical studies. Evogliptin was spotted in the blood stream of foetus. Evogliptin was eliminated in milk of lactating rats.

Metabolism

- The most of evogliptin circulating in blood is the intact drug (more than 80%). The biotransformation mechanism generates five metabolites that have no inhibitory effect on DPP-IV and are mainly found in urine and plasma.
- Evogliptin is usually metabolised with CYP3A4. According to In vitro studies evogliptin did not induce CYP1A2, 2B6, 3A4 enzymes & did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 enzymes.

Excretion

- At doses of 1.25-60 mg, the average elimination half-life (t1/2) ranged from 32.5 to 39.8 hours after a single administration of evogliptin.
- The average excretion half-life after several administration was from 32.9 to 38.8 hours.
- About 42.8% of the dose taken by healthy adult volunteers is eliminated via faeces (including metabolites) and 46.1% of the dose is eliminated via urine.

Dosing

- The normal adult dose of Evogliptin is 5 mg taken once a day orally.

- Use in Paediatrics: Safety and efficacy in paediatrics are yet to be determined.
- There hasn't been enough research done on the administration of elderly patients. Since the elders usually have decreased physiological functions such as renal and hepatic functions, care should be practised during administration while keeping an eye on the patient's condition

Therapeutic Indication

- For the treatment of type-II diabetes mellitus as an adjunct to Exercise & diet to increase glycaemic control, if used as a monotherapy or in combination with metformin.

Contraindication

- Evogliptin Tablets are not approved for those who have a hypersensitivity to the medication or any of its ingredient's Type 1 diabetes, extreme ketosis, diabetic coma or pre-coma.

Side effects

- Hypoglycaemia in combination with insulin or sulfonylurea, inflammation of the throat, upper respiratory tract infection.

Safety Information[10]

1. Heart failure

The use of evogliptin in patients with functional class II-IV is not approved by the New York Heart Association (NYHA) due to a lack of clinical trials in these patients.

2. Renal impairment

In healthy adults, around 46.1% of the administered radioactivity was eliminated in urine while approximately 42.8% in feces. It includes both the unchanged form and its metabolites.

3. Hepatic impairment

There was no study conducted in patients with hepatic impairment.

4. Acute pancreatitis

Acute pancreatitis has not been reported in patients taking evogliptin. Patients should be mindful of the effects of acute pancreatitis, which include constant, intense abdominal pain. If pancreatitis is suspected, evogliptin should be stopped; if acute pancreatitis is confirmed, it should not be restarted. Patients with a history of pancreatitis should be treated with caution.

Use during Pregnancy and Lactation

Use in pregnant women

There are no comparable research findings for pregnant women. Animal tests revealed that 2 hours after administration, evogliptin was found in the bloodstream of the foetus through the placenta in up to 61.7 percent of pregnant rats and 14.1 percent of pregnant rabbits. As a result, use of pregnant women is not advised.

Use in Nursing women

The amount of evogliptin excreted in human milk has not been determined. Evogliptin can not be used in breastfeeding mothers because animal tests have shown that it is secreted in milk.[8]

Drug-Drug Interaction

CYP3A4 is the enzyme that metabolises evogliptin the most. evogliptin was shown to be neither an inhibitor nor an inducer of the CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 enzymes.

evogliptin is unlikely to cause interactions with other drugs acting as a substrate of such enzymes.

Interaction of evogliptin with other drugs

Metformin: The pharmacokinetics of evogliptin 5 mg and twice daily metformin 1,000 mg (an OCT1 and OCT2 substrate) did not improve clinically meaningfully until a stable state was achieved.[8]

Clarithromycin: Single administration of evogliptin at a dose of 5 mg resulted in a 2.17-fold increase of evogliptin Cmax and a 2.02-fold increase in evogliptin AUC compared to multiple administration of potential CYP3A4 inhibitor clarithromycin at a daily dose of 1,000 mg until the steady concentration was achieved. Precautions should be taken since the pharmacokinetic parameters of evogliptin can increase if it is administered with a CYP3A4 inhibitor.[12]

CONCLUSION

The review article carried out an overview about Evogliptin tartrate. Evogliptin tartrate is a DPP-IV inhibitor which is used in diabetes mellitus. It is also used as anti-atherosclerosis drug when it targets arterial inflammation. DPP4 inhibitors (DPP4i) are a modern class of

diabetes medications that retain incretin hormones while increasing postprandial insulin secretion.

ACKNOWLEDGEMENT

I am thankful to Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India.

REFERENCE

1. World Health Organization "About diabetes". March 2021.
2. RSSDI textbook of diabetes mellitus (Revised 2nd ed.). Jaypee Brothers Medical Publishers, 2012; 235.
3. Saedi, E Gheini, MR; Faiz, F Arami, MA (15 September 2016), "Diabetes mellitus and cognitive impairments", World Journal of Diabetes, 7(17): 412–22.
4. Diabetes .co .UK, "DPP-4 inhibitors", March 2021. https://www.diabetes.co.uk/diabetes-medication/dpp-4-inhibitors.html
5. Luye Pharma Group, Dong A. Pharma Co Ltd. Luye Pharma obtains the exclusive license of new antidiabetic preparation in China from Dong-A Phama Co., Ltd.—DPP-IV inhibitor DA-1229 [media release].
6. Springer link.com "evogliptin – first global approval", March 2021. https://link.springer.com/article/10.1007/s40265-015-0496-5
7. New drug approval, "evogliptin", March 2021. https://newdrugapprovals.org/?s=evogliptin+tartrate&submit=
8. Dong-A ST's DPP-4 inhibitor SUGANON, got approved for diabetes in Korea, 2 oct 2015. https://pipelinereview.com/index.php/2015100259148/Small-Molecules/Dong-A-STs-DPP4-inhibitor-SUGANON-got-approved-for-type-2-diabetes-in-Korea.html
9. CDSCO, "Evogliptin tartrate", February 2021. https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTA0Mg==
10. Alkemlabs.com "Evogliptin", March 2020. https://www.alkemlabs.com/pdf/adverse/Evogliptin.pdf
11. Park KJ, Shim HJ. Metabolism and excretion of [14C]evogliptin, a DPP-4 inhibitor, in rats [abstract no. P323]. Drug Metab Rev, 2014; 45(Suppl 1): 195.
12. PubChem (135395528), "Evogliptin tartrate" March 2021. https://pubchem.ncbi.nlm.nih.gov/compound/135395528

13. Drug bank (DB12625), “Evogliptin”, March 2021. https://go.drugbank.com/drugs/DB12625
14. Clearsynth.com (CAS Registry No. – 1222102-51-3), “Evogliptin Tartrate”, March 2021. https://clearsynth.com/en/CSP01335.html
15. GEROPHARM, “evogliptin tartrate”, March 2021. https://geropharm.com/portfolio/endokrinologiya/evodin-evogliptin