

**REVIEW ARTICLE**

**Alogliptin – A Narrative Review**

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**ABSTRACT:**

Diabetes mellitus is a metabolic disorder that is characterised by raised blood glucose level in the body as a result of insulin resistance and pancreatic beta-cell failure and defects in insulin secretion or insulin action. Pharmacological therapy for the management of type II diabetes currently includes six classes of Oral Antidiabetic drugs. They are Biguanides, Sulfonylureas, Meglitinides, Thiazolidinediones, Dipeptidyl peptidase IV inhibitors (DPP4) and  $\alpha$ -Glucosidase inhibitors. The five accessible DPP-4 inhibitors are sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, which are also called as “Gliptins”. Alogliptin has been well established as the treatment option in the management of type 2 diabetes. Alogliptin is available as three new combination which is used with diet and exercise which helps in further improvement of glycemic control. Alogliptin is a Pro-drug, in which the active substance is alogliptin benzoate. The main advantage of using alogliptin over other drugs in its class is that the selectivity for DPP-IV is much higher than the next closest competitor drug. The cost of drug acquisition is low and affordable both as a single drug or in combination when compared to other DPP4 inhibitors.

**KEYWORDS:** DPP4 – Dipeptide Peptidase inhibitor; GLP-1 - glucagon-like peptide-1; GIP - glucose-dependent insulinotropic peptide; DM – Diabetes Mellitus.

**INTRODUCTION:**

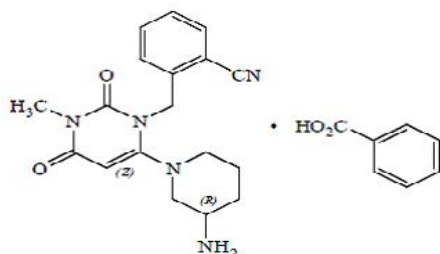
Diabetes mellitus is a metabolic disorder that is characterised by raised blood glucose level in the body as a result of insulin resistance and pancreatic beta-cell failure and defects in insulin secretion or insulin action<sup>1</sup>. Type II diabetes is a progressive disease which may require lifelong therapy. Management includes a life style modification such as diet, regular exercise and medicine to reduce blood glucose levels.

Pharmacological therapy for the management of type II diabetes currently includes six classes of Oral Antidiabetic drugs : 1)Biguanides (Metformin), 2)Sulfonylureas (Glimepiride, Gliclazide, Glipizide, Glibenclamide, Tolbutamide), 3)Meglitinides (Repaglinide, Nateglinide), 4)Thiazolidinediones (Pioglitazone), 5)Dipeptidyl peptidase IV inhibitors (Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, Linagliptin), and 6)  $\alpha$ -Glucosidase inhibitors (Acarbose, Voglibose, Miglitol). This treatment has shown high effectiveness in reducing blood glucose levels, however they are associated with an increased risk of hypoglycaemia. Adverse effects such as weight gain and gastrointestinal intolerance are seen with Sulphonylureas, Thiazolidinediones and insulin. These unwanted adverse effects may act as barrier to regulate the blood glucose level.<sup>2</sup> It has been found that, newer and safer management to control blood sugar level are continuously being explored and elaborated. The GLP-1

agonists and DPP-4 inhibitors are best examples of such development.<sup>3</sup> Though there are some differences in the pharmacokinetic and pharmacodynamic properties of the different DPP-4 inhibitors, all are orally active compounds with similar HbA1c-lowering efficacy. They control blood sugar level in Type II DM, without increasing the risk of hypoglycaemia or weight gain<sup>4</sup>. The five accessible DPP-4 inhibitors are sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, which are also called as “Gliptins”. These are small molecules with generally same clinical efficacy and safety outline in Type II diabetes patients.<sup>5</sup> The newest DPP-4 inhibitor, alogliptin, was authorized in January 2013. Alogliptin has been well established as the treatment option in the management of type 2 diabetes. Alogliptin is available as three new combination which is used with diet and exercise which helps in further improvement of glycemic control. Alogliptin is available as a single ingredient agent (Nesina) as well as in combination with pioglitazone (Oseni) and metformin (Kazano).<sup>6</sup> This review will focus on alogliptin, a member of gliptin family.

Alogliptin is an Oral Hypoglycemic drug in the class DPP-4 inhibitor. Molecular formula for Alogliptin is C<sub>18</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub> with IUPAC name 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-(2H)yl}methyl) benzonitrile. It is an orally administered anti-diabetic drug, which is accessible in 6.25mg, 12.5mg and 25mg in the form of tablets.<sup>7</sup>

Alogliptin is a Pro-drug, in which the active substance is alogliptin benzoate. It is a white crystalline odourless powder, soluble in dimethylsulfoxide, economically soluble in methanol, moderately soluble in tetrahydrofuran, and virtually insoluble in toluene and diethyl ether.<sup>8</sup>



#### MECHANISM OF ACTION:

Dipeptidyl-peptidase IV (DPP-4) inhibitors inhibit the degeneration of the incretins, GLP-1 and GIP.<sup>9</sup> DPP-4 is a omnipresent enzyme demonstrated on the aspect of most cell types that inactivates a variety of bioactive peptides, including GIP and GLP-1; thus, its inhibition could probably affect blood sugar level regulation

through numerous effects.<sup>10</sup>

When blood sugar levels are raised after a meal, GLP-1 is released from the GIT, and it does the followings like: Stimulates insulin secretion from the pancreatic  $\beta$ -cells, Reduces glucagon secretion from the pancreatic  $\alpha$ -cells, Improves  $\beta$ -cell function and slows gastric emptying<sup>2,20</sup>. Alogliptin exerts its effect on blood sugar level by:

1. Reducing fasting and postprandial glucose concentrations.
2. Slowing the inactivation of incretin hormones (GLP-1) and GIP by the DPP-4 enzyme.<sup>11</sup>
3. Increasing the amount of active plasma incretins which helps with glycemic control.<sup>12</sup>

#### THERAPEUTIC USE:

HbA1c is the principle measure that is used to determine the level of blood sugar control and guide the approach to therapy. DPP4 have obtained worldwide use in combination with metformin because of their neutrality in weight, efficacy and safety. Metformin has an unassuming effect to increase GLP-1 secretion. Therefore, the combination of metformin and DPP4 therapy may result in increased GLP-1 levels and an additional glucose-lowering effect. When it is used in triple combination therapy with metformin and Thiazolidinedione (TZD) i.e, pioglitazone it results in preferable glycemic control when compared with double combination therapy, but few pioglitazone dose-dependent side effects like edema and weight gain may occur in triple combination therapy. Alogliptin performs the following functions, They have superior blood sugar-lowering efficacy,

- They assist weight loss, and
- They safeguard  $\beta$ -cell function<sup>13</sup>

Alogliptin decreases HbA1c by 0.5–0.6 % in patients with an initial HbA1c between 7.6–9.3 %, which is same as the other DPP-4 inhibitors. It is recommended as an additional drug to other blood sugar lowering drugs including metformin, sulfonylureas, pioglitazone or insulin, or as triple therapy with metformin and a pioglitazone or insulin.<sup>14</sup>

#### DOSING INFORMATION:

The usual recommended dose of alogliptin is 25 mg orally once in a day. Other available doses are 12.5 mg and 6.25 mg orally once in a day. This is to improve blood sugar control in combination with other blood sugar-lowering drugs like insulin, along with diet and exercise. The indicated combination therapy in use are:<sup>15</sup>

- Dual therapy in combination with metformin, or a sulfonylurea or insulin and
- Triple therapy with metformin and a thiazolidinedione or insulin.

Alogliptin is an alternative drug to other DPP4 like sitagliptin, vildagliptin, saxagliptin and linagliptin. The price of alogliptin is 16 - 20% lower when compared with other DPP-4 inhibitors. The dual therapy alogliptin plus metformin combination cost the same as alogliptin alone.<sup>16</sup>

### SAFETY OF ALOGLIPTIN:

Although newer glucose-lowering drugs are effective at decreasing HbA1c levels, they all lack strong clinical outcome data, mainly around their cardiovascular effects and long-term safety in people with type II diabetes. Improvements in HbA1c levels automatically present with benefits on mortality or morbidity and risks may become apparent only over time when these agents have more widespread use in a diverse population.<sup>17</sup>

Alogliptin usually does not cause low glucose level. Sometimes, low glucose level may occur when it is used along with certain other medicines like insulin, sulfonylureas, etc. Low glucose level may cause distress, increased perspiration, weakness, dizziness, drowsiness, or fatigue. It may also cause the heart to pump faster than the normal, and make changes in the vision, cause headache, chills, or tremors or it cause increase in appetite. It is a good idea to carry a constant source of glucose like tablets or gel to treat low sugar level in the blood. If this is not available, you should eat or drink a quick source of sugar like honey, chocolate, orange juice, or non-diet soda. This will raise your blood glucose level immediately. One Should inform the physician, as soon as it happens. To prevent low glucose level, one should intake food at constant time regularly everyday and should not skip the meal at anycost.<sup>18</sup>

Alogliptin should be used with extreme caution in children, safety and effectiveness in children have not been confirmed. During pregnancy, one should first need to discuss the benefits and risks of taking alogliptin with the physician. It is not known whether alogliptin is excreted in breast milk and it should be discussed with physician for any possible risks to the baby.<sup>19</sup>

### CONCLUSION:

The main advantage of using alogliptin over other drugs in its class is that the selectivity for DPP-IV is much higher than the next closest competitor drug. As stated in MTRAC guidance that, "if a gliptin is need to be used, it is recommended that the gliptin is selected based on the appropriate indications, with the lowest acquisition cost", the cost of drug acquisition (Alogliptin) is low and affordable both as a single drug or in combination when compared to other DPP4 inhibitors.

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