Zydus receives USFDA approval for ZITUVIMET™ to treat adult patients with type 2 diabetes mellitus

The company received final approval from the USFDA for its New Drug Application (NDA) for **ZITUVIMET™** *(Sitagliptin and Metformin Hydrochloride) tablets, 50 mg/500 mg and 50 mg/1000 mg.*

November 06, 2023, Ahmedabad, India

Zydus Lifesciences Limited (including its subsidiaries/affiliates, hereafter referred to as "Zydus") today announced that the U.S. Food and Drug Administration (FDA) approved its New Drug Application (NDA) for ZITUVIMET™ (Sitagliptin and Metformin hydrochloride) tablets, 50 mg/500 mg and 50 mg/1000 mg.

ZITUVIMET™ contains active ingredients sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The approval of ZITUVIMET™ is based on research, development, regulatory, and manufacturing work performed by Zydus teams. ZITUVIMET™ has undergone quality testing for Nitrosamines and potential genotoxic impurities as per current USFDA standards. ZITUVIMET™ is compliant with current USFDA standards of Nitrosamines in Sitagliptin containing products.

"The ZITUVIMET™ approval further builds on our previous approval of ZITUVIO™ (Sitagliptin) and offers an increased accessibility and affordability to healthcare systems with regard to prescription drugs for type II diabetes. The ZITUVIMET™ approval provides an affordable treatment option for healthcare systems to reduce the rate of growth in drug spending and improves the financial sustainability of the healthcare programs," said Dr. Sharvil Patel, Managing Director of Zydus Lifesciences Limited.

According to IQVIA™ (MAT Aug-2023), U.S. market for DPP-IV inhibitors and their combinations is US$ 10 bn.

About Zydus

The Zydus Group with an overarching purpose of empowering people with freedom to live healthier and more fulfilled lives, is an innovative, global life sciences company that discovers, develops, manufactures, and markets a broad range of healthcare therapies. The group employs 25000 people worldwide and is driven by its mission to unlock new possibilities in life sciences through quality healthcare solutions that impact lives. The group aspires to transform lives through pathbreaking discoveries. For more details visit www.zyduslife.com.

PRESS RELEASE

For further information please contact :
The Corporate Communications Department

Zydus Lifesciences Limited
(formerly known as Cadila Healthcare Limited)
Regd. Office : 'Zydus Corporate Park', Scheme No. 63, Survey No. 536, Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, S. G. Highway, Ahmedabad 382 481, Gujarat, India. | Phone : +91-79-71800000, +91-79-48040000 | website : www.zyduslife.com
CIN : L24230GJ1995PLC025878

IMPORTANT SAFETY INFORMATION FOR ZITUVIMET™ (*Sitagliptin and Metformin Hydrochloride) tablets*

INDICATIONS AND USAGE

ZITUVIMET™ is a fixed dose combination of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use:

- ZITUVIMET™ is not recommended in patients with type 1 diabetes mellitus.
- ZITUVIMET™ has not been studied in patients with a history of pancreatitis.

DOSAGE AND ADMINISTRATION

The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin and 500 mg metformin HCl twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin. (2.1)

The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin HCl 850 mg twice daily, the recommended starting dose of ZITUVIMET™ is 50 mg sitagliptin and 1,000 mg metformin HCl twice daily. (2.1). Dosage adjustment is recommended for patients with eGFR less than 45 mL/min/1.73 m2.

DOSAGE FORMS AND STRENGTHS

Tablets:

Sitagliptin 50 mg and metformin HCl 500 mg tablets
Sitagliptin 50 mg and metformin HCl 1,000 mg tablets

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CONTRAINDICATIONS

ZITUVIMET™ is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m2) [see Warnings and Precautions.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis.
- A history of a serious hypersensitivity reaction to sitagliptin, metformin, or any of the
- excipients in ZITUVIMET™. Serious hypersensitivity reactions including anaphylaxis or angioedema have been reported.

WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of ZITUVIMET™.

In ZITUVIMET™ treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin HCl is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue ZITUVIMET™ and report these symptoms to their health care provider.

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For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment

The post-marketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include

[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]:

- Before initiating ZITUVIMET™, obtain an estimated glomerular filtration rate (eGFR).
- ZITUVIMET™ is contraindicated in patients with an eGFR below 30 mL/min/1.73 m_2 *[see Contraindications (4)]*.
- ZITUVIMET™ is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m_2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination ZITUVIMET™ product.
- Obtain an eGFR at least annually in all patients taking ZITUVIMET™. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions
The concomitant use of ZITUVIMET™ with specific drugs may increase the risk of metformin associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation *[see Drug Interactions (7)]*. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater
The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients *[see Use in Specific Populations*
(8.5)].

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Radiological Studies with Contrast

Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop ZITUVIMET™ at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m_2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart ZITUVIMET™ if renal function is stable.

Surgery and Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. ZITUVIMET should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States

Several of the post-marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue ZITUVIMET™.

Excessive Alcohol Intake
Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving ZITUVIMET™.

Hepatic Impairment
Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of ZITUVIMET™ in patients with clinical or laboratory evidence of hepatic disease.

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5.2 Pancreatitis

There have been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. After initiation of ZITUVIMET™, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, ZITUVIMET™ 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 ZITUVIMET.

5.3 Heart Failure

An association between DPP-4 inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of ZITUVIMET™ prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and 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 ZITUVIMET™.

5.4 Acute Renal Failure

There have been post-marketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with ZITUVIMET and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and ZITUVIMET™ discontinued if evidence of renal impairment is present. ZITUVIMET™ is contraindicated in patients with severe renal impairment *[see Contraindications and Warnings and Precautions]*.

5.5 Vitamin B_{12} Deficiency

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} measurements at 2- to 3-year intervals in patients on ZITUVIMET™ and manage any abnormalities.

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5.6 Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
ZITUVIMET™ may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue (e.g., sulfonylurea) *[see Adverse Reactions (6)]*. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with ZITUVIMET™ *[see Drug Interactions (7)]*.

5.7 Hypersensitivity Reactions
There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of ZITUVIMET™. 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 ZITUVIMET™, assess for other potential causes for the event, and institute alternative treatment for diabetes *[see Adverse Reactions (6.2)]*.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 ZITUVIMET™.

5.8 Severe and Disabling Arthralgia
There have been post-marketing 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. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.9 Bullous Pemphigoid
Post-marketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP- 4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving ZITUVIMET™. If bullous pemphigoid is suspected, ZITUVIMET™ should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

For additional information, refer to full **Prescribing Information.**

To report SUSPECTED ADVERSE REACTIONS, contact Zydus Pharmaceuticals (USA) Inc. at 1-877-993-8779 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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