BIOS LAB PVT. LTD.

·8, MILAN COMPLEX, SARKHEJ, AHMEDABAD

QUALITY CONTROL DEPARTMENT

CERTIFICATE OF ANALYSIS

The Drugs & Cosmetics Act 1940 and The Rules thereunder

Report No. :	**AAFP/A2508-014/18**
Sample Name :	**BIOTENLY®- M FORTE TABLET**
Generic Name :	**Teneligliptin 20 mg and Metformin Hydrochloride (Extended Release) 1000 mg Tablet**

Product Name	**BIOTENLY®- M FORTE**	**A.R.No.**	BRDII/08/18/PC0040TF
Batch No.	PCBP18058A		
Mfg. Date	AUG. 18	**Sample Qty.**	80 Tablets
Exp. Date	JUL. 20	**Test as per**	Manufacturer Specification
Date of Receipt	9/1/2018	**Date of Release**	9/1/2018

S NO.	TEST	RESULT	SPECIFICATION
1.	Description	Yellow and white colored caplet Shaped uncoated bilayer tablet, central break line on one side and plain on white side.	Yellow and white colored caplet shaped uncoated bilayer tablet, central break line on one side and plain on white side.
2.	Identification (By HPLC)	Complies	To Comply
3.	Average weight	1.3916 gm	1.3900 gm ± 5.0%
4.	Uniformity of weight	Min. 1.3751 gm, Max. 1.4085 gm	± 5.0% of average weight
5.	Thickness	Min. 7.10 mm, Max. 7.28 mm	7.10 mm ± 0.2 mm
6.	Friability	0.14%	NMT 1.0%
7.	Hardness	Min. 14.0 kg/cm^2	NLT 3.00 kg/cm^2
8.	Uniformity of content (For Teneligliptin)	Min. 91.72%, Max. 100.32%, Mean 95.39%	NLT 85.00% & NMT 115.00% of the average content
9	Dissolution		
	(1) Teneligliptin - 20mg (By HPLC) (2) Metformin - 1000mg (By UV)	Min. 96.69%, Max 113.66%, Mean 107.61%	NLT 75%
		Min. 38.06%, Max.39.71%, Mean 38.72%	1st Hr - Between 20-45%
		Min. 67.13%, Max 71.38%, Mean 69.26%	3rd Hrs - Between 50-80%
		Min. 97.86%, Max. 100.22%, Mean 99.20%	6th Hrs - Not Less than 75%
10	*Related Substances (By HPLC)		
	For Teneligliptin:		
	1.Teneligliptin Impurity A	Not Detected	NMT 0.5%
	2.Teneligliptin Impurity B	Not Detected	NMT 0.5%
	3.Any other Indivdual Impurity	Not Detected	NMT 0.5%
	4.Total Impurities	Not Detected	NMT 2.0%
	*Related Substances (By HPLC)		
	For Metformin		
	1.Single Max Impurity	Not Detected	NMT 0.2%
	2.Total Impurity	Not Detected	NMT 1.0%
11	ASSAY (By HPLC)		
	Each Uncoated bilayered tablet contains		
	Teneligliptin Hydrobromide Hydrate		NLT 18.00 mg & NMT 22.00 mg
	Eq. to Teneligliptin 20 mg	20.22 mg , 101.1%	NLT 90.00% & NMT 110.00%
	Metformin Hydrochloride IP 1000 mg	970.96 mg, 97.1%	NLT 900.0 mg & NMT 1100.0 mg
	(Extended Release Form)		NLT 90.00% & NMT 110.0%

Remarks: The Above Sample Complies/Does not comply as per IP/BP/USP/Manufacturer Specification No. ADL/STP/022

* Test Complies as per Ashirvad Lab Reports No. AAFP/A2508-014/18

* Manufactured by: PRECISE CHEMIPHARMA PVT. LTD.

BIOTENLY®-M FORTE TABLETS

Each Tablet Contains

Teneligliptin – 20mg

Metformin HCl ER – 1000mg

PHARMACEUTICAL DESCRIPTION-

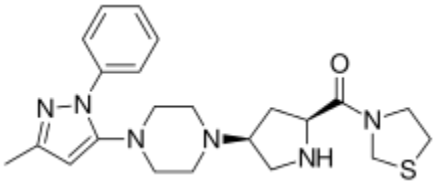
TENELIGLIPTIN:

Generic name: Teneligliptin

Chemical name: {(2*S*,4*S*)-4-[4-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl}(1,3-thiazolidin-3-yl)methanone

Molecular mass: 426.58 g/mol

Structural formula:



Empirical formula – $C_{22}H_{30}N_6OS$

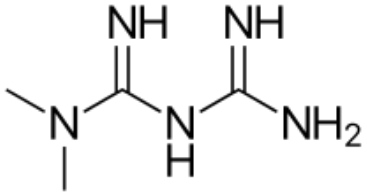
METFORMIN:

Generic name: Metformin HCl

Chemical name: *N*, *N*-Dimethyl imidodi carbonimidic diamide

Molecular mass: 129.16364 g/mol

Structural formula:



Empirical formula - $C_4H_{11}N_5$

PHARMACOKINETIC PROPERTIES –

Teneligliptin

After oral administration of a single 20 mg and 40 mg dose to healthy subjects, teneligliptin was rapidly absorbed, with peak plasma concentrations (mean T_{max}) occurring at 1.8 hours and 1 hour post dose. Plasma AUC of teneligliptin increased in a dose-proportional manner. Following a single oral 20 mg and 40 mg dose to healthy volunteers, mean plasma AUC of teneligliptin was 2028.9 and 3705.1 ng*hr/ml, C_{max} was 187.2 and 382.4 ng/ml, and apparent terminal half- life ($t_{1/2}$) was 24.2 and 20.8 hours. Plasma AUC of teneligliptin increased following 20 mg doses at steady-state compared

to the first dose. Co-administration with food reduces the C_{max} by 20%, increases the T_{max} from 1.1 to 2.6 hours but does not affect the AUC of teneligliptin as compared to that in the fasting state. The plasma protein binding rate is 77.6 – 82.2%.

Following a 20 mg single oral dose of [14C] teneligliptin, 5 metabolites M1, M2, M3, M4 and M5 were observed. In vitro studies indicated that CYP3A4 and flavin-containing monooxygenase (FMO1 and FMO3) are involved in the metabolism of teneligliptin. Teneligliptin does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, CYP2E1, It is a weak inhibitor of CYP2D6, CYP3A4, and FMO (IC50 value : 489.4, 197.5 and 467.2 μmol/l) and does not induce CYP3A4 and CYP1A2.

Following a 20 mg single oral dose of [14C] teneligliptin, 45.4% of administered radioactivity was excreted in urine and 46.5% in faeces till 216 hours after dose. The cumulative urinary excretion rates for up to 120 hours for un-metabolized, M1, M2, and M3 were 14.8%, 17.7%, 1.4% and 1.9% respectively while the cumulative faecal excretion rates for un-metabolized, M1, M3, M4 and M5 were 26.1%, 4.0%, 1.6%, 0.3% and 1.3% respectively.

The single administration of teneligliptin at 20 mg in patients with renal impairment revealed no remarkable changes in C_{max} and $t_{1/2}$ corresponding to the level of renal impairment. Compared with healthy adult subjects, the AUC0–∞ of subjects with mild renal impairment (50 ≤ creatinine clearance [Ccr] ≤ 80 mL/minute), moderate renal impairment (30 ≤ Ccr <50 mL/minute), and severe renal impairment (Ccr < 30 mL/minute) was approximately 1.25 times, 1.68 times, and 1.49 times higher than that of healthy adult subjects, respectively.

A single administration of teneligliptin 20 mg in patients with hepatic impairment revealed that the C_{max} of subjects with mild hepatic impairment (Child–Pugh classification: total score 5–6) and moderate hepatic impairment (Child–Pugh classification: total score 7–9) was approximately 1.25 times and 1.38 times that of healthy adult subjects, respectively. Compared to healthy adult subjects, the AUC0–∞ of subjects with mild and moderate hepatic impairments was approximately 1.46 times and 1.59 times higher than that of healthy adult subjects, respectively. There have been no previous clinical studies using teneligliptin in patients with severe hepatic impairment (Child–Pugh classification: total score was greater than 9).

Metformin Extended-Release

The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin tablets of 500 mg or 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Following a single oral dose of metformin sustained-release, C_{max} is achieved within 4-8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin immediate release, however, the extent of absorption (as measured by AUC) is similar to immediate release. Both high and low fat meals had the same effect on the pharmacokinetics of sustained release. Protein binding of Metformin is Minimal and Metabolism is not done by liver Moreover Biological Half-life is 4-8.7 hours and Excretion us done by Urine (90%).

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION –

Teneligliptin

Teneligliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by teneligliptin, 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 lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, teneligliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

Metformin

Metformin improves glucose tolerance in patients with type-2 diabetes (NIDDM), 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.

INDICATION –

Type 2 diabetes mellitus

- The drug product should be used only in patients who have not sufficiently responded to either of the following treatments.
  (a) Diet and/or exercise therapy alone
  (b) Use of sulfonylureas in addition to diet and/or exercise therapy
  (c) Use of thiazolidinediones in addition to diet and/or exercise therapy

CONTRAINDICATIONS –

Teneligliptin

Teneligliptin is contraindicated in the following:

- Any patient with a known hypersensitivity to teneligliptin or any of the components in the formulation,
- Severe ketosis, diabetic coma or history of diabetic coma, type 1 diabetic patients,
- Patients with severe infection, surgery, severe trauma (blood sugar control should preferably be done by insulin).

Metformin

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (arbitrarily defined as creatinine levels over 150 μmol/l (1.7 mg/dl), lung disease and liver disease. According to the prescribing information, heart failure (in particular, unstable or acute congestive heart failure) increases the risk of lactic acidosis with metformin.

DOSAGE AND ADMINISTRATION –

The usual adult dosage is 20 mg of teneligliptin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 40 mg once daily while closely monitoring the clinical course. The usual adult dosage is 500mg of metformin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 2550 mg once daily

ADVERSE EFFECTS –

Teneligliptin

The most common adverse reactions reported with teneligliptin are hypoglycemia and constipation.

Other adverse reactions reported with teneligliptin are:

- **Gastrointestinal Disorders:** Intestinal obstruction, abdominal bloating, abdominal discomfort, nausea, abdominal pain, flatulence, stomatitis, gastric polyps, colon polyps, duodenal ulcer, reflux esophagitis, diarrhea, loss of appetite, increased amylase, lipase increased, acute pancreatitis.
- **Kidney and Urinary system:** Proteinuria, Urine ketone-positive.
- **Skin and Subcutaneous Tissue Disorders:** Eczema, rash, itching, allergic dermatitis.
- **Investigations:** Increase in AST, ALT, γ-GTP and ALP.
- **Others:** Increased CPK, increased serum potassium, fatigue, allergic rhinitis, elevation of serum uric acid

Metformin

The most common adverse effect of metformin is gastrointestinal irritation, including diarrhea, cramps, nausea, vomiting, and increased flatulence; metformin is more commonly associated with gastrointestinal side effects than most other antidiabetic drugs.[The most serious potential side effect of metformin use is lactic acidosis; this complication is very rare, and the vast majority of these cases seem to be related to comorbid conditions, such as impaired liver or kidney function, rather than to the metformin itself. Metformin has also been reported to decrease the blood levels of thyroid-stimulating hormone in people with hypothyroidism, The clinical significance of this is still unknown.

OVERDOSAGE

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.

WARNINGS AND PRECAUTIONS

Teneligliptin should be administered carefully in the following:

- Patients with advanced liver failure (safety has not been established),
- Patients with congestive heart failure (NYHA category III-IV) (safety has not been established),
- Patients with pituitary insufficiency or adrenal insufficiency, poor nutritional state, starvation, an irregular dietary intake, or debilitating condition, intense muscle movement or excessive alcohol intake (may cause low blood sugar),
- Patients with history of abdominal surgery or with a history of bowel obstruction (may cause bowel obstruction),
- Patients with arrhythmia, severe bradycardia or its history, patients with heart disease such as congestive heart failure or patients with low serum potassium, congenital prolonged QT syndrome, history of Torsades de pointes or patients using antiarrhythmic drugs (may cause QT prolongation),
- Patients using an insulin secretagogue (e.g., sulfonylurea) (risk of severe hypoglycemia).

DRUG INTERACTIONS –

Teneligliptin

Teneligliptin should be used with caution with drugs that can enhance the blood glucose lowering effect (like β blockers, MAO inhibitors, etc.) and attenuate the blood glucose lowering effect (like steroids, thyroid hormones, etc).

On concomitant therapy with ketoconazole, the geometric least squares mean ratio (concomitant therapy/teneligliptin monotherapy) of C_{max} and AUC0-t of unchanged plasma teneligliptin with their two-sided 90% CI is 1.37 [1.25, 1.50] and 1.49 [1.38, 1.60], respectively.

Metformin

The H_2-receptor antagonist cimetidine causes an increase in the plasma concentration of metformin, by reducing clearance of metformin by the kidneys; both metformin and cimetidine are cleared from the body by tubular secretion, and both, particularly the cationi (positively charged) form of cimetidine, may compete for the same transport mechanism. A small double-blind, randomized study found the antibiotic cephalexin to also increase metformin concentrations by a similar mechanism; theoretically, other cationic medications may produce the same effect.

SPECIAL POPULATIONS:

Teneligliptin

Teneligliptin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Safe use of teneligliptin during pregnancy has not been established. Teneligliptin should be avoided by breastfeeding mothers (transition to milk has been reported in laboratory animals).

Safety and effectiveness of teneligliptin in pediatric patients have not been established.

Metformin

Patients with Type 2 Diabetes

- In the presence of normal renal function, there are no differences between single- or multiple- dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.
- The pharmacokinetics of metformin hydrochloride extended-release tablets in patients with type 2 diabetes is comparable to those in healthy normal adults.

Renal Insufficiency

- In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Insufficiency

- No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Geriatrics

- Limited data from controlled pharmacokinetic studies of metformin hydrochloride tablets in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. Metformin hydrochloride extended release tablets treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

STORAGE CONDITION-

- Store below 30°C in dry place. Keep out of reach of children.

PRESENTATION – Teneligliptin 20 mg + Metformin HCl ER 1000 mg tablets

PACKING- 1*10 TAB

BIOS LAB PVT. LTD.

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