SUMMARY OF PRODUCT CHARACTERISTICS

1.1 Name of the Medicinal Product

Nilten-M 20/1000(Teneligliptin and Metformin Hydrochloride)

1.2 Strength

20mg/1000mg

2. Qualitative and Quantitative Composition

Each uncoated bilayer tablet contains:

Teneligliptin Hydrobromide Hydrate Equivalent to Teneligliptin	20 mg
Metformin Hydrochloride BP (As Extended-Release)	1000 mg
Excipients	Q.S.

Approved colours used.

3. Pharmaceutical Form

Oral Solid dosage Form (Tablet)

Description: Pale yellow coloured (Teneligliptin layer) and white to off white coloured (Metformin layer), capsule shaped, biconvex, uncoated, bilayered tablets with break line on one side and plain on other side.

4. Clinical Particulars

4.1 Therapeutic Indications

The product is indicated in patients with T2DM whose diabetes is not adequately controlled on Metformin or Teneligliptin alone or who are already treated with the combination of Teneligliptin and Metformin, as separate tablets.

4.2 Posology and Method of Administration

Tablet shall be taken once a day or as directed by the physician.

Tablets are to be administered orally without regard to meal. Do not crush or chew tablets.

4.3 Contraindications

History of hypersensitivity to Teneligliptin / Metformin or to any of its excipients. Patients having severe ketoacidosis, diabetic coma or pre-coma and Type 1 DM (Since a prompt correction of hyperglycemia is required by transfusion of insulin, the administration of Teneligliptin is not suitable). In conditions such as severe infection, perioperative, severe trauma and severe external injury (since Glycemic Control is desired by insulin injection), the administration of Teneligliptin / Metformin is not recommended.

4.4 Special Warnings and Precautions for Use

Teneligliptin should be administered carefully in the following: Patients with advanced liver failure, Patients with congestive heart failure (NYHA category III-IV), 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 hypoglycaemia).

In patients taking Metformin, lactic acidosis should be suspected in any

diabetic patient with metabolic acidosis lacking evidence of ketoacidosis. Warn patients against excessive alcohol intake due to high risk of lactic acidosis.

4.6 Pregnancy and Lactation

Teneligliptin and Metformin shall be given with precaution in conditions like pregnancy, breastfeeding and trying to conceive. Safe use of teneligliptin during pregnancy has not been established.

4.6 Drug Interactions

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 Cmax 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.

4.7 Effects on Ability to Drive and use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be alerted to the risk of hypoglycaemia especially when Teneligliptin co- administered with sulphonylurea and/or insulin.

4.8 Undesirable Effects

Teneligliptin studies reported few adverse reactions such as hypoglycemia, intestinal obstruction, liver dysfunction and interstitial pneumonia. Metformin commonly causes GI related adverse effects e.g. diarrhea, nausea, vomiting, abdominal pain, constipation, distention abdomen, dyspepsia/heartburn, flatulence and taste disturbance.

Reporting of suspected adverse reactions:

Healthcare professionals are requested to report any suspected adverse reactions to report any suspected adverse reactions to the National Re

4.9 Overdose and its Treatment

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 if required.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Teneligliptin: The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal, in response to meal. This promotes insulin secretion from pancreas and regulates blood glucose post meal by controlling glucagon secretion. Teneligliptin exhibits a hypoglycemic effect by controlling the degradation of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity. Thus increases blood concentration of active GLP-1.

Metformin: Metformin is a biguanide derivative producing an anti-hyperglycemic effect, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin may decrease hepatic glucose production, decrease intestinal absorption of glucose, and improve insulin sensitivity by increasing peripheral glucose uptake and utilization.

5.2 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, Cmax 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. Coadministration with food reduces the Cmax by 20%, increases the Tmax 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.

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 upto 120 hours for un-metabolized, M1, M2, and M3 were 14.8%, 17.7%, 1.4% and 1.9% respectively while the cumulative fecal 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 Cmax and t1/2 corresponding to the level of renal impairment.

A single administration of teneligliptin 20 mg in patients with hepatic impairment revealed that the Cmax of subjects with mild hepatic impairment and moderate hepatic impairment 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.

Metformin: The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50-60%. Following a single oral dose of metformin sustained-release, Cmax 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. Studies using single oral doses of Metformin hydrochloride immediate-release tablets 500 mg to 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. Both high and low fat meals had the same effect on the pharmacokinetics of sustained release. Food decreases the extent of and slightly delays the absorption of Metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850-mg tablet of Metformin with food, compared to the same tablet strength administered

fasting. The clinical relevance of these decreases is unknown.

Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from 500 mg Metformin tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged Metformin Tmax by approximately 3 hours but Cmax was not affected.

The apparent volume of distribution (V/F) of Metformin following single oral doses of Metformin hydrochloride tablets 850 mg 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 hydrochloride tablets, steady state plasma concentrations of Metformin are reached within 24–48 hours and are generally <1 µg/mL. During controlled clinical trials of Metformin, maximum Metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Intravenous single-dose studies in normal 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.

Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

5.3 Preclinical Safety Data

No additional data of relevance.

6. Pharmaceutical Particulars

6.1 List of Excipients

Mannitol BP Maize Starch BP
Hydroxypropyl Cellulose (HPC-LM) USP
Low substituted Hydroxypropyl Cellulose (LH-11) NF
Colour Yellow Oxide of Iron IH
Isopropyl Alcohol BP.
Low substituted Hydroxypropyl Cellulose (LH-11) NF
Aerosil (Colloidal Silicon Dioxide) BP
Magnesium Stearate BP
Metformin Hydrochloride BP

Hypromellose (Metolose 90SH-100000) USP

Magnesium Hydroxide BP

Carbomer Homopolymer Type A (Carbopol 971 P) USP/NF

Purified Water BP

Hypromellose (Metolose 90SH-100000) USP

Magnesium Hydroxide BP

Carbomer Homopolymer Type A (Carbopol 971 P) USP/NF

Carbomer Homopolymer Type A (Carbopol 71 G) USP/NF

6.2 Shelf life

24 Months

6.3 Special Precautions for Storage

Store below 30°C. Protect from light and moisture. Keep the medicine out of reach of children.

6.4 Nature and Contents of Container

15 Tablets are packed in Alu/Alu Blister pack. Such 2 blister is to be packed in a printed carton along with pack insert.

7. Marketing Authorization Holder

CTD11852

8. Date of first authorization

6/04/2026