TALVUS 10

Teneligliptin Hydrobromide Hydrate Tablets 10 mg

COMPOSITION:

Each Film coated Tablet contains:
Teneligliptin Hydrobromide Hydrate
Eq. to Teneligliptin 10 mg
Excipients q.s.
Colour : Ferric oxide Yellow USP-NF Titanium Dioxide BP

DESCRIPTION:

Film coated tablet.

THERAPEUTIC INDICATIONS:

Monotherapy: TALVUS 10 is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus Combination therapy: TALVUS 10 is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, sulfonylureas, PPAR agonist (e.g., thiazolidinediones), rapid insulin secretagogues, alpha-glucosidase inhibitors, sodium glucose co-transporter 2 inhibitor, or insulin when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

POSOLOGY AND METHOD OF ADMINISTRATION

The usual adult dosage is 20 mg of teneligliptin administered orally once daily. If efficacy is insufficient, the dose may be increased to 40 mg once daily with close monitoring of clinical course.

CONTRAINDICATIONS

TALVUS 10 is contraindicated in the following patients.
1) Patients with a history of hypersensitivity to any of the ingredients of this product
2) Patients with severe ketosis, diabetic coma or precoma, and type 1 diabetes mellitus [Treatment with this product is not appropriate because such patients require rapid correction of hyperglycaemia with transfusion and insulin.]
3) Patients with severe infection, pre- or post-operative patients, and patients with serious traumatic 2 injury .

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Careful Administration
TALVUS 10 should be administered with care in the following patients.
1) Patients with severe hepatic impairment
2) Patients with cardiac failure (NYHA class III or IV)
3) Patients receiving sulfonylurea or insulin
4) The following patients or conditions [Hypoglycaemia may occur.]
- Pituitary insufficiency or adrenal insufficiency
- Malnutrition, starvation, irregular diet, insufficient food intake or hyposthenia
- Extreme muscle exercise
- Patients with excessive alcohol intake.
5) Patients with a history of abdominal operation or a history of intestinal obstruction
6) Patients prone to QT interval prolongation (patients with current or a history of arrhythmia such as severe bradycardia, patients with cardiac disease such as congestive cardiac failure, patients with hypokalaemia, etc.)

Important Precautions

1) Prior to the use of this product, patients should be instructed to recognize hypoglycemic symptoms and their management. In particular, when used in combination with sulfonylurea or insulin, this product may increase the risk of hypoglycaemia. In order to decrease the risk of hypoglycaemia associated with coadministration with sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered when this product is coadministered with these drugs.
2) Use of this product should be considered only in patients with established diagnosis of diabetes mellitus. It should be noted that there are other diseases than diabetes mellitus that have symptoms similar to those of diabetes mellitus (renal glycosuria, abnormal thyroid function, etc.), such as impaired glucose tolerance and positive urine sugar.
3) Use of this product should be considered only when there is inadequate response to diet and exercise therapy, which are fundamental for treatment of diabetes mellitus, after adequate trial of the therapies.
4) During treatment with this product, blood glucose should be regularly monitored, and the effect of the drug should be checked. If the response to this product is inadequate after 3 months of treatment, a change to other treatment should be considered
5) During continued treatment with this product, it may become unnecessary to administer the product or it may become necessary to reduce a dose of the product. In addition, there may be no or inadequate response to the product due to patient's failure to take care of themselves or a complication of infection, etc. Therefore, attention should be paid to the amount of food intake, blood glucose level and presence/absence of infection to judge continuation of treatment, doses and selection of drugs.
6) Adverse drug reactions such as prolonged QT may occur. Treatment with this product should preferably be avoided in patients with current or a history of QT interval prolongation.
7) Both GLP-1 receptor agonists and this product have an antihyperglycaemic action mediated by GLP-1 receptor. No results of clinical trials studying a combined therapy with both drugs are available and the efficacy and safety of the coadministration have not been proved.
8) Acute pancreatitis may occur. Patients should be instructed to consult with a physician immediately 3 if initial symptoms including persistent and intense abdominal pain and/or vomiting occur.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION.

This product is primarily metabolized by CYP3A4 and flavin-containing monooxygenase (FMO1 and FMO3), and urinary excretion of unchanged drug was 14.8% to 22.1%.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs for diabetes mellitus Sulfonylurea Rapid-acting insulin secretagogues Alpha-glucosidase inhibitors Biguanides Thiazolidines GLP-1 receptor agonists SGLT2 inhibitors Insulin, etc.	When this product is coadministered, patients should be carefully observed since hypoglycemic symptoms may occur. In particular, when used in combination with sulfonylurea or insulin, the risk of hypoglycaemia may be increased. In order to decrease the risk of hypoglycaemia associated with coadministration with sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered . When hypoglycemic symptoms appear, sucrose should normally be administered. When this product is coadministered with an alpha-glucosidase inhibitor, glucose should be administered.	Antihyperglycaemic action is intensified.
Drugs that intensify antihyperglycaemic action Beta-blockers Salicylic acid Monoamine oxidase inhibitors, etc.	When this product is coadministered, blood glucose level and patient's other conditions should be carefully observed since blood glucose may further be decreased.	Antihyperglycaemic action is intensified.
Drugs that reduce antihyperglycaemic action Adrenalin Adrenocortical hormones Thyroid hormones, etc.	When this product is coadministered, blood glucose level and patient's other conditions should be carefully observed since blood glucose may be increased.	Antihyperglycaemic action is reduced.
Drugs that are known to cause QT interval prolongation Class IA antiarrhythmic (quinidine sulfate hydrate, procainamide hydrochloride, etc.) Class III antiarrhythmic (amiodarone hydrochloride, sotalol hydrochloride, etc.)	When this product is coadministered, QT interval prolongation, etc. may occur.	These drugs are associated with QT interval prolongation even when administered alone

PREGNANCY AND LACTATION

1) This product should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product for use during pregnancy has not been established. An animal study (in rats) has reported that this product is transferred to the fetus.]
2) In lactating women, breast-feeding must be discontinued during treatment. [An animal study (in rats) has reported that this product is excreted in breast milk.]

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since hypoglycemic symptoms may occur, attention should be paid to patients engaged in work at altitude or driving a car, etc.

UNDESIRABLE EFFECTS.

In Japanese clinical studies, 232 adverse drug reactions (including abnormal laboratory values) were observed in 156 patients (9.5%) of total 1645 patients. Main adverse drug reactions were hypoglycaemia in 43 patients (2.6%) and constipation in 14 patients (0.9%).

Clinically significant adverse drug reactions

1) Hypoglycaemia (1.1–8.9%): Hypoglycaemia may occur with coadministration of this product with other drugs for diabetes mellitus. In particular, some cases of serious hypoglycemic symptoms that resulted in loss of consciousness have been reported in coadministration with insulin products or sulfonylurea. Dose reduction of insulin products or sulfonylurea should be considered when this product is coadministered with these drugs. Hypoglycaemia has also been reported with this product when not coadministered with other drugs for diabetes mellitus. If hypoglycemic symptoms are observed, appropriate therapeutic measures, such as intake of sugar-containing food, should be taken .
2) Intestinal obstruction (0.1%): Intestinal obstruction may occur. The patient should be carefully monitored, and if any abnormalities, such as severe constipation, abdominal distension, persistent abdominal pain and vomiting, are observed, this product should be discontinued and appropriate therapeutic measures should be taken.
3) Hepatic impairment (incidence unknown): Hepatic impairment accompanied by increased AST (GOT) or ALT (GPT) may occur. The patients should be carefully monitored, and if any abnormalities are observed, appropriate therapeutic measures including discontinuation of administration should be taken.
4) Interstitial pneumonia (incidence unknown): Interstitial pneumonia may occur. If any abnormalities,such as cough, dyspnoea, pyrexia and lung crepitation, are observed, laboratory tests including chest X-ray, chest CT, serum marker, etc. should be promptly performed. If interstitial pneumonia is suspected, this product should be discontinued and appropriate therapeutic measures including administration of corticosteroids should be taken.
5) Pemphigoid (incidence unknown): Pemphigoid may occur. If blister, erosion, or other signs and symptoms are observed, patients should be referred to a dermatologist, and appropriate therapeutic measures such as discontinuation of administration should be taken
6) Acute pancreatitis (incidence unknown): Acute pancreatitis may occur. Patients should be instructed to consult with a physician immediately if initial symptoms including persistent and intense abdominal pain and/or vomiting occur.

Other adverse drug reactions

If any adverse drug reactions are observed, appropriate therapeutic measures, such as discontinuation of this product, should be taken.

Incidence / Type	≥0.1% to <1%	<0.1%	Incidence unknown
			Dizziness
Psychiatric/ Neurological			
Gastrointestinal	Constipation, abdominal distension, abdominal discomfort, nausea, abdominal pain, flatulence, stomatitis, gastric polyps, colonic polyp, duodenal ulcer, reflux esophagitis, diarrhoea, decreased appetite, increased amylase, increased lipase		
Hepatic	Increased AST (GOT), increased ALT (GPT), increased γ-GTP	Increased Al-P	
Renal/ Urinary system	Proteinuria, urine ketone body present, blood urine present.		
Dermatologic	Eczema, rash, itching, allergic dermatitis		
Others	Increased serum CK (CPK), increased serum potassium, malaise, allergic rhinitis, increased serum uric acid		Peripheral Oedema

OVERDOSE

The maximum doses of teneligliptin in clinical studies were 320 mg for a single dose in healthy adult subjects and 80 mg once daily for 7 days for repeated doses in healthy adult subjects. No serious adverse drug events and adverse drug events leading to discontinuation of the study treatment were reported after administration of teneligliptin at the 2 doses.
QT interval prolongation has been reported after administration of this product at a dose of 160 mg once daily.

PHARMACODYNAMIC PROPERTIES

Mechanism of action

Glucagon-like peptide-1 (GLP-1) is secreted from the gastrointestinal tract in response to meal ingestion and regulates postprandial blood glucose level by stimulating insulin secretion from the pancreas and suppressing glucagon secretion. Teneligliptin inhibits the degradation of GLP-1 through the inhibition of dipeptidyl peptidase-4 (DPP-4) and reduces blood glucose levels by increasing blood concentration of active GLP-1.

Inhibitory effect on DPP-4 and suppressive action on GLP-1 degradation

1) Teneligliptin inhibited the activity of DPP-4 in human plasma in a concentration-dependent manner, with IC50 of 1.75 nmol/L (in vitro).
2) Teneligliptin prevented the degradation of active GLP-1 in rat plasma in a concentration-dependent manner (in vitro).
3) In a glucose tolerance test in Zucker Fatty rats, a model of obesity with insulin resistance and impaired glucose tolerance, a single oral administration of teneligliptin increased plasma active GLP-1 and plasma insulin levels.
4) In patients with type 2 diabetes mellitus, once-daily administration of teneligliptin 20 mg inhibited plasma DPP-4 activity and increased the concentration of active GLP-1 in plasma.

Improvement of glucose tolerance

1) In a glucose tolerance test in Zucker Fatty rats, a model of obesity with insulin resistance and impaired glucose tolerance, a single oral administration of teneligliptin improved post-loaded hyperglycemia.
2) In patients with type 2 diabetes mellitus, once-daily administration of teneligliptin 20 mg improved blood glucose after breakfast, lunch and dinner and fasting blood glucose.

PHARMACOKINETIC PROPERTIES.

After oral administration of a single 10 mg , 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 10 mg , 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 (t1/2) 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 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. Teneligliptin does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1, 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 Cmax and t1/2 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 Cmax 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 AUC 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.

SHELF LIFE:

36 Months

PACKAGING:

10 Tablets are packed in Alu-Alu blister and such 3 blisters are packed in a carton along with pack insert.

STORAGE CONDITION:

Store in dry place below 30°C.

Keep out of reach of children.

MANUFACTURED BY:

CIAN HEALTHCARE LTD.
(An ISO 9001 : 2008 & WHO GMP Certified Co.)
Kh. No. : 248, Village Sisona, Bhagwanpur,
Roorkee, Haridwar, Uttarakhand, India.
® Regd. Trademark.

Marketed by:

RBIOMEDS
Singapore
25,Ang Mo Kio Avenue 9,
11-17 Nuovo,Singapore.
569788