Evogliptin Tablets 5 mg

VALERA

1. NAME OF THE MEDICINAL PRODUCT

VALERA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film-coated tablet contains:

Evogliptin tartrate 6.869 mg equivalent to Evogliptin 5 mg

Excipients… q.s.

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of type 2 diabetes mellitus as an adjunct to diet and Exercise to improve glycaemic control, when used as a monotherapy or in combination with metformin.

4.2 Posology and method of administration

Posology

The usual adult dosage is 5 mg of Evogliptin administered orally once daily. Use in Paediatrics:

Safety and efficacy in paediatrics have not been established. Use in the Elderly:

There were 119 elderly patients (22.6%) aged 65 years or older out of a total of 527 patients in the phase II and III clinical studies of evogliptin. The administration in elderly patients has not been fully investigated. Since the elderly generally have decreased physiological functions such as hepatic and renal functions, caution needs to be exercised during administration while monitoring the patient's condition.

4.3 Contraindications

Evogliptin Tablets are contraindicated in patients with:

Hypersensitivity to the drug or any of its components

Severe ketosis, diabetic coma or pre-coma and type 1 diabetes

4.4 Special warnings and precautions for use

1)Heart failure: Caution should be exercised for patients with functional class I heart failure based on the New York Heart Association (NYHA) criteria as experience of administration is limited in such patients. Use of Evogliptin is not recommended to patients with functional class II-IV based on the NYHA criteria due to the absence of clinical experience in such patients.

2)Renal impairment: It is confirmed that approximately 46.1% of the administered radioactivity was excreted in urine and approximately 42.8% in feces in healthy adults. This figure includes both the unchanged form and its metabolites. Since there is a concern that increased blood concentration of the unchanged form may persist in patients with moderate to severe renal impairment compared to patients with normal renal function, Evogliptin should be cautiously administered while monitoring the patient's condition. As there is no clinical experience of Evogliptin in patients with end-stage renal impairment requiring dialysis, administration of Evogliptin is not recommended in such patients.

3)Hepatic impairment: Dosage and administration adjustment is not needed in patients with mild to moderate hepatic impairment. No study was conducted in patients with severe hepatic impairment. Therefore, caution should be exercised in such patients.

4)Acute pancreatitis: Use of DPP4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis; persistent, severe abdominal pain. If pancreatitis is suspected, Evogliptin should be discontinued; if acute pancreatitis is confirmed, Evogliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

In postmarketing experience of Evogliptin, there have been spontaneously reported adverse reaction of acute pancreatitis.

4.5 Interaction with other medicinal products and other forms of interaction

1)Evogliptin is mainly metabolized by CYP3A4. In in vitro studies, evogliptin was not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 enzymes or an inducer of CYP1A2, 2B6, and 3A4 enzymes. Thus, evogliptin is unlikely to cause interactions with other drugs acting as a substrate of such enzymes. Although evogliptin was proved to be a p-glycoprotein (P-gp) substrate and weak BCRP substrate based on in vitro studies, it did not inhibit transport mediated by these transporters. In addition, evogliptin was not a substrate of OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 and did not inhibit them. Therefore, evogliptin is unlikely to cause interactions with drugs that act as a substrate of such transporters in the clinical dose.

2)Interaction of evogliptin with other drugs

- Metformin: Multiple administration of evogliptin 5 mg and twice daily metformin 1,000 mg (a substrate of OCT1 and OCT2) until steady state was reached did not show clinically meaningful change in the pharmacokinetics of evogliptin or metformin.
- Clarithromycin: Multiple administration of a potent CYP3A4 inhibitor, clarithromycin 1,000 mg/day, until steady state was reached and single administration of evogliptin 5 mg showed increased Cmax of evogliptin by 2.1 times and its AUC by 2.0 times. Caution needs to be exercised as pharmacokinetic exposure of evogliptin may increase with concomitant administration of CYP3A4 inhibitors.

- Rifampicin: Multiple administration of a potent CYP3A4 inducer, rifampicin 600 mg/day, until steady state was reached and single administration of evogliptin 5 mg showed no significant change in Cmax of evogliptin but showed a decrease in AUC by 63%.

Drug-Drug Interaction Study with Pioglitazone:

This study, in which Evogliptin 5 mg and Pioglitazone 30 mg were repeatedly administered individually or in combination with healthy volunteers to evaluate the drugs' pharmacokinetics, pharmacodynamics, tolerability and safety.

For Evogliptin, the geometric mean ratio (GMR of E/(E + P)), and 90% confidence interval (CI) for Cmax,ss and AUCτ,ss after co-administration of Evogliptin and Pioglitazone (E+P), compared to the administration of Evogliptin alone, were 1.01 (0.97-1.05) and 1.01 (0.98- 1.04), respectively. For Pioglitazone, the geometric mean ratio (GMR of P/(E + P)) and 90% confidence interval (CI) for Cmax,ss and AUCτ,ss after co- administration of Evogliptin and Pioglitazone (E+P), compared to the administration of Pioglitazone alone, were 1.07 (0.99-1.17) and 1.08 (0.99–1.17), respectively.

Drug-Drug Interaction Study with Glimepiride:

This study in which Evogliptin 5 mg and Glimepiride 4 mg were repeatedly administered individually or in combination in healthy volunteers to evaluate pharmacokinetics, pharmacodynamics, tolerability, and safety of these drugs.

For Evogliptin, the geometric mean ratio (GMR of (E+G)/E) and the 90% confidence interval (CI) for Cmax,ss and AUCτ,ss after co-administration of Evogliptin and Glimepiride (E+G) compared to administration of Evogliptin alone (E) were 1.02 (0.98 - 1.06) and 0.97 (0.95 – 1.00)), respectively. For Glimepiride, the geometric mean ratio (GMR of (E+G)/G)) and the 90% confidence interval (CI) for Cmax,ss and AUCτ,ss after co-administration of Evogliptin and Glimepiride (E+G) compared to administration of Glimepiride alone (G) were 1.08 (1.01 - 1.17) and 1.08 (1.02 – 1.14)), respectively.

4.6 Use during Pregnancy, Delivery, or Lactation

Use in Pregnant women:

No comparative study result is available in pregnant women. Results of animal studies showed that evogliptin was detected in the blood stream of fetus across the placenta up to 61.7% in pregnant rats and 14.1% in pregnant rabbits 2 hours after administration. Therefore, use in pregnant women is not recommended.

Use in Nursing Mothers:

It is not evaluated whether evogliptin is excreted in human milk. Since animal studies confirmed that evogliptin is secreted in the milk, evogliptin should not be used in nursing mothers.

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 Evogliptin is co-administered with sulphonylurea and/or insulin.

4.8 Undesirable effects

1)Monotherapy

In the 12-week placebo-controlled monotherapy study using 2.5 mg, 5 mg, or 10 mg of evogliptin or placebo once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 1.

Table 1. Adverse events reported in 3% or more patients in the 12-week placebo-controlled monotherapy study (regardless of investigator's causality assessment)

Adverse event	**Evogliptin 2.5 mg N=39**	**Evogliptin 5 mg N=44**	**Evogliptin 10 mg N=38**	**Placebo N=36**
Gastritis	2 (5.1%)	1 (2.3%)	0 (0.0%)	0 (0.0%)
Periodontitis	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)
Nasopharyngitis	1 (2.6%)	4 (9.1%)	1 (2.6%)	1 (2.8%)
Erectile dysfunction	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)

In the 24-week placebo-controlled monotherapy study using 5 mg of evogliptin or placebo once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 2.

Table 2. Adverse events reported in 3% or more patients in the 24-week placebo-controlled monotherapy study (regardless of investigator's causality assessment)

Adverse event	**Evogliptin 5 mg N=78**	**Placebo N=80**
Dyspepsia	0 (0.0%)	3 (3.8%)
Nasopharyngitis	5 (6.4%)	5 (6.3%)
Arthralgia	3 (3.8%)	0 (0.0%)

In patients administering evogliptin 5 mg once daily as monotherapy for 52 weeks, the adverse events that occurred during the extension period (last 28 weeks) regardless of causality with increased frequency by 1% or higher compared to those of the 24-week study were toothache (3.1% vs. 1.3%) and contact dermatitis (3.1% vs. 1.3%). Compared to the 24-week study, there was no newly reported adverse event that occurred in two or more subjects (3.1%).

2)Combination therapy

In the 24-week active-drug-controlled combination therapy study with stable doses of metformin and either evogliptin 5 mg or Sitagliptin 100 mg once daily, the adverse events reported with a frequency of 3% or higher are listed in Table 3.

Table 3. Adverse events reported in 3% or more patients in the 24-week active-controlled combination therapy study (regardless of investigator's causality assessment)

Adverse event	**Evogliptin 5 mg N=111**	**Sitagliptin 100 mg N=108**
Dyspepsia	5 (4.5%)	3 (2.8%)
Diarrhoea	4 (3.6%)	1 (0.9%)
Nasopharyngitis	8 (7.2%)	9 (8.3%)

Pruritus	4 (3.6%)	1 (0.9%)

In the 52-week study using evogliptin 5 mg once daily combined with metformin, the adverse events that occurred during the extension period (last 28 weeks) regardless of causality with increased frequency by 1% or higher compared to those of the 24-week study were gastritis (2.2% vs. 0.9%) and upper respiratory tract infection (4.3% vs. 2.7%). Compared to the 24-week study, sciatica (2.2%) was a newly reported adverse event that occurred in two or more subjects (2.2%).

3)Hypoglycemia

In the 24-week monotherapy and combination therapy study with evogliptin 5 mg, hypoglycemia was each reported in one patient (monotherapy 1.3%, combination therapy 0.9%). All reported hypoglycemia cases were mild in severity and resolved without any action taken.

4)Vital signs

No clinically significant change in vital signs was observed in patients treated with Evogliptin.

Phase III clinical trial done by Alkem: A total of 38 (20.7%) patients reported 43 treatment emergent adverse events (TEAEs) during the study. No serious TEAEs were reported. No action was required (with IP or patient) for these 43 TEAEs. None of the TEAEs were severe or life threatening or fatal. No action was taken against study medication for all the 38/184 (20.7%) patients with 43 TEAEs. The study medication was neither interrupted nor discontinued for any patient. No patient was withdrawn from the study due to TEAEs. Majority of the TEAEs were mild in nature, dyslipidemia was most common, 6 events were reported in Evogliptin treatment group while 4 events were reported in Sitagliptin treatment group.

General Precautions:

1)Concomitant administration with drugs known to cause hypoglycemia: Insulin secretagogues such as insulin or sulfonylurea may cause hypoglycemia. Thus, lowering the dose of insulin or insulin secretagogues may be required to minimize the risk of hypoglycemia in case of concomitant administration with evogliptin. Severe and disabling joint pain

2)Severe and disabling joint pain has been reported in patients administering other DPP-4 inhibitors in post- marketing studies. The time to onset of symptoms following initiation of drug therapy varied from 1 day to years. Patients experienced relief of symptoms upon discontinuation of the medication. Some patients had a recurrence of severe joint pain when restarted on either their original DPP-4 inhibitor medication or another DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue evogliptin if appropriate.

4.9 Overdose

In clinical trials of evogliptin, single dose of evogliptin up to 60 mg daily was administered in healthy adults. In case of an overdose, perform symptomatic therapy (e.g., remove unabsorbed substance from the gastrointestinal tract, conduct clinical monitoring including electrocardiogram), and perform supportive therapy depending on the patient’s condition.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of Action

The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal in response to meal that promotes insulin secretion from pancreas and regulates blood sugar post meal by controlling glucagon secretion. Evogliptin exhibits a hypoglycemic effect by controlling the decomposition of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity and thereby increasing blood concentration of active form GLP-1

In accordance with the results from biochemical studies, it was demonstrated that Evogliptin non-covalently binds to the catalytic site of human DPP4 enzyme in crystal structures complexed to human DPP4. ter-butoxy residue of Evogliptin distinictively interacts with Arg125 of human DPP4 unlike Sitagliptin and this hydrophobic interaction may contribute to the high binding affinity of Evogliptin.

Evogliptin is a competitive and reversible inhibitor of dipeptidyl peptidase IV (DPP-IV). The inhibitory activity of evogliptin is about 10-fold compared to Sitagliptin, also the selectivity of evogliptin for DPP-IV is 6,000-fold higher as compared to DPP8/9.

Pre-clinical studies on evogliptin demonstrated significant DPP-IV inhibitory activity, increased active plasma GLP1 level, reduced blood glucose excursion in a dose-dependent manner. By virtue of DPP-IV inhibitory effect, evogliptin exhibited significant improvement in the fasting and post-prandial blood glucose levels.

Comparisons of inhibitory potencies of Evogliptin and Sitagliptin against human plasma DPP4 activity

Compounds	**Human Plasma DPP4 Inhibition**	
	IC50	**IC80**
Evogliptin	3.0 ng/ml (7.5 nM)	6.8 ng/ml (16.9 nM)
Sitagliptin	13.9 ng/ml (34.1 nM)	46.3 ng/ml (113.7 nM)

Evogliptin is highly selective to DPP4 enzyme more than 6,000-fold against DPP4 closely-related enzymes, which was comparable or superior to those of Sitagliptin. Evogliptin is a selective DPP4 inhibitor and Evogliptin has little possibility of causing adverse events due to inhibition of DPP4 closely-related proteases.

The pharmacodynamic parameters of Evogliptin were also assessed in this Phase I study. The inhibition of DPP4 activity by Evogliptin, which is a primary pharmacodynamic evaluation parameter, was measured and calculated as the equation: (([Baseline DPP4 activity – DPP4 activity]*100)/ Baseline DPP4 activity). The time to reach maximum inhibition of DPP4 activity was generally consistent with the time to reach maximum plasma concentration of Evogliptin, Tmax of Evogliptin, which ranged from 2.5 to 5.5 hours. However, the maximum inhibition of DPP4 activity was reached before Tmax of Evogliptin in 40 mg and 60 mg dose groups. The maximum degree of inhibition showed a dose-dependent increase, reaching highest 97.1% inhibition from baseline at a dose of 60 mg. The dose groups of 10 mg and higher showed more than 80% inhibition of DPP4 activity, and this inhibition was sustained over a 24-hour period. The duration of DPP4 inhibition for more than 80% inhibition increased in a dose-dependent manner.

Evogliptin Monotherapy in Patients with Type II DM

The study was designed to evaluate the efficacy and safety of Evogliptin 5 mg oral dose and determine the optimal dose and regimen in T2DM patients with inadequate glycemic control on exercise and diet.

The difference of changes in HbA1c (primary efficacy endpoint) between Evogliptin versus placebo from baseline to 24 weeks of treatment was -0.28%, which was statistically significant ($p<0.0001$).

Evogliptin in Combination with Metformin in Patients with Type II DM

The study was designed to evaluate the efficacy and safety of Evogliptin + metformin versus Sitagliptin + metformin in T2DM patients with inadequate glycemic control on metformin monotherapy.

Following 24 weeks of treatment, the difference of change from baseline in the mean HbA1c (primary efficacy endpoint) between Evogliptin versus Sitagliptin was 0.06 with the upper limit of 0.22% for its 95% CI, which was lower than the pre-specified inferiority margin, 0.35%, demonstrating the non-inferiority of Evogliptin to Sitagliptin.

5.2 Pharmacokinetic properties

The maximum Evogliptin concentrations (Cmax) were observed at 3.0 to 5.5 hours (median value), and the average half-lives (t1/2) were estimated to be 32.5 to 39.8 hours. The average Cmax and AUClast values increased as the dose increased while dose-dependent changes were not shown in Tmax and t1/2.

Multiple ascending dose (MAD) study: The maximum Evogliptin concentrations (C_{max}) were observed at

4.0 to 5.0 hours (median value) after the last administration of Evogliptin at 5, 10, and 20 mg (Day 10), and the average half-lives ($t_{1/2}$) were estimated to be 32.9 to 38.8 hours. Dose-dependent changes were not shown in T_{max} and $t_{1/2}$ while the average $C_{max,ss}$ and $AUC_{216\text{-}249h,ss}$ values increased as the doses increased. The accumulation ratios were 1.44, 1.38 and 1.50 at 5, 10, and 20 mg of Evogliptin, respectively.

The absolute bioavailability of Evogliptin was 50.247%. Plasma protein binding of Evogliptin is 46%.

In in vitro and in vivo metabolism study of Evogliptin in rat, dog, monkey, and human liver microsome, total seventeen kinds of metabolites were identified. Among them, M7 and M8 (mono-hydroxylated metabolites), and M16 (glucuronide metabolite) were major metabolites. CYP3A4 plays the major role in hydroxylation of Evogliptin to M7 and M8, and UGT2B7 plays the major role in the glucuronidation of M7 to M16.

In CYP inhibition assay in human liver microsome using in vitro cocktail of probe substrates, Evogliptin up to 50 μM did not show significant inhibition against activities of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4, suggesting the negligible CYP inhibition activity of the drug. In addition, it was found that Evogliptin has negligible potential of CYP1A2, 2B6 and 3A4 induction in cryopreserved human hepatocytes. Evogliptin was found to be a substrate of P-gp, but not a substrate of BCRP, OAT1B1, OAT1B3, OAT1, OAT3, or OCT2, and not an inhibitor of any of these transporters.

Renal Impairment: In study cohorts classified using the MDRD eGFR, the geometric means ratio (90% CIs) of C_{max} and AUC_{last} were 1.52 (1.22 - 1.89) and 1.98 (1.59 - 2.46) for those with severe renal impairment versus healthy volunteers and 1.32 (1.08 – 1.61) and 1.8 (1.47 – 2.21) for those with moderate renal impairment versus healthy volunteers, respectively. In contrast, patients with mild renal impairment showed the PD parameters comparable to healthy volunteers; the corresponding geometric means ratio (90% CIs) of C_{max} and AUC_{last} were 1.04 (0.85 - 1.27) and 1.2 (0.98 - 1.47)

5.3 Preclinical safety data

The toxicity of Evogliptin has been characterized in single and repeated oral dosing toxicity studies in mice, rats and dogs. Safety pharmacology studies and genotoxicity assessments have been also conducted. Carcinogenicity studies for 104 weeks in rats and dogs are on-going. In the acute toxicity study in rats, the lethal dose of Evogliptin was observed to be above 2,000 mg/kg. In the repeated dosing studies in mice, rats, and dogs, the no-observed-adverse-effect-level (NOAEL) was determined to be 300 mg/kg/day, 300 mg/kg/day, and 200 mg/kg/day, respectively.

In the study of bacterial reverse mutation, Evogliptin showed a negative response. Evogliptin did not induce chromosomal aberrations in cultured CHL cells. In vivo micronucleus test in bone marrow cells of ICR mice showed that Evogliptin did not induce an increased frequency of micronuclei in the bone marrow cells of ICR mice.

In safety pharmacology studies, it was confirmed that Evogliptin did not affect central nervous system and respiratory system after oral administration in rats, up to dose of 300 mg/kg. In a dog telemetry study, increase of heart rate, vomiting, and several changes of ECG parameter were observed at a high dose (300 mg/kg). But, there were no effects on blood pressure and body temperature even at the high dose (300 mg/kg). In hERG channel assay, an IC50 value of Evogliptin was approximately 143.4 μM. In consideration of Cmax at 5 mg administration in humans, this IC50 value represents an enough safety margin over 10,000 times.

Pre-clinical studies revealed no carcinogenicity, mutagenicity and/or fertility impairment. Evogliptin showed no drug-related tumors in either sex of mice or rats upto the highest dose of 100 mg/kg/day (>25-fold or >80- fold higher exposure than in humans, respectively) for a period of two years.

6 PHARMACEUTICAL PARTICULARS

6.1 Shelf-life : 36 months

6.2 Special Precautions for Storage

Store below 25°c. Protect from light.

6.3 Nature and Contents of Container

1 Blister Strips of 15 Tablets Each.

7 MARKETED BY

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8 DATE OF PREPARATION

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