Trelaget™

[T r e l a g l i p t i n]

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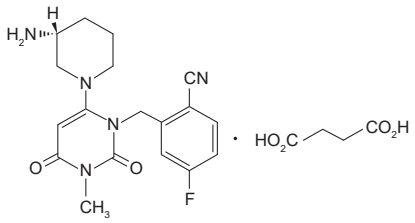
Film-Coated Tablets
50mg and 100mg

DESCRIPTION

Trelaget contains Trelagliptin as the active ingredient. Trelagliptin is a dipeptidyl peptidase (DPP)-4 inhibitor. The chemical name of Trelagliptin is (1S, 2-({6-[(3R)-3-Aminopiperidin-1-yl]-3-methyl-2,4 dioxo-3,4-dihydropyrimidin-1(2H)-yl}methyl)-4-fluorobenzonitrile monosuccinate. Its molecular formula is $C_{18}H_{20}FN_5O_2 \cdot C_4H_6O_4$ and structural formula is:



Trelagliptin Succinate

QUALITATVIVE AND QUANTITATIVE COMPOSITION

Trelaget (Trelagliptin) Tablets are available for oral administration as:

Trelaget Tablets 50mg
Each film-coated tablet contains:
Trelagliptin Succinate equivalent to Trelagliptin…. 50mg

Trelaget Tablets 100mg
Each film-coated tablet contains:
Trelagliptin Succinate equivalent to Trelagliptin…. 100mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Trelagliptin inhibits dipeptidyl-peptidase-4 (DPP-4) activity which inactivates glucagon-like peptide-1 (GLP-1) secreted into blood from the intestine upon stimulation after oral intake of meals, trelagliptin increases the blood concentration of GLP-1 and promotes insulin secretion by the pancreas dependently on glucose concentration.

Pharmacokinetics

Absorption

Single dose: When trelagliptin (50mg and 100mg) was administered to 8 healthy adults in a single dose 30 minutes before breakfast, the pharmacokinetic parameters of trelagliptin were presented in table as follows:

Dosage	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{∞} (ng·h/mL)	$T_{1/2\,z}$ (h)	C_{168} (ng/mL)
50mg	8	268.3 (88.8)	1.3 (1.0, 3.0)	3106.7 (329.3)	53.9 (6.6)	1.2 (0.5)
100mg	8	619.4 (77.3)	1.3 (1.0, 2.0)	6601.7 (845.4)	54.3 (7.9)	2.1 0.7
Mean(S.D.), Tmax is expressed by median (minimum, maximum)						

Multiple dose: When 100mg of trelagliptin was administered to 9 healthy adults in a single dose 30 minutes before breakfast (on day 1) and once daily 30 minutes before breakfast for 11 days (from day 4 to 14), the mean (S.D.) C_{max} and AUC_{∞} on day 1 were 544.3(122.0)ng/mL and 5572.3(793.2)ng·h/mL, respectively, and the mean (S.D.) C_{max} and AUC_{τ} on day 14 were 602.6(149.5)ng/mL and 5292.9(613.8)ng·h/mL, respectively.

Effect of food

When 100mg of trelagliptin was administered to 12 healthy adults 30 minutes after the start of breakfast, the C_{max} increased by 16.8% and AUC_{∞} decreased by 2.5% compared with those after administration under fasting conditions.

Distribution

When [^{14}C] trelagliptin was added to human plasma at the concentration of 0.01-10μg/ml, the protein binding ratio was 22.1% - 27.6%.
The percent distribution of trelagliptin at the concentration of 0.1-10μg/mL in blood cells is 49.2% - 55.0%

Metabolism

Trelagliptin is metabolized into an active metabolite M-I via N-demethylation mainly by CYP2D6. Human plasma concentrations of an active metabolite M-I were less than 1% of trelagliptin.

Elimination

When trelagliptin (50mg and 100mg) was administered to 8 healthy adults in a single dose 30 minutes before breakfast, the cumulative urinary excretion rate of trelagliptin up to 168 hours after administration was 71.45% and 75.96%, respectively. The renal clearance of trelagliptin was 11.6 L/h.

Special Population

Impaired Renal Function

When 50mg of trelagliptin was administered to patients with renal impairment and healthy adults in a single dose, AUC_{last} and C_{max} increased by 55.7% and 36.3% in 6 patients with mild renal impairment (C_{cr} = 50-80 mL/min), increased by 105.7% and 12.9% in 6 patients with moderate renal impairment (C_{cr} = 30-50 mL/min), increased by 201.4% and 9.1% in 6 patients with severe renal impairment (C_{cr} <30 mL/min), and increased by 268.1% and decreased by 13.8% in 6 patients with end-stage renal disease as compared with those of age, sex, race, and weight-matched healthy adults. In addition, 9.2% of the dose of trelagliptin was removed from the body during a 4-hour dialysis procedure.

Impaired Hepatic Function

When 50mg of trelagliptin was administered to 8 patients with moderate hepatic impairment (Child-Pugh score of 7-9) and 8 healthy adults in a single dose, AUC_{∞} and C_{max} in patients with moderate hepatic impairment increased by 5.1% and decreased by 4.3%, respectively.

THERAPEUTIC INDICATION

Trelaget (Trelagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

DOSAGE AND ADMINISTRATION

For adults, 100mg of Trelaget (Trelagliptin) is orally administered once a week. Do not break or crush the tablet.

Special Population

Elderly Patients

Since the elderly often have reduced renal function,

precautions should be taken against the onset of adverse reactions and careful administration should be performed under close observation.

Impaired Renal Function
Since blood concentrations of Trelaget (Trelagliptin) may increase due to a delay in the excretions in patients with moderate renal impairment, therefore the 100mg dose is not recommended. Trelaget (Trelagliptin) 50mg is recommended dose for subjects with moderate renal impairment.

ADVERSE REACTIONS
Hypersensitivity: Rash and pruritus.
Cardiovascular: Atrial fibrillation.
Hepatic: ALT increased, AST increased and γ-GTP increased.
Others: Lipase increased, amylase increased, CPK increased, urinary occult blood positive nasopharyngitis.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Trelagliptin is contraindicated in patients with:
- hypersensitivity to Trelagliptin or to any of the excipients of the product.
- severe renal impairment or end-stage renal failure on dialysis.

PRECAUTIONS
Hypoglycemia
The risk of hypoglycemia may increase with concomitant use of trelagliptin and sulfonylureas or insulin preparations. Therefore, reduction of the dosage of sulfonylureas or insulin preparations should be considered to reduce the risk of hypoglycemia when used in combination with trelagliptin.

Acute Pancreatitis
Acute pancreatitis has been associated with other DPP-4 inhibitors. After initiation of trelagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, trelagliptin should be promptly discontinued and appropriate management should be initiated.

Pregnancy
Trelagliptin should not be administered to women who are or may be pregnant, unless the expected therapeutic benefit is thought to outweigh any possible risk.

Nursing Mothers
During the treatment with trelagliptin, nursing should be avoided if the administration of this drug is necessary for the mother.

DRUG INTERACTION
No clinically meaningful interactions (with both drug and food) were observed, and no need for dose adjustment of trelagliptin or other concomitantly administered drugs was identified.

OVERDOSAGE
In thorough QT/QTc study with single administration of trelagliptin 200mg or 800mg in healthy subjects, QT prolongation was observed in the trelagliptin 800 mg group. Trelagliptin is modestly dialyzable; after 4 hours of hemodialysis, approximately 9.2% of the drug was removed.

STORAGE
Do not store above 30°C.
Protect from sunlight & moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Trelaget (Trelagliptin) Tablets 50mg are available in blister pack of 4's.
Trelaget (Trelagliptin) Tablets 100mg are available in blister pack of 4's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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