Galvecta®

(Vildagliptin)

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COMPOSITION

Galvecta 50mg tablet
Each film coated tablet contains……. Vildagliptin 50mg
(Manufacturer's Specs)

DESCRIPTION

GALVECTA tablets contain Vildagliptin, a member of the class that enhances islet cell insulin secretion via an augmented incretin effect, is a high affinity dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control. Vildagliptin is chemically designated as 1-[(3-Hydroxy-adamant-1-ylamino)acetyl]-pyrrolidine-2(S)-carbonitrile. The molecular formula of Vildagliptin is $C_{17}H_{25}N_3O_2$

CLINICAL PHARMACOLOGY

Mechanism of action
The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide). By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.
The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to improved glycemic control

Pharmacokinetics

Absorption
Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours, but does not alter the overall exposure (AUC). Administration of vildagliptin with food results in a decreased Cmax (19%). However, the magnitude of change is not clinically significant, so that Vildagliptin can be given with or without food. The absolute bioavailability is 85%.

Distribution
The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (Vss) is 71 litres, suggesting extravascular distribution.

Metabolism
Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the glucuronide (BQS867) and the amide hydrolysis products (4% of dose). In vitro data in human kidney microsomes suggest that the kidney may be one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. Vildagliptin is not metabolised by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. Vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Elimination
Following oral administration of vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounts for 23% of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 and 13 L/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.

INDICATIONS

GALVECTA (Vildagliptin) is indicated in the treatment of type 2 diabetes mellitus in adults:

As monotherapy
• In patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.

As dual oral therapy in combination with
• Metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin,
• A sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance,
• A thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.

As triple oral therapy in combination with
• A sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
• Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

In combination with insulin
• Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and exercise plus a stable dose of insulin do not provide adequate glycaemic control.

DOSAGE AND ADMINISTRATION

Adult dosage

- When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.
- When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily is no more effective than vildagliptin 50 mg once daily.
- When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.
- Doses higher than 100 mg are not recommended.
- If a dose of GALVECTA (Vildagliptin) is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.
- The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established.

Dosing Consideration in Special Populations

Elderly (≥ 65 years)
No dose adjustment is necessary in elderly patients.

Paediatric
Vildagliptin is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Vildagliptin in children and adolescents (< 18 years) have not been established.

Renal impairment
There is limited experience in patients with End Stage Renal Disease (ESRD) on haemodialysis. Vildagliptin should be used with caution in these patients. (See DOSAGE AND ADMINISTRATION)

Hepatic impairment
Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x ULN (greater than three time the upper limit of normal).

Administration Requirements
GALVECTA (Vildagliptin) is for oral use and can be administered with or without a meal

CONTRAINDICATIONS

Hypersensitivity condition.

WARNINGS AND PRECAUTIONS

General
Vildagliptin is not a substitute for insulin in insulin-requiring patients. Vildagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Renal impairment
Vildagliptin should be used with caution in these patients.

Hepatic impairment
Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 3x ULN

Liver enzyme monitoring
Hepatic dysfunction(including hepatitis) have been reported in rare cases. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function test results returned to normal after discontinuation of treatment. Liver function tests should be performed prior to the initiation of treatment with Vildagliptin in order to know the patient's baseline value. Liver function should be monitored during treatment with Vildagliptin at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormalities returns to normal. Should an increase in AST or ALT of 3x ULN or greater persist, withdrawal of Vildagliptin therapy is recommended.
Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Vildagliptin. Following withdrawal of treatment with Vildagliptin and LFT normalisation, treatment with Vildagliptin should not be re-initiated.

Cardiac failure
Vildagliptin in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Skin disorders
Monitoring should be required for skin disorders, such as blistering or ulceration, in routine care of diabetic patients prescribed vildagliptin. There have been post-marketing reports of bullous and exfoliative skin lesions.

Acute pancreatitis
Use of vildagliptin has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

Hypoglycaemia
Sulphonylureas are known to cause hypoglycaemia. Patients receiving vildagliptin in combination with a sulphonylurea may be at risk for hypoglycaemia. Therefore, a lower dose of sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Patients who experience dizziness as an adverse reaction with vildagliptin should avoid driving vehicles or using machines.

ADVERSE REACTIONS
Adverse reactions reported in patients who received Vildagliptin in double-blind studies as monotherapy and add-on therapies are listed below:

Monotherapy with Vildagliptin

Infections and infestations
Very rare Upper respiratory tract infection, Nasopharyngitis
Metabolism and nutrition disorders
Uncommon Hypoglycaemia
Nervous system disorders
Common Dizziness
Uncommon Headache
Vascular disorders
Uncommon Oedema peripheral
Gastrointestinal disorders
Uncommon Constipation
Musculoskeletal and connective tissue disorders
Uncommon Arthralgia

Vildagliptin with metformin

Metabolism and nutrition disorders
Common Hypoglycaemia
Nervous system disorders
Common Tremor , Headache, Dizziness
Uncommon Fatigue
Gastrointestinal disorders
Common Nausea

Vildagliptin with sulfonylurea

Infections and infestations
Very rare Nasopharyngitis
Metabolism and nutrition disorders
Common Hypoglycaemia
Nervous system disorders
Common Tremor , Headache, Dizziness, Asthenia
Gastrointestinal disorders
Uncommon Constipation

Vildagliptin with thiazolidinedione

Metabolism and nutrition disorders
Common Weight increase
Uncommon Hypoglycaemia
Nervous system disorders
Uncommon Headache, Asthenia
Vascular disorders
Common Oedema peripheral

Vildagliptin with metformin and sulfonylurea

Metabolism and nutritional disorders
Common Hypoglycaemia
Nervous system disorders
Common Dizziness, tremor
Skin and subcutaneous tissue disorders
Common Hyperhidrosis
General disorders and administration site conditions
Common Asthenia

Vildagliptin with insulin (with/without) metformin

Metabolism and nutrition disorders
Common Decreased blood glucose
Nervous system disorders
Common Headache, chills
Gastrointestinal disorders
Common Nausea, gastro-oesophageal reflux disease
Uncommon Diarrhoea, flatulence

Following adverse reactions have been reported with vildagliptin as spontaneous reports post-approval:

Gastrointestinal disorders
Frequency Not known Pancreatitis
Hepatobiliary disorders
Not known Hepatitis (reversible), Abnormal liver function tests (reversible)
Musculoskeletal and connective tissue disorders
Not known Myalgia
Skin and subcutaneous tissue disorders
Not known Urticaria, Bullous or exfoliative skin lesions

DRUG INTERACTIONS

Vildagliptin has a low potential for drug interactions. Since vildagliptin is not a cytochrome (CYP) P450 enzyme substrate and does not inhibit or induce CYP P450 enzymes, it is not likely to interact with the concomitant medications that are substrates, inhibitors or inducers of these enzymes, nor does it affect metabolic clearance of co-medications metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5.

ACE inhibitors
There may be an increased risk of angioedema in patients concomitantly taking ACE-inhibitors with Vildagliptin.

Reduction of hypoglycemic effect
As with other oral antidiabetic medicinal products the hypoglycaemic effect of vildagliptin may be reduced by certain active substances, including thiazides, corticosteroids, thyroid products and sympathomimetics.

USE IN SPECIAL POPULATIONS

Pregnancy
There are no adequate data from the use of vildagliptin in pregnant women. The potential risk for humans is unknown. Due to lack of human data, Vildagliptin should not be used during pregnancy.

Nursing mothers
It is unknown whether vildagliptin is excreted in human milk. Vildagliptin should not be used during breast-feeding.

Gender
No differences in the pharmacokinetics of vildagliptin were observed between male and female subjects with a diverse range of age and body mass index (BMI).DPP-4 inhibition by vildagliptin was unaffected by gender.

Hepatic Impairment
The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >3 X the upper limit of normal

Renal Impairment
Dosage adjustment may be required in patients with renal impairment (see DOSAGE AND ADMINISTRATION).Vildagliptin is removed by haemodialysis to a limited extent (3% over a 3-4 hour haemodialysis session starting 4 hours post dose).

OVERDOSAGE

Symptoms
Information on the likely symptoms of overdose was taken from a rising dose tolerability study in healthy subjects given Vildagliptin for 10 days. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and a transient increase in lipase levels. At 600 mg, one subject experienced oedema of the feet and hands, and increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), C - reactive protein (CRP) and myoglobin levels. Three other subjects experienced oedema of the feet, with paraesthesia in two cases. All symptoms and laboratory abnormalities resolved without treatment after discontinuation of the study medicinal product.

Management
In the event of an overdose, supportive management is recommended. Vildagliptin cannot be removed by haemodialysis. However, the major hydrolysis metabolite (LAY 151) can be removed by haemodialysis to a limited extent (3% over a 3-4 hour haemodialysis session starting 4 hours post dose).

PRESENTATION

Galvecta 50mg: Pack of 10's tablets.

DOSAGE & INSTRUCTIONS

As advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.

خوراک وہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فراہم کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔

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