NOVARTIS

JALRAMET 50 mg/850 mg tablet

JALRAMET 50 mg/1 000 mg tablet

Vildagliptin 50 mg per tablet

Metformin hydrochloride 850 mg or 1000 mg per tablet

Professional Information

Document status: Final

Release date: 06 July 2022

SCHEDULING STATUS S3

1 NAME OF THE MEDICINE

JALRAMET 50 mg/850 mg tablet

JALRAMET 50 mg/1 000 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

JALRAMET 50 mg/850 mg: Each tablet contains 50 mg vildagliptin and 850 mg metformin hydrochloride.

JALRAMET 50 mg/1 000 mg: Each tablet contains 50 mg vildagliptin and 1 000 mg metformin hydrochloride.

3 PHARMACEUTICAL FORM

JALRAMET 50 mg/850 mg: yellow, ovaloid bevelled edge, film-coated tablet imprinted with "NVR" on one side and "SEH" on the other side.

JALRAMET 50 mg/1 000 mg: dark yellow, ovaloid bevelled edge, film-coated tablet imprinted with "NVR" on one side and "FLO" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For patients with Type 2 diabetes mellitus (T2DM):

JALRAMET is indicated as an adjunct to diet and exercise in patients who are already stabilised with the combination of vildagliptin and metformin hydrochloride at the same dosages, as separate tablets.

JALRAMET is indicated as add-on to insulin as an adjunct to diet and exercise in patients on a stable dose of insulin plus vildagliptin and metformin hydrochloride.

JALRAMET is indicated as an add-on to insulin at the same dosages as the separate tablets of vildagliptin and metformin hydrochloride.

JALRAMET is indicated in combination with sulphonylurea (SU) (i.e. triple combination therapy) as an adjunct to diet and exercise in patients stabilised on vildagliptin, metformin hydrochloride and a sulphonylurea.

JALRAMET can be used to replace the vildagliptin and metformin hydrochloride at the same dosages as the separate tablets.

4.2 Posology and Method of administration

In using JALRAMET do not exceed the maximum daily dose of vildagliptin (100 mg).

The recommended starting dose of JALRAMET should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride. JALRAMET should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride.

Use in combination with sulphonylurea or with insulin:

The dose of JALRAMET should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

Patients with renal impairment:

A GFR should be assessed before initiation of treatment with metformin-containing products (such as JALRAMET) and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3 to 6 months. The maximum daily dose of metformin should preferably be divided into 2 to 3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin-containing products (such as JALRAMET) in patients with GFR < 60 ml/min. JALRAMET is contraindicated in patients with GFR < 30 ml/min because of its metformin component (see section 4.3).

The following dosing recommendations apply to metformin and vildagliptin, used separately or in combination, in patients with renal impairment. If no adequate strength of JALRAMET is available, individual components should be used instead of the fixed dose combination.

Dose adjustments in patients with renal impairment

GFR **ml/min**	**Metformin**	**Vildagliptin**
60 - 89	Maximum daily dose is 3000 mg*. Dose reduction may be considered if renal function declines.	Maximal daily dose is 100 mg.

45 - 59	Starting dose should not be more than 1000 mg with a maximum daily dose of 2000 mg*.	Maximal daily dose is 50 mg.
30 - 44	Starting dose should not be more than 500 mg with a maximum daily dose of 1000 mg.	
< 30	Metformin is contraindicated.	

*If metformin doses higher than those achievable with JALRAMET alone are considered necessary.

Patients with hepatic impairment:

JALRAMET is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST > 2, 5 x the ULN (see section 4.4).

Elderly:

As metformin is excreted via the kidneys, and elderly patients tend to exhibit decreased renal function, elderly patients taking metformin-containing products (such as JALRAMET) should have their renal function monitored regularly. The dosage of JALRAMET for elderly patients should be adjusted based on renal function (see section 4.3 "Renal disease" and section 4.4 "Monitoring of renal function").

Paediatric patients:

Safety and efficacy of JALRAMET in paediatric patients have not been established. Therefore, JALRAMET is not recommended for use in children below 18 years of age.

4.3 Contraindications

Hypersensitivity:

JALRAMET is contraindicated in patients with known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients of JALRAMET.

Renal disease:

JALRAMET is contraindicated in patients with severe renal impairment (GFR < 30 ml/min) (see section 4.2 and 4.4).

Patients with hepatic impairment:

JALRAMET is contraindicated in patients with hepatic impairment, including patients with a pre-treatment ALT or AST > 2,5 x the upper limit of normal (see section 4.4).

Congestive heart failure:

JALRAMET is contraindicated in patients with congestive heart failure requiring pharmacological treatment (see section 4.4).

Metabolic acidosis:

JALRAMET is contraindicated in patients with acute or chronic metabolic acidosis, including lactic acidosis or diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

4.4 Special warnings and precautions for use

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

If metabolic acidosis is suspected, treatment with JALRAMET should be discontinued and the patient hospitalised immediately (see section 4.9).

JALRAMET should be discontinued if evidence of renal impairment is present.

Alcohol intake

Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving metformin containing products (such as JALRAMET).

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Administration of intravascular iodinated contrast materials

JALRAMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function and increase the risk of lactic acidosis. In patients undergoing such studies, JALRAMET should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hepatic impairment

Vildagliptin is not recommended in patients with hepatic impairment, including patients with pre-treatment ALT or AST > 2, 5 x the ULN (see section 4.3).

Liver enzyme monitoring

Cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with JALRAMET. LFTs should be monitored during JALRAMET treatment 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 abnormality(ies) return to normal. Should an increase in AST or ALT of 3 x ULN or greater persist, withdrawal of therapy with JALRAMET is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue JALRAMET and contact their physician immediately. Following withdrawal of treatment with JALRAMET and LFT normalisation, JALRAMET should not be reinitiated.

Heart Failure

A clinical study of 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 studies in patients with NYHA functional class IV and therefore use is not recommended in these patients.

Vildagliptin as contained in JALRAMET may cause arthralgia that can be severe.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP-4 inhibitors including JALRAMET. SCARs are regarded as a class effect of DPP-4 inhibitors such as JALRAMET. If a patient develops SCAR, treatment with DPP-4 inhibitors such as JALRAMET must immediately be discontinued and appropriate treatment instituted. Patients should continue with an alternative class of anti-diabetic medicines.

Rhabdomyolysis

Rhabdomyolysis has been reported during use of DPP-4 inhibitor containing products such as JALRAMET. However, causality could not be assessed due to confounding factors such as concomitant use of medicines (statins, colchicine, etc.) or co-morbid conditions (Renal failure, hypovolemia, etc.), known to cause or predispose to development of rhabdomyolysis. Close monitoring of patients using DPP-4 inhibitor containing products in presence of predisposing risk factors is recommended.

Metformin hydrochloride

Lactic Acidosis

Lactic acidosis is a serious metabolic complication that most often occurs with acute worsening of renal function, or cardiorespiratory illness or sepsis. Metformin accumulation occurs with acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (e.g. due to severe diarrhoea or vomiting, fever or reduced fluid intake), the patient should stop taking metformin-containing products (such as JALRAMET) and seek immediate medical attention.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in patients treated with metformin-containing products (such as JALRAMET). Other risk factors for lactic acidosis are excessive alcohol intake, hepatic impairment, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see section 4.3 and 4.5).

Diagnosis of lactic acidosis

Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH (< 7,35), increased plasma lactate levels > 5 mmol/L and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with metformin-containing products (such as JALRAMET) should be discontinued and the patient should be immediately hospitalised.

Monitoring of renal function

GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Metformin-containing products (such as JALRAMET) are contraindicated in patients with GFR < 30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

Metformin hydrochloride is substantially excreted by the kidneys, and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Since advancing age is associated with reduced renal function, metformin-containing products (such as JALRAMET) should be carefully titrated in the elderly to establish the minimum dose for adequate glycaemic effect, and renal function should be monitored regularly (see section 4.2).

Concomitant medications that may affect renal function or metformin hydrochloride disposition

Concomitant medications that may affect renal function, result in significant haemodynamic change or interfere with the disposition of metformin hydrochloride, such as cationic medicines that are eliminated by renal tubular secretion should be used with caution (see section 4.5).

Hypoxic states

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxaemia have been associated with lactic acidosis and may also cause prerenal uraemia. If such events occur in patients receiving JALRAMET therapy, the medication should be promptly discontinued.

Surgical procedures

Use of JALRAMET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Impaired hepatic function

Since impaired hepatic function has been associated with some cases of lactic acidosis, a risk associated with metformin hydrochloride, metformin-containing products (such as JALRAMET) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels

The metformin component of JALRAMET has been associated with a decrease in serum vitamin B_{12} levels without clinical manifestations, in approximately 7 % of patients. Such decrease, is very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B_{12} supplementation. Measurement of haematological parameters on at least an annual basis is advised for patients receiving metformin-containing products (such as JALRAMET) and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g. those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at minimally two-to-three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes

A patient with type 2 diabetes previously well-controlled on JALRAMET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis of either form occurs, JALRAMET must be stopped immediately and appropriate measures initiated.

Hypoglycaemia

Hypoglycaemia does not usually occur in patients receiving JALRAMET alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or ethanol use. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking medicines.

Hypoglycaemia may occur when JALRAMET is used as add-on therapy to other anti-diabetic medicines.

Loss of control of blood glucose

When a patient stabilised on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold JALRAMET and temporarily administer insulin. JALRAMET may be reinstituted after the acute episode is resolved.

4.5 Interaction with other medicines and other forms if interaction

JALRAMET

No clinically relevant pharmacokinetic interaction was observed when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1 000 mg once daily). Medicine interactions for each component of JALRAMET have been extensively studied. However, the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions.

The following statements reflect the information available on the individual active substances (vildagliptin and metformin).

Vildagliptin

Vildagliptin, as contained in JALRAMET, has a low potential for medicine interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induces CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Medicine-medicine interaction studies were conducted with commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, and metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin hydrochloride

The following is known about metformin:

Furosemide - Furosemide increased C_{max} and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased C_{max} blood AUC of furosemide, with no change in renal clearance of furosemide.

Nifedipine - Nifedipine increased absorption, C_{max} and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.

Glyburide- Glyburide produced no changes in metformin PK/PD parameters. Decreases in C_{max} blood AUC of glyburide were observed, but were highly variable. Therefore the clinical significance of this finding was unclear.

Cationic medicines- Cationic medicines (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60 % and 40 % respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin-containing products (such as JALRAMET) and such medications are recommended.

Other - Some medicines can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin-containing products (such as JALRAMET), close monitoring of renal function is necessary. Certain medicines tend to cause hyperglycaemia and may lead to loss of glycaemic control. These medicines include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking medicines, and isoniazid. Close monitoring of glycaemic control and metformin dose adjustments are recommended when such medicines are administered or withdrawn for these patients.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to metformin. Avoid consumption of alcohol and medicinal products containing alcohol (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Lactation

Safety in lactation has not been established.

JALRAMET should not be administered to breastfeeding women.

4.7 Effect on ability to drive and use machines

JALRAMET may cause dizziness. Patients who experience dizziness should avoid driving vehicles or using machines.

4.8 Undesirable effects

JALRAMET

The data presented here refers to the administration of vildagliptin and metformin as a free or fixed combination.

Cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on

therapy studies lasting up to 24 weeks in duration, the incidence of ALT or AST elevations ≥ 3 x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0,2 %, 0,3 % and 0,2 % for vildagliptin 50 mg daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

In clinical studies with JALRAMET 0,4 % of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg bid + metformin or the placebo + metformin treatment groups.

In clinical studies, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0,9 %), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0,5 %) and in patients receiving placebo and metformin (0,4 %). No severe hypoglycaemic events were reported in the vildagliptin arms.

Adverse reactions reported in patients who received vildagliptin in double-blind studies as add-on to metformin and as monotherapy, are listed below, for each indication, by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Other adverse reactions reported in patients who received vildagliptin 50 mg once daily (n = 233) or 50 mg twice daily (n = 183) as add-on therapy metformin compared to placebo plus metformin in double-blind studies.

Nervous system disorders
Common: Tremor, dizziness, headache.

Long term clinical studies of up to more than 2 years did not show any additional safety signal or unforeseen risks when vildagliptin was added on to metformin.

When vildagliptin was studied as initial combination therapy with metformin, no additional safety signal or unforeseen risk was observed.

Table 2: Adverse reactions reported in patients who received Galvus (vildagliptin) 50 mg twice daily in combination with insulin (with or without metformin) (n = 371)

Nervous system disorders	
Common:	Headache
Gastrointestinal disorders	
Common:	Nausea, gastroesophageal reflux disease
Uncommon:	Diarrhoea, flatulence
General disorders and administration site conditions	
Common:	Chills
Metabolism and nutrition disorders	
Common:	Hypoglycaemia

Table 3: Adverse reactions reported in patients who received Galvus (vildagliptin) 50 mg twice daily in combination with metformin and sulphonylurea (with or without metformin) (n = 157)

Nervous system disorders	
Common:	Dizziness, tremor
General disorders and administration site condition	
Common:	Asthenia
Metabolism and nutrition disorders	
Common:	Hypoglycaemia
Skin and subcutaneous tissue disorders	
Common:	Hyperhidrosis

Vildagliptin

Adverse reactions for vildagliptin component from monotherapy double blind studies in Table 4.

Table 4: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n = 409) or 50 mg twice daily (n = 1 373) as monotherapy in double-blind studies

Nervous system disorders	
Common:	Dizziness
Uncommon:	Headache
Gastrointestinal disorders	
Uncommon:	Constipation
General disorders and administration site conditions	
Uncommon:	Oedema peripheral

Post-marketing Experience

During post-marketing experience the following additional adverse drug reactions have been reported:

- Cases of hepatitis reversible upon discontinuation of treatment (see section 4.4)
- Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid
- Pancreatitis
- Arthralgia, sometimes severe

Rhabdomyolysis

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP - 4 inhibitors including JALRAMET.

Metformin hydrochloride:

Known adverse reactions for metformin component are summarized in Table 5.

Table 5: Known adverse reactions for metformin

Metabolism and nutrition disorders
Very common: Decreased appetite
Very rare: Lactic acidosis
Nervous system disorders
Common: Metallic taste

Gastrointestinal disorders Very common: Flatulence, nausea, vomiting, diarrhoea, abdominal pain
Hepatobiliary disorders Very rare: Liver function test abnormalities, hepatitis**
Skin and subcutaneous tissue disorders Very rare: Skin reactions such as erythema, pruritus, urticaria
Investigations Very rare: Decrease of vitamin B_{12} absorption*

*A decrease of vitamin B_{12} absorption with decrease of serum levels has been very rarely observed in patients treated long-term with metformin and appears generally to be without clinical significance. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

**Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

Gastrointestinal adverse effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP- 4 inhibitors including JALRAMET.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms

Vildagliptin

Reports include muscle pain, paraesthesia, fever and oedema. Increases in lipase levels (2 x ULN), creatine phosphokinase (CPK) levels, aspartate aminotransferase (AST), C-reactive protein, and myoglobin may occur. Vildagliptin is not dialysable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

Metformin Hydrochloride

Hypoglycaemia may develop and should be monitored for. Lactic acidosis has been reported in approximately 32 % of metformin hydrochloride overdose cases. Metformin hydrochloride is dialysable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated medicine from patients in whom metformin hydrochloride overdosage is suspected.

In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

5 PHARMACOLOGICAL PROPERTIES

Pharmacological Classification: A 21.2. Oral hypoglycaemics

5.1 Pharmacodynamic properties

JALRAMET

JALRAMET combines two antihyperglycaemic agents with different mechanisms of action to improve glycaemic control in patients with type 2 diabetes: vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.

Vildagliptin

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control.

The administration of vildagliptin results in inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results 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. Treatment with 50 to 100 mg daily in patients with type 2 diabetes significantly improved markers of beta-cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose appropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance.

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 reduced glycaemia.

The known effect of increased GLP-1 levels to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipaemia that is not associated with vildagliptin's incretin mediated effect to improve islet function, has been observed.

Metformin hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increase the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.

5.2 Pharmacokinetic properties

Absorption

JALRAMET

In the bioequivalence studies of JALRAMET at two dose strengths (50 mg/850 mg and 50 mg/1 000 mg), versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (C_{max}) of both the vildagliptin component and the metformin hydrochloride component of the JALRAMET tablets were demonstrated to be bioequivalent to that of free combination tablets.

Food does not affect the extent and rate of absorption of vildagliptin from JALRAMET. The C_{max} and AUC of the metformin hydrochloride component from JALRAMET were decreased by 26 % and 7 % respectively when given with food. The absorption of metformin hydrochloride was also delayed as reflected by the T_{max} (2, 0 to 4, 0 hours) when given with food. These changes in C_{max} and AUC are consistent but lower than those observed when metformin hydrochloride was given alone under fed conditions. The effects of food on the pharmacokinetics of both the vildagliptin component and metformin hydrochloride component of JALRAMET were similar to the pharmacokinetics of vildagliptin and metformin hydrochloride when given alone with food.

Vildagliptin

Following oral administration in the fasting state, vildagliptin is well absorbed with peak plasma concentrations observed at 1,75 hours. Co-administration with food slightly decreases the rate of

absorption of vildagliptin, as characterised by a 19 % decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2,5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

Metformin hydrochloride

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50 to 60 %. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1 500 mg, and 850 mg to 2 550 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. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40 % lower mean peak plasma concentration (C_{max}), a 25 % lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered under fasting conditions. The clinical relevance of these decreases is unknown.

Linearity

Vildagliptin is well absorbed with an absolute oral bioavailability of 85 %. Peak plasma concentrations for vildagliptin and the area under the plasma concentration versus time curve (AUC) increased in an approximately dose-proportional manner over the therapeutic dose range.

Distribution

Vildagliptin

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 (V_{ss}) is 71 L, suggesting extravascular distribution.

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 L. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90 % protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally < 1 µgram/mL. During controlled clinical studies of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 µgram/mL, even at maximum doses.

Metabolism

Vildagliptin

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69 % of the dose. The major metabolite, LAY151, is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57 % of the dose, followed by the amide hydrolysis product (4 % of the dose). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in an *in-vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolised by cytochrome P450 enzymes to any quantifiable extent. *In-vitro* studies demonstrated that vildagliptin does not inhibit or induce cytochrome P450 enzymes.

Metformin Hydrochloride

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Excretion and elimination

Vildagliptin

Following oral administration of [^{14}C]-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 an intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 litres/hour and 13 litres/hour, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours and is independent of dose.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3,5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90 % of the absorbed medicine is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6,2 hours. In blood, the elimination half-life is approximately 17,6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special populations

Obesity

Vildagliptin

BMI does not show any impact on the pharmacokinetic parameters of vildagliptin. DPP-4 inhibition by vildagliptin was unaffected by BMI.

Hepatic impairment

Vildagliptin

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in subjects with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic function. The exposure to vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20 % and 8 %, respectively), while the exposure to vildagliptin for subjects with severe impairment was increased by 22 %. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30 %, which is not considered to be clinically relevant. There was no correlation between the severity of hepatic function impairment and changes in exposure to vildagliptin.

The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2,5 x the ULN (upper limit of normal).

Metformin Hydrochloride

No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic impairment.

Renal impairment

Vildagliptin

Vildagliptin AUC increased on average 1.4, 1.7 and 2 -fold in patients with mild, moderate and severe renal impairment, respectively, compared to normal healthy subjects. AUC of the metabolites LAY151 increased 1.6, 3.2 and 7.3 -fold and that of BQS867 increased 1.4, 2.7 and 7.3 -fold in patients with mild, moderate and severe renal impairment, respectively, compared to healthy volunteers. Limited data from patients with end stage renal disease (ESRD) indicate that vildagliptin exposure is similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2-3-fold higher than in patients with severe renal impairment.

Vildagliptin was removed by haemodialysis to a limited extent (3 % over a 3 - 4 hour haemodialysis session starting 4 hours post dose).

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Elderly

Vildagliptin

In otherwise healthy elderly subjects (≥ 70 years), the overall exposure to vildagliptin (100 mg once daily) was increased by 32 % with an 18 % increase in peak plasma concentration compared to younger healthy subjects (18 to 40 years). These changes are not considered to be clinically relevant. DPP-4 inhibition by vildagliptin is not affected by age in the age groups studied.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

JALRAMET treatment should not be initiated in patients 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Paediatric

No pharmacokinetic data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

JALRAMET 50 mg/850 mg: Hydroxypropyl cellulose, hypromellose, iron oxide yellow, magnesium stearate, polyethylene glycol, talc, titanium dioxide.

JALRAMET 50 mg/1000 mg: Hydroxypropyl cellulose, hypromellose, iron oxide yellow, magnesium stearate, polyethylene glycol, talc, titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

6.4 Special precautions for storage

Store at or below 30 °C in the original package. Protect from moisture.

Do not remove blister from carton until required for use.

6.5 Nature and contents of container

10, 30, 60, 120, 180 or 360's tablets in PA / Al / PVC (polyamide / aluminium / polyvinylchloride) blisters with an aluminium foil backing. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not Applicable

7 HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West,

Waterfall City

Jukskei View,

Johannesburg

2090

8 REGISTRATION NUMBER(S)

JALRAMET® 50 mg/850 mg tablet: 48/21.2/0729

JALRAMET® 50 mg/1 000 mg tablet: 48/21.2/0730

Namibia

JALRAMET® 50 mg/850 mg: 20/21.2/0126 NS2

JALRAMET® 50 mg/1 000 mg: 20/21.2/0127 NS2

9 DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of Registration of medicine: May 2019

10 DATE OF REVISION OF TEXT

06 July 2022