AUSTRALIAN PRODUCT INFORMATION – JANUMET® (sitagliptin phosphate monohydrate/metformin hydrochloride) 50 mg/500 mg, 50 mg/850 mg & 50 mg/1000 mg

JANUMET® XR (sitagliptin phosphate monohydrate/metformin hydrochloride modified release) 50 mg/500 mg, 50 mg/1000 mg & 100 mg/1000 mg

1 NAME OF THE MEDICINE

sitagliptin phosphate monohydrate/metformin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

JANUMET and JANUMET XR both contain sitagliptin phosphate and metformin hydrochloride. JANUMET tablets consist of sitagliptin and an immediate-release formulation of metformin, and JANUMET XR tablets consist of sitagliptin and a modified release formulation of metformin.

JANUMET is available for oral administration as film-coated tablets containing sitagliptin phosphate monohydrate and metformin hydrochloride equivalent to: 50 mg sitagliptin as free base and 500 mg metformin hydrochloride (JANUMET 50 mg/500 mg), 850 mg metformin hydrochloride (JANUMET 50 mg/850 mg) or 1000 mg metformin hydrochloride (JANUMET 50 mg/1000 mg).

JANUMET XR is available for oral administration as film-coated tablets containing sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin as free base and either 500 mg metformin hydrochloride modified release (JANUMET XR 50 mg/500 mg*), or 1000 mg metformin hydrochloride modified release (JANUMET XR 50 mg/1000 mg). Additionally, JANUMET XR is available for oral administration as tablets containing sitagliptin phosphate monohydrate equivalent to 100 mg sitagliptin as free base and 1000 mg metformin hydrochloride modified release (JANUMET XR 100 mg/1000 mg).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

JANUMET 50 mg/500 mg - a light pink, film coated tablet with "575" on one side and plain on the other.

JANUMET 50 mg/850 mg - a pink, film coated tablet with "515" on one side and plain on the other.

JANUMET 50 mg/1000 mg - a red, film coated tablet with "577" on one side and plain on the other.

JANUMET XR consists of a modified release metformin core tablet coated with an immediate release layer of sitagliptin. The sitagliptin layer is coated with a soluble polymeric film that provides taste masking.

JANUMET XR is available in the following presentations:

JANUMET XR 50 mg/500 mg[1] – a light blue, bi-convex oval, film coated tablet, debossed "78" on one side and plain on the other.

JANUMET XR 50 mg/1000 mg – a light green, bi-convex oval, film coated tablet, debossed "80" on one side and plain on the other.

JANUMET XR 100 mg/1000 mg - a blue, bi-convex oval, film coated tablet, debossed "81" on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

JANUMET and JANUMET XR (sitagliptin phosphate monohydrate and metformin hydrochloride) are indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.

[see 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials and 4.2 DOSE AND METHOD OF ADMINISTRATION].

4.2 DOSE AND METHOD OF ADMINISTRATION

Life-threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and the use of high doses of metformin above 2000 mg per day.

General

The dosage of antihyperglycaemic therapy with JANUMET and JANUMET XR should be individualised on the basis of the patient's current regimen, effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin.

JANUMET should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. Patients should only be prescribed one strength of JANUMET at a time.

JANUMET XR should be given once daily with a meal preferably in the evening. The dose should be escalated gradually to reduce the gastrointestinal (GI) side effects due to metformin. Additionally, administration of JANUMET XR with food enhances plasma concentrations of metformin. To preserve the modified-release properties, the tablets must not be split, broken, crushed, or chewed before swallowing. There have been reports of incompletely dissolved JANUMET XR tablets being eliminated in the faeces. It is not known whether this material seen in faeces contains active drug. If a patient reports repeatedly seeing tablets in faeces, the healthcare provider should assess adequacy of glycaemic control.

[1] Presentation not currently marketed in Australia.

Dosage

The starting dose of JANUMET or JANUMET XR should be based on the patient's current regimen.

JANUMET should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg metformin hydrochloride
50 mg sitagliptin/850 mg metformin hydrochloride
50 mg sitagliptin/1000 mg metformin hydrochloride

JANUMET XR should be given once daily with a meal preferably in the evening. JANUMET XR tablets are available in the following strengths:

50 mg sitagliptin/500 mg modified release metformin hydrochloride[2]
50 mg sitagliptin/1000 mg modified release metformin hydrochloride
100 mg sitagliptin/1000 mg modified release metformin hydrochloride

For patients using the 50 mg sitagliptin/500 mg metformin hydrochloride modified release tablet or the 50 mg sitagliptin/1000 mg metformin hydrochloride modified release tablet, two tablets should be taken together once daily. The 100 mg sitagliptin/1000 mg metformin hydrochloride modified release tablet should be taken as a single tablet once daily.

As initial therapy

For patients with type 2 diabetes mellitus, whose hyperglycaemia is inadequately controlled with diet and exercise alone, when dual therapy is appropriate, the recommended total daily starting dose of JANUMET or JANUMET XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride. Patients with inadequate glycaemic control on this dose should have their metformin dose increased up to a maximum of 100 mg sitagliptin/2000 mg metformin hydrochloride daily.

For patients inadequately controlled on sitagliptin monotherapy

For patients inadequately controlled on sitagliptin alone, the recommended starting dose of JANUMET or JANUMET XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride daily. Patients may be titrated up to 100 mg sitagliptin/2000 mg metformin hydrochloride daily to achieve glycaemic control. Patients taking sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to JANUMET (see Section 4.3 CONTRAINDICATIONS).

For patients inadequately controlled on metformin monotherapy

For patients not adequately controlled on metformin alone, the usual starting dose of JANUMET or JANUMET XR should provide sitagliptin 100 mg total daily dose plus the dose of metformin already being taken.

For patients switching from sitagliptin coadministered with metformin

For patients switching from sitagliptin coadministered with metformin, JANUMET or JANUMET XR may be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with metformin and a sulfonylurea

The usual starting dose of JANUMET or JANUMET XR should provide sitagliptin 100 mg total daily dose and the dose of metformin already being taken. Patients may require lower sulfonylurea doses to reduce the risk of sulfonylurea-induced hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

[2] Presentation not currently marketed in Australia

For patients inadequately controlled on dual combination therapy with metformin and insulin
The usual starting dose of JANUMET or JANUMET XR should provide 100 mg total daily dose of sitagliptin. In determining the starting dose of the metformin component, the patient's level of glycaemic control and current dose of metformin should be considered. Patients currently on or initiating insulin therapy may require lower doses of insulin to reduce the risk of hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Sitagliptin phosphate monohydrate*, Hypoglycaemia).

Recommendations for use in renal impairment
No dose adjustment is needed for patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2). An eGFR should be assessed before initiation of treatment with JANUMET 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 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase risk of lactic acidosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) should be reviewed before considering initiation of metformin in patients with eGFR < 60 mL/min/1.73 m^2. See table below for recommended daily dose.

JANUMET
JANUMET is prescribed twice daily.
JANUMET is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2 (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). JANUMET is not recommended in patients with an eGFR ≥ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2 because these patients require a lower dosage of sitagliptin than what is available in the fixed combination JANUMET product.

JANUMET XR
JANUMET XR is prescribed once daily.
JANUMET XR is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Discontinue JANUMET XR if the patient's eGFR later falls below 30 mL/min/1.73 m^2 (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Initiation of JANUMET XR in patients with an eGFR ≥ 30 mL/min/1.73 m^2 and < 45 mL/min/1.73 m^2 is not recommended. In patients taking JANUMET XR whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy and limit dose of the sitagliptin component to 50 mg once day.

eGFR mL/min/1.73 m^2	**Metformin**	**Sitagliptin**
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50 mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25 mg.

Discontinuation for iodinated contrast imaging procedures
Discontinue JANUMET or JANUMET XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JANUMET or JANUMET XR if renal function is acceptable (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Elderly
As metformin and sitagliptin are excreted by the kidney, JANUMET or JANUMET XR should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see Section 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Metformin hydrochloride*, Lactic Acidosis).

Paediatric Population
JANUMET or JANUMET XR should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. JANUMET and JANUMET XR have not been studied in children younger than 10 years of age.

Previous therapies
No studies have been performed specifically examining the safety and efficacy of JANUMET or JANUMET XR in patients previously treated with other oral antihyperglycaemic agents and switched to JANUMET or JANUMET XR. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycaemic control can occur.

4.3 CONTRAINDICATIONS

JANUMET (sitagliptin phosphate monohydrate/metformin hydrochloride) and JANUMET XR (sitagliptin phosphate monohydrate/metformin hydrochloride modified release) are contraindicated in patients with:

1. Severe renal impairment (eGFR < 30 mL/min/1.73 m^2)
   (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
2. Known hypersensitivity to sitagliptin phosphate monohydrate, metformin hydrochloride or any other component of JANUMET or JANUMET XR
   (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Sitagliptin phosphate monohydrate*, Hypersensitivity Reactions and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), *Postmarketing Experience*).
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

JANUMET and JANUMET XR should be temporarily discontinued in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE; *Metformin hydrochloride*).

JANUMET and JANUMET XR are not currently indicated for use in children below 18 years.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

JANUMET and JANUMET XR
JANUMET and JANUMET XR should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis: There have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)), in patients taking sitagliptin. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, JANUMET or JANUMET XR and other potentially suspect medicinal products should be discontinued.

Monitoring of renal function: Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. JANUMET and JANUMET XR are contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m^2 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.3 CONTRAINDICATIONS, Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Metformin hydrochloride*, Lactic acidosis).

Before initiation of therapy with JANUMET or JANUMET XR and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and JANUMET or JANUMET XR discontinued if evidence of renal impairment is present.

Sitagliptin phosphate monohydrate
Hypoglycaemia: In clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin or pioglitazone), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. As is typical with other antihyperglycaemic agents, hypoglycaemia has been observed when sitagliptin were used in combination with insulin or a sulfonylurea (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycaemia, a lower dose of sulfonylurea or insulin may be considered (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET and JANUMET XR. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET or JANUMET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes (See Section 4.3 CONTRAINDICATIONS and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), *Postmarketing Experience*.)

Arthralgia: There have been post-marketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with DPP-4 inhibitors.

Bullous Pemphigoid: Postmarketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving JANUMET or JANUMET XR. If bullous pemphigoid is suspected, JANUMET or JANUMET

XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Metformin hydrochloride

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET (sitagliptin phosphate monohydrate/metformin hydrochloride) or JANUMET XR (sitagliptin phosphate monohydrate/metformin hydrochloride modified release); when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxaemia. Lactic acidosis is characterised by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 microgram/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, *Recommendations for use in renal impairment*). Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxaemia, are at increased risk of lactic acidosis.

The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in elderly). In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxaemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilised on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis

and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonaemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialysable (with a clearance of up to 170 mL/min under good haemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see Section 4.3 CONTRAINDICATIONS).

Patients with known or suspected mitochondrial diseases: In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Hypoglycaemia: Hypoglycaemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognise in the elderly, and in people who are taking β-adrenergic blocking drugs.

Use of concomitant medications that may affect renal function or metformin disposition: Concomitant medication(s) that may affect renal function or result in significant haemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, *Metformin hydrochloride*), should be used with caution.

Radiological studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see Section 4.3 CONTRAINDICATIONS). Therefore, in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m^2, in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, JANUMET or JANUMET XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be acceptable (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Hypoxic states: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxaemia have been associated with lactic acidosis and may also cause prerenal azotaemia. When

such events occur in patients on JANUMET or JANUMET XR therapy, the drug should be promptly discontinued.

Surgical procedures: Use of JANUMET or JANUMET XR 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 acceptable (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Alcohol intake: Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving JANUMET or JANUMET XR.

Impaired hepatic function: Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET or JANUMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels: In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on JANUMET or JANUMET XR and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (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 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 JANUMET or JANUMET XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, JANUMET or JANUMET XR must be stopped immediately and other appropriate corrective measures initiated.

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

Hypothyroidism: Metformin induces a reduction in thyrotropin (thyroid stimulating hormone (TSH)) levels in patients with treated or untreated hypothyroidism (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Regular monitoring of TSH levels is recommended in patients with hypothyroidism.

Studies have shown that metformin reduces plasma TSH levels, often to subnormal levels, when it is administered to patients with untreated hypothyroidism or to hypothyroid patients effectively treated with Levothyroxine. The metformin-induced reduction of plasma TSH levels is not observed when metformin is administered to patients with normal thyroid

function. Metformin has been suggested to enhance the inhibitory modulation of thyroid hormones on TSH secretion.

Levothyroxine can reduce the hypoglycaemic effect of metformin. Careful monitoring of blood glucose levels is recommended in patients with hypothyroidism treated with Levothyroxine, especially when thyroid hormone therapy is initiated, changed, or stopped (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Levothyroxine).

Use in the elderly

JANUMET and JANUMET XR
Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET or JANUMET XR should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Monitoring of Renal Function).

Sitagliptin phosphate monohydrate
In clinical studies, the safety and effectiveness of sitagliptin in the elderly (≥ 65 years,) were comparable to those seen in younger patients (< 65 years).

Metformin hydrochloride
Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Paediatric use

Safety and effectiveness of JANUMET or JANUMET XR in paediatric patients under 18 years have not been established.

JANUMET and JANUMET XR should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Sitagliptin was associated with an increased risk of hypoglycaemia in paediatric patients on or not on background insulin (see Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

JANUMET and JANUMET XR have not been studied in paediatric patients under 10 years of age.

Effects on laboratory tests

Sitagliptin phosphate monohydrate

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Metformin hydrochloride
In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Metformin hydrochloride*).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Sitagliptin and Metformin
Coadministration of multiple doses of sitagliptin (50 mg b.i.d.) and metformin (1000 mg b.i.d.) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with JANUMET or JANUMET XR have not been performed; however, such studies have been conducted with the individual components of JANUMET and JANUMET XR (sitagliptin phosphate monohydrate and metformin hydrochloride).

Sitagliptin phosphate monohydrate
***In Vitro* Assessment of Drug Interactions**

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6 at therapeutic concentrations, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilise these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

***In Vivo* Assessment of Drug Interactions**
Effect of Sitagliptin on Other Drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, ertugliflozin, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Multiple doses of sitagliptin slightly increased digoxin concentrations; however, these increases are not considered likely to be clinically meaningful and are not attributed to a specific mechanism.

Sulfonylureas: Single-dose pharmacokinetics of glibenclamide, a CYP2C9 substrate, were not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g. glipizide, tolbutamide, and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Ertugliflozin: Single-dose administration of sitagliptin 100 mg had no clinically meaningful effect on the exposure of ertugliflozin 15 mg. The geometric mean ratios (GMR) and 90% CI (expressed as percentages) for ertugliflozin AUC_{inf} and C_{max} for coadministration with sitagliptin vs. ertugliflozin alone were 102.27% (99.72%, 104.89%) and 98.18% (91.20%, 105.70%), respectively.

Simvastatin: Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8-mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-mediated metabolism.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Since S(-) warfarin is primarily metabolised by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Coadministration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%. These increases are not considered to be clinically meaningful.

Effect of Other Drugs on Sitagliptin
Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications:

Ertugliflozin: No clinically meaningful change in sitagliptin exposure was observed following concomitant administration of a single 100 mg sitagliptin dose with 15 mg ertugliflozin compared to sitagliptin alone. The GMR and 90% CI (expressed as percentages) for sitagliptin AUC_{inf} and C_{max} for coadministration with ertugliflozin vs. sitagliptin alone were 101.67% (98.40%, 105.04%) and 101.68% (91.65%, 112.80%), respectively.

Ciclosporin: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100 mg oral dose of JANUVIA® and a single 600 mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Population Pharmacokinetics: Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on sitagliptin pharmacokinetics. Medications assessed were those that are commonly administered to patients with type 2 diabetes including cholesterol-lowering agents (e.g. statins, fibrates, ezetimibe), anti-platelet agents (e.g. clopidogrel), antihypertensives (e.g. ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g. naproxen, diclofenac, celecoxib), anti-depressants (e.g. bupropion, fluoxetine, sertraline), antihistamines (e.g. cetirizine), proton-pump inhibitors (e.g. omeprazole, lansoprazole), and medications for erectile dysfunction (e.g. sildenafil).

Metformin hydrochloride
Glibenclamide: In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glibenclamide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glibenclamide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the

lack of correlation between glibenclamide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide (Frusemide): A single-dose, metformin-furosemide (frusemide) drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide (frusemide) increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of frusemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in frusemide renal clearance. No information is available about the interaction of metformin and furosemide (frusemide) when coadministered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Levothyroxine: Levothyroxine can reduce the hypoglycaemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), and dosage adjusted as necessary.

Drugs that reduce metformin clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Other: Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET or JANUMET XR the patient should be closely observed to maintain adequate glycaemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies have been conducted with the combined components of JANUMET or JANUMET XR to evaluate the effects on fertility.

Sitagliptin phosphate monohydrate
No adverse effects on fertility were observed in male and female rats given sitagliptin orally at doses up to 1000 mg/kg daily (up to approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day) prior to and throughout mating.

Metformin hydrochloride
Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Use in pregnancy (Category C)

There are no adequate and well-controlled studies in pregnant women with JANUMET, JANUMET XR or its individual components; therefore, the safety of JANUMET and JANUMET XR in pregnant women is not known. JANUMET and JANUMET XR, like other oral antihyperglycaemic agents, are not recommended for use in pregnancy.

No animal studies have been conducted with the combined components of JANUMET or JANUMET XR to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin phosphate monohydrate
Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg/day or in rabbits given up to 125 mg/kg/day during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg). In rats, a slight increase in the incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg). Slight decreases in mean birth weight and preweaning and postweaning body weight gains were observed in the offspring of rats given sitagliptin at an oral dose of 1000 mg/kg/day from gestation day 6 to lactation day 20. However, animal reproduction studies are not always predictive of the human response. Sitagliptin crosses the placenta in rats and rabbits.

Metformin hydrochloride
Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This dose is about 3 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of foetal concentrations demonstrated a partial placental barrier to metformin.

Use in lactation

No studies in lactating animals have been conducted with the combined components of JANUMET or JANUMET XR. In studies performed with the individual components, both sitagliptin and metformin were excreted in the milk of lactating rats. For sitagliptin, excretion occurred at a milk to plasma ratio of 4:1. Treatment of rats with sitagliptin during pregnancy and lactation caused decreased pup body weight gain (see Use in Pregnancy). It is not known whether sitagliptin is excreted in human milk; some excretion of metformin in human milk has been observed. Therefore, JANUMET or JANUMET XR should not be used by a woman who is nursing.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies of the effects of JANUMET or JANUMET XR on the ability to drive and use machines have been performed. However, JANUMET and JANUMET XR are not expected to affect the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

In placebo-controlled clinical trials, in patients with type 2 diabetes mellitus on metformin monotherapy, the addition of sitagliptin 100 mg daily was well tolerated. The overall incidence of adverse experiences reported in patients receiving sitagliptin and metformin was similar to that reported with patients receiving placebo and metformin.
In an additional, 104-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥ 5% of patients are shown in Table 1.

Table 1 Initial Therapy with Combination of Sitagliptin and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)†

	Number of Patients (%)			
	Placebo/ Metformin 1000 mg bid	**Sitagliptin (JANUVIA) 100 mg QD**	**Metformin 500 or 1000 mg bid††**	**Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid ††**
	N = 176	N = 179	N = 364††	N = 372††
Diarrhoea	12 (6.8)	8 (4.5)	37 (10.1)	44 (11.8)
Nausea	4 (2.3)	2 (1.1)	25 (6.9)	22 (5.9)
Bronchitis	8 (4.5)	3 (1.7)	14 (3.8)	27 (7.3)
Influenza	5 (2.8)	8 (4.5)	25 (6.9)	20 (5.4)
Upper Respiratory Tract Infection	13 (7.4)	12 (6.7)	37 (10.2)	45 (12.1)
Urinary Tract Infection	4 (2.3)	0 (0)	21 (5.8)	19 (5.1)
Arthralgia	3 (1.7)	7 (3.9)	18 (4.9)	20 (5.4)
Back Pain	9 (5.1)	9 (5.0)	16 (4.4)	24 (6.5)
Headache	7 (4.0)	6 (3.4)	21 (5.8)	27 (7.3)

† Intent-to-treat population.
†† Data pooled for the patients given the lower and higher doses of metformin.

Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The overall incidence of pre-specified adverse reactions of hypoglycaemia in patients with type 2 diabetes mellitus inadequately controlled on diet and exercise was 2.8% in patients given placebo, 1.1% in patients given sitagliptin alone, 1.9% in patients given metformin alone and 3.8% in patients given sitagliptin in combination with metformin.

With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

Treatment-emergent adverse events were reported in similar numbers across all treatment groups. Over the two-year treatment period, discontinuation due to loss of efficacy was reported more commonly in the 100 mg sitagliptin group than other treatment groups.

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin and metformin in this study and at least 2 fold more commonly than in patients treated with metformin are listed below:

Infections and Infestations: Bronchitis, sinusitis
Nervous System Disorders: Headache
Musculoskeletal and Connective Tissue Disorders: Arthralgia
Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal pain

Sitagliptin as add-on Combination Therapy to Metformin
In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin regimen (> 1500 mg), there were no adverse experiences reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse experiences was similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%).

Hypoglycaemia and Gastrointestinal Adverse Experiences
In the placebo-controlled studies of combination therapy with sitagliptin and metformin, the incidence of hypoglycaemia (regardless of investigator assessment of causality) reported in patients treated with the combination of sitagliptin and metformin was similar to that reported for patients treated with metformin and placebo. Adverse experiences of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidences of pre-specified gastrointestinal adverse experiences in patients treated with the combination of sitagliptin and metformin were similar to those reported for patients treated with metformin alone (see Table 2).

Table 2 Hypoglycaemia and Pre-specified Gastrointestinal Intestinal Adverse Experiences (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy

	Number of Patients (%)	
	Study of Sitagliptin as Add-on to Metformin	
	Placebo and Metformin ≥ 1500 mg daily	**Sitagliptin 100 mg and Metformin ≥ 1500 mg daily**
	N= 237	**N= 464**
Hypoglycaemia	5 (2.1)	6 (1.3)
Diarrhoea	6 (2.5)	11 (2.4)
Nausea	2 (0.8)	6 (1.3)
Vomiting	2 (0.8)	5 (1.1)
Abdominal Pain	9 (3.8)	10 (2.2)

With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin and metformin in this study and at least 2 fold more commonly than in patients treated with metformin and placebo are listed below:

Musculoskeletal and Connective Tissue Disorders: Arthralgia

Sitagliptin as Add-on Combination Therapy with Metformin and a Sulfonylurea
In a trial of sitagliptin as add-on combination therapy with metformin and a sulfonylurea (placebo-controlled for 24 weeks, followed by a 30-week active-controlled phase), the only adverse experience reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo was hypoglycaemia (see Table 3). Discontinuation of therapy due to clinical adverse experiences was similar to the control group (at 24 weeks, sitagliptin, metformin, and sulfonylurea, 1.0% vs placebo, metformin, and sulfonylurea 1.4%; at 54 weeks, sitagliptin, metformin, and sulfonylurea, 1.4% vs placebo/pioglitazone, metformin, and sulfonylurea 3.8%).

Table 3 Hypoglycaemia (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy

	Number of Patients (%)	
	Study of Sitagliptin as Add-on to Metformin and Sulfonylurea	
	Sitagliptin + Metformin + Sulfonylurea	**Placebo + Metformin + Sulfonylurea**
	N = 210	N = 212
Metabolism and Nutrition Disorders		
Hypoglycaemia	31 (14.8)‡	10 (4.7)‡

‡ Weeks 0-24.

When sitagliptin was added to metformin and a sulfonylurea, over the 54-week study duration hypoglycaemia was reported in 38 (18.1%) patients treated with sitagliptin + metformin + sulfonylurea compared to 31 (14.6%) patients in the control group (placebo + metformin + sulfonylurea for 24 weeks followed by pioglitazone + metformin + sulfonylurea for 30 weeks). Symptomatic episodes assessed as likely to be hypoglycaemia were reported as adverse experiences regardless of whether fingerstick blood glucose determination was performed at the time of symptoms. Severe hypoglycaemia was noted in 2 (1.0%) patients treated with sitagliptin + metformin + sulfonylurea compared to one patient (0.5%) treated with placebo/pioglitazone + metformin + sulfonylurea.

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin, metformin and a sulfonylurea in this study and at least 2 fold more commonly than in patients treated with placebo, metformin and a sulfonylurea are listed below:

Infections and Infestations: Influenza, Nasopharyngitis
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity

Sitagliptin in Combination with Metformin and Insulin
In a 24 week placebo-controlled study of sitagliptin 100 mg once daily added to ongoing combination treatment with metformin and stable-dose insulin (sitagliptin, N=229; placebo, N=233), the only adverse experience reported regardless of causality assessment in ≥ 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycaemia (see Table 4); the incidence of discontinuation due to clinical adverse reactions was slightly higher than placebo (discontinuation rates: add-on to insulin, with or without metformin, 3.4% vs placebo and insulin, with or without metformin, 1.3%).

Table 4 Hypoglycaemia (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy

	Number of Patients (%)	
	Study of Sitagliptin as Add-on to Insulin and Metformin	
	Sitagliptin 100 mg + Insulin + Metformin	Placebo + Insulin + Metformin
	N= 229	N= 233
Metabolism and Nutrition Disorders		
Hypoglycaemia	35 (15.3)	19 (8.2)

Adverse reactions reported in 2% to 5% of patients treated with sitagliptin, metformin and insulin in this study and at least 2 fold more commonly than in patients treated with placebo, metformin and insulin are listed below:

Nervous system disorders: Headache

Sitagliptin in Combination with Metformin and Ertugliflozin
The safety of sitagliptin used in combination with metformin and the SGLT2 inhibitor ertugliflozin has been evaluated in 796 patients with type 2 diabetes mellitus treated for 26 weeks in two studies. The incidence and type of adverse reactions in these two studies were consistent with that observed in studies with the individual components, sitagliptin, metformin and ertugliflozin.

Pancreatitis
In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomised to receive sitagliptin 100 mg/day (N=5,429) or corresponding (active or placebo) control (N=4,817), the incidence of non-adjudicated acute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4,708 patient-years for sitagliptin and 4 patients with an event in 3,942 patient-years for control) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Pancreatitis*). (See also *TECOS Cardiovascular Safety Study* below).

In another 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), the only drug-related adverse reaction reported in $\geq$ 1% in patients treated with sitagliptin and metformin and more commonly than in patients treated with placebo and metformin was vomiting (sitagliptin and metformin, 1.1%; placebo and metformin, 0.4%).

Adverse Reactions Reported with Sitagliptin
The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo was nasopharyngitis.

Adverse Reactions Reported with Metformin
The most common (> 5%) established adverse experiences due to initiation of metformin therapy are diarrhoea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

TECOS Cardiovascular Safety Study
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with JANUVIA, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA_{1c} and CV risk factors. The overall incidence of serious adverse events in patients receiving JANUVIA was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.7% in JANUVIA-treated patients and 2.5% in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0% in JANUVIA-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in JANUVIA-treated patients and 0.2% in placebo-treated patients.

Paediatric population
In a pooled analysis of two placebo-controlled clinical studies with JANUMET and JANUMET XR in paediatric patients aged 10 to 17 years with type 2 diabetes mellitus, the profile of adverse reactions was comparable to that observed in adults. In paediatric patients on or not on background insulin, sitagliptin was associated with an increased risk of hypoglycaemia.

Postmarketing Experience
Additional adverse reactions have been identified during postmarketing use of JANUMET, JANUMET XR or sitagliptin, one of the components of JANUMET and JANUMET XR. These reactions have been reported when JANUMET, JANUMET XR or sitagliptin have been used alone and/or in combination with other antihyperglycaemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: upper respiratory tract infection; nasopharyngitis
Nervous system disorders: headache
Gastrointestinal disorders: acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Pancreatitis*); constipation; vomiting
Musculoskeletal and connective tissue disorders: arthralgia; myalgia; pain in extremity; back pain
Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis)

Hypersensitivity reactions (including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, pruritus, bullous pemphigoid (see PRECAUTIONS, Bullous Pemphigoid), and exfoliative skin conditions, including Stevens-Johnson syndrome) have been reported with use of sitagliptin (see Section 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Hypersensitivity Reactions*).

Reduction of TSH level in patients with treated or untreated hypothyroidism has been reported with postmarketing use of metformin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Sitagliptin phosphate monohydrate
During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin (see Section 5.1 PHARMACODYNAMIC PROPERTIES *Cardiac Electrophysiology*). There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g. remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

Metformin hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Metformin hydrochloride*). Metformin is dialysable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

JANUMET and JANUMET XR combine two antihyperglycaemic agents with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin phosphate monohydrate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Mechanism of action

Sitagliptin phosphate monohydrate

Sitagliptin phosphate monohydrate is a member of a class of oral antihyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors, which improve glycaemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones.

Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system

involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signalling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of GLP-1 and GIP are glucose-dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not observed. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyses the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. This glucose-dependent mechanism is unlike the mechanism seen with sulfonylureas, whereby insulin is released even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A_{1c} (HbA_{1c}) and lower fasting and postprandial glucose concentrations. Sitagliptin inhibits DPP-4 with nanomolar potency (IC_{50} 18 nM). It does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Inhibition of DPP-8 or DPP-9 is associated with toxicity in preclinical animal models and alteration of immune function *in vitro*.

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal.

In Phase III clinical studies of 18- and 24-week duration, treatment with sitagliptin 100 mg daily in patients with type 2 diabetes significantly improved beta cell function, as assessed by several markers, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In Phase II studies, sitagliptin 50 mg twice daily provided similar glycaemic efficacy compared to sitagliptin 100 mg once daily.

In a randomised, placebo-controlled, double-blind, double-dummy, four-period crossover two-day study in healthy adult subjects, the effects on post-meal plasma concentrations of active and total GLP-1 and glucose after coadministration of sitagliptin and metformin were compared with those after administration of sitagliptin alone, metformin alone or placebo, each administered for two days. The incremental 4-hour post-meal weighted mean active GLP-1 concentrations were increased approximately 2-fold after either administration of sitagliptin alone or metformin alone compared with placebo. The effect on active GLP-1 concentrations after coadministration of sitagliptin and metformin were additive, with active GLP-1 concentrations increased by approximately 4-fold compared with placebo. Sitagliptin alone increased only active GLP-1 concentrations, reflecting inhibition of DPP-4, whereas metformin alone increased active and total GLP-1 concentrations to a similar extent. These data are consistent with different mechanisms for the increase in active GLP-1 concentrations. Results from the study also demonstrated that sitagliptin, but not metformin, enhances active GIP concentrations.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycaemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent.

Effects on blood pressure

In a randomised, placebo-controlled crossover study in hypertensive patients on one or more anti-hypertensive drugs (including angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, calcium-channel blockers, beta-blockers and diuretics), coadministration with sitagliptin was generally well tolerated. In these patients, sitagliptin had a modest blood pressure lowering effect; 100 mg per day of sitagliptin reduced 24-hour mean ambulatory systolic blood pressure by approximately 2 mm Hg, as compared to placebo. Reductions have not been observed in subjects with normal blood pressure.

Cardiac Electrophysiology

In a randomised, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours postdose was 8.0 msec. This small increase was not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose.
In patients with type 2 diabetes administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

Metformin hydrochloride

Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycaemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Metformin hydrochloride*) and does not cause hyperinsulinaemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Clinical trials

Clinical studies of the coadministration of sitagliptin and metformin demonstrated significant improvements in glycaemic control in patients with type 2 diabetes. None of the clinical efficacy studies described below was conducted with JANUMET or JANUMET XR tablets; however, bioequivalence of JANUMET tablets with coadministered sitagliptin and immediate-release metformin hydrochloride tablets and JANUMET XR tablets with coadministered sitagliptin and modified release metformin tablets was demonstrated for all tablet strengths, respectively.

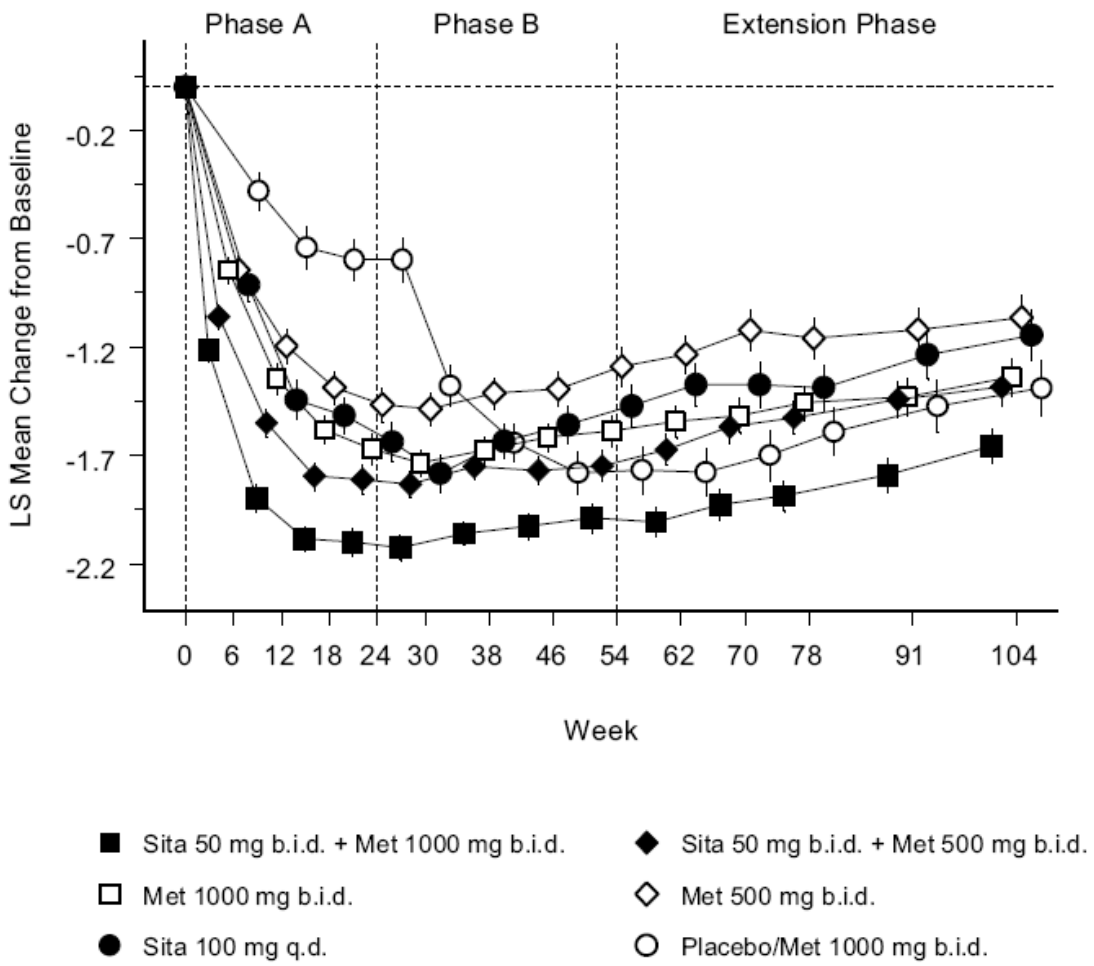
Sitagliptin and Metformin as Initial Therapy in Patients with Type 2 Diabetes

This study consisted of a 24-week, placebo-controlled Phase A, a 30-week, active-controlled Phase B, and a 50-week active-controlled Extension Phase, where 1091 patients with type 2 diabetes and inadequate glycaemic control on diet and exercise were enrolled in a randomised, double-blind, parallel-group factorial study designed to assess the safety and efficacy of initial therapy with the combination of sitagliptin and metformin. Patients on an antihyperglycaemic agent (N=541) underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycaemic

control (A_{1c} 7.5% to 11%) were randomised after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycaemic agents at study entry (N=550) with inadequate glycaemic control (A_{1c} 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomised. A total of 685 patients entered the 50-week extension study, and among these patients, 517 (74.5%) completed the study. Approximately equal numbers of patients were randomised to receive initial therapy with placebo; 100 mg of sitagliptin once daily; 500 mg or 1000 mg of metformin twice daily; or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients receiving active therapy continued with their assigned treatment regimen until the end of the study, unless rescue (glibenclamide) was required. Patients receiving placebo were switched to 1000 mg of metformin twice daily at the beginning of Phase B.

Initial combination therapy with sitagliptin 100 mg and metformin 1000 mg or 2000 mg daily provided sustained improvements in HbA_{1c} and FPG and 2-hour PPG compared with either corresponding monotherapy dose over 104 weeks; (see Figure 1 and Table 5). An improvement in FPG, with near maximal FPG reduction, was achieved by the 3-week time point (the first time point assessed after initiation of therapy) and sustained over time. A slight upward trend in the reduction in HbA_{1c} was observed during the extension phase in each treatment group. Measures of beta cell function, HOMA-β and the proinsulin to insulin ratio generally showed greater improvement with the coadministration of sitagliptin and metformin compared with either monotherapy alone. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo. Mean reductions from baseline in HbA_{1c} compared with placebo were generally greater for patients with higher baseline HbA_{1c} values. The improvement in HbA_{1c} was generally consistent across subgroups defined by gender, age, race, or baseline BMI. Mean reductions from baseline in HbA_{1c} for patients not on an antihyperglycaemic agent at study entry were: sitagliptin 100 mg once daily, -1.14%; metformin 500 mg bid, -1.20%; metformin 1000 mg bid, -1.22%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.65%; and sitagliptin 50 mg bid with metformin 1000 mg bid, -1.74%; and for patients receiving placebo/metformin, -1.11%.

Figure 1 Mean Change from Baseline for HbA_{1c} over 104 Weeks with Sitagliptin and Metformin, Alone and in Combination as Initial Therapy in Patients with Type 2 Diabetes*



* Statistical comparisons apply only to Phase A - formal statistical comparisons are not possible for Phase B and the extension phase.

Table 5 Glycaemic Parameters and Body Weight at Final Visit (24-Week Study) for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy†

	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 mg b.i.d.	Sitagliptin 50 mg b.i.d. + Metformin 500 mg b.i.d.	Metformin 1000 mg b.i.d.	Sitagliptin 50 mg b.i.d + Metformin 1000 mg b.i.d.
HbA_{1c} (%)Þ	**N = 165**	**N = 175**	**N = 178**	**N = 183**	**N = 177**	**N = 178**
Baseline (mean)	8.68	8.87	8.90	8.79	8.68	8.76
Change from baseline (adjusted mean‡)	0.17	-0.66	-0.82	-1.40	-1.13	-1.90
Difference from placebo (adjusted mean‡)	-	-0.83§	-0.99§	-1.57§	-1.30§	-2.07§
Patients (%) achieving HbA_{1c} < 7%	15 (9.1)	35 (20.0)	41 (23.0)	79 (43.2)	68 (38.4)	118 (66.3)
% Patients receiving rescue medication	32	21	17	8	12	2
FPG (mmol/L) β	**N = 169**	**N = 178**	**N = 179**	**N = 183**	**N = 179**	**N = 180**
Baseline (mean)	10.90	11.18	11.39	11.32	10.94	10.92
Change from baseline (adjusted mean‡)	0.32	-0.97	-1.52	-2.61	-1.63	-3.55
Difference from placebo (adjusted mean‡)	-	-1.29§	-1.84§	-2.94§	-1.95§	-3.87§
2-hour PPG (mmol/L) β	**N = 129**	**N = 136**	**N = 141**	**N = 147**	**N = 138**	**N = 152**
Baseline (mean)	15.37	15.84	16.25	16.20	15.73	15.93
Change from baseline (adjusted mean‡)	0.02	-2.88	-2.96	-5.13	-4.33	-6.47
Difference from placebo (adjusted mean‡)		-2.90§	-2.98§	-5.15§	-4.35§	-6.49§
Body Weight (kg)ǁ	**N = 167**	**N = 175**	**N = 179**	**N = 184**	**N = 175**	**N = 178**
Baseline (mean)	90.1	85.9	88.1	90.0	89.4	88.2
Change from baseline (adjusted mean‡)	-0.9	0.0	-0.9	-0.6	-1.1	-1.3
Difference from placebo (adjusted mean‡)		0.9¶	0.1#	0.4#	-0.1#	-0.3#

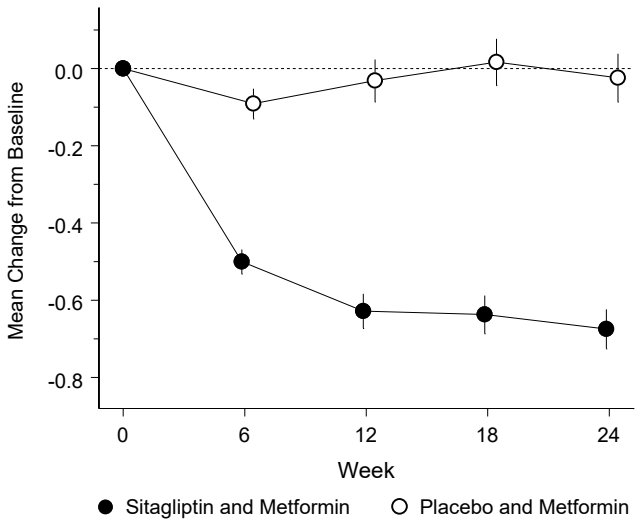
† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.
§ p < 0.001 compared to placebo.
ǁ All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
¶ p=0.005 compared to placebo.
# Not statistically significant (p≥0.05) compared to placebo.
Þ Primary efficacy outcome
β Secondary efficacy outcome

In addition, this study included patients (N=117) with more severe hyperglycaemia (HbA_{1c} > 11% or blood glucose > 15.54 mmol/L) who were treated with open-label sitagliptin at 50 mg and metformin at 1000 mg twice daily for 24 weeks, but were not eligible to enter Phase B of the study. In this group of patients, the baseline HbA_{1c} value was 11.15%, FPG was 17.45 mmol/L, and 2-hour PPG was 24.48 mmol/L. After 24 weeks, decreases from baseline of -2.94 % for HbA_{1c}, -7.03 mmol/L for FPG, and -11.54 mmol/L for 2-hour PPG were observed. In this open-label cohort, a modest increase in body weight of 1.3 kg was observed at 24 weeks.

Sitagliptin Add-on Therapy in Patients Inadequately Controlled on Metformin Alone
The combination of sitagliptin and metformin has been evaluated for safety and efficacy in two double-blind, placebo-controlled clinical studies in patients with type 2 diabetes mellitus. In both studies, patients with inadequate glycaemic control on stable doses of metformin ≥ 1500 mg were randomised to receive either sitagliptin 100 mg per day or placebo in addition to ongoing treatment with metformin.

In one study, 701 patients received 100 mg of sitagliptin or placebo once daily for 24 weeks. This study used the reduction from baseline in haemoglobin A1c (HbA_{1c}) as the primary outcome variable. Pre-specified secondary endpoints included FPG and 2-hour PPG. The addition of sitagliptin to ongoing metformin treatment provided significant improvements compared with the addition of placebo to ongoing metformin treatment in HbA_{1c} (-0.65%), FPG (-1.41 mmol/L), and 2-hour PPG (-2.81 mmol/L) (see Figure 2 and Table 6). This improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c} value, prior antihyperglycaemic therapy, gender, age, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Compared to patients taking placebo, patients taking sitagliptin demonstrated slight decreases in total cholesterol, non-HDL cholesterol and triglycerides. A similar decrease in body weight was observed for both treatment groups.

Figure 2 Mean Change from Baseline for HbA_{1c} (%) over 24 Weeks with Sitagliptin 100 mg – Total Daily Dose added to Metformin (≥ 1500 mg) or Placebo added to Metformin (≥ 1500 mg) in Patients with Type 2 Diabetes† ‡



† Patients with inadequate glycaemic control on metformin monotherapy.
‡ All Patients Treated Population Least squares means adjusted for prior antihyperglycaemic therapy and baseline value.

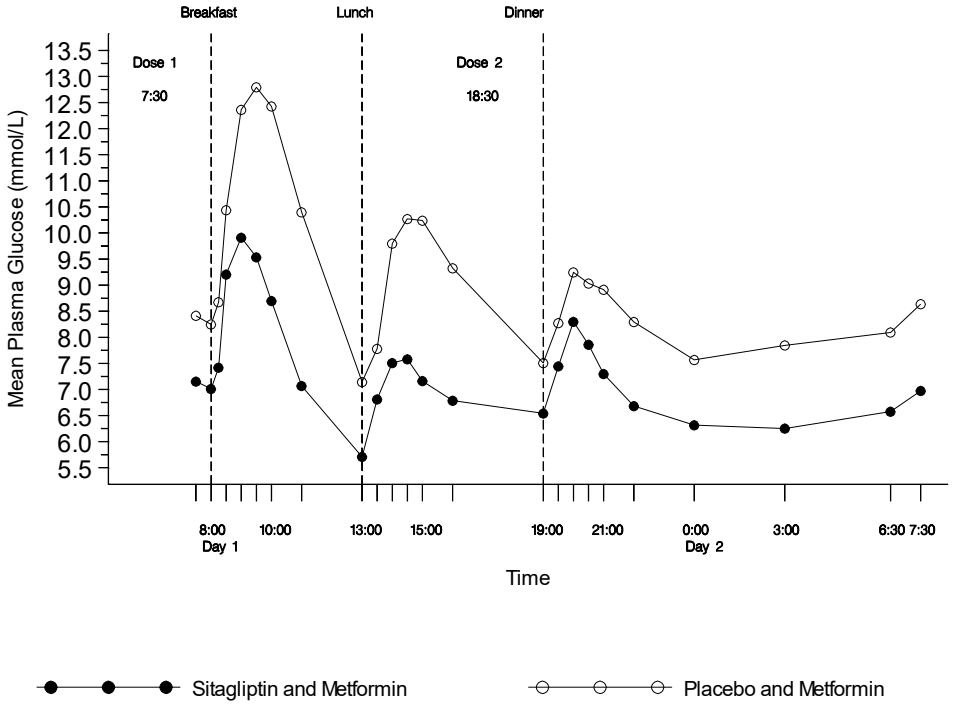
Table 6 Glycaemic Parameters and Body Weight at Final Visit (24-Week Study) Sitagliptin as Add-on Therapy in Patients with Inadequate Glycaemic Control on Metformin†

	Sitagliptin 100 mg q.d. + Metformin	Placebo + Metformin
HbA_{1c} (%)	**N = 453**	**N = 224**
Baseline (mean)	7.96	8.03
Change from baseline (adjusted mean‡)	-0.67	-0.02
Difference from placebo + metformin (adjusted mean‡)	-0.65§	
Patients (%) achieving HbA_{1c} <7%	213 (47.0)	41 (18.3)
FPG (mmol/L)	**N = 454**	**N = 226**
Baseline (mean)	9.44	9.63
Change from baseline (adjusted mean‡)	-0.94	0.47
Difference from placebo + metformin (adjusted mean‡)	-1.41§	
2-hour PPG (mmol/L)	**N = 387**	**N = 182**
Baseline (mean)	15.24	15.12
Change from baseline (adjusted mean‡)	-3.44	-0.63
Difference from placebo + metformin (adjusted mean‡)	-2.81§	
Body Weight (kg) ‖	**N = 399**	**N = 169**
Baseline (mean)	86.9	87.6
Change from baseline (adjusted mean‡)	-0.7	-0.6
Difference from placebo + metformin (adjusted mean‡)	-0.1¶	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for prior antihyperglycaemic therapy and baseline value.
§ $p<0.001$ compared to placebo + metformin.
‖ All Patients as Treated (APaT) population, excluding data following glycaemic rescue therapy.
¶ Not statistically significant ($p\geq0.05$) compared to placebo + metformin.

In a separate study, 24-hour plasma glucose values were assessed. This study used the reduction in 24-hour weighted mean glucose (WMG) as the primary outcome variable. Twenty-eight patients received either 50 mg sitagliptin or placebo twice daily for 4 weeks in addition to their twice daily metformin regimen. Following 4 weeks of treatment, the difference in glucose lowering efficacy was assessed as WMG based upon collection of multiple blood samples, including those obtained before and after meals as well as overnight. Sitagliptin 50 mg coadministered twice daily with metformin significantly lowered the 24-hour WMG (-1.82 mmol/L) compared to placebo coadministered with metformin. In addition, sitagliptin administered with metformin, compared with placebo administered with metformin, substantially lowered fasting glucose concentrations and demonstrated smaller glucose excursions after all three meals (see Figure 3). In patient-collected glucose measurements, treatment with sitagliptin administered with metformin also provided significant reductions compared to placebo administered with metformin in mean fasting plasma glucose (-1.13 mmol/L), 7-point glucose average (-1.55 mmol/L), and 2 hour post-glucose concentrations (-2.03 mmol/L).

Figure 3 24-hour Plasma Glucose Profile after 4-Week Treatment with Sitagliptin 50 mg Twice Daily and Metformin (≥ 1500 mg) or Placebo and Metformin (≥ 1500 mg) in Patients with Type 2 Diabetes†



†Patients with inadequate glycaemic control on metformin monotherapy.

Active (Glipizide)-Controlled Study in Combination with Metformin

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes and inadequate glycaemic control on metformin monotherapy at ≥ 1500 mg/day. In this study, patients were randomised to the addition of either sitagliptin 100 mg daily (N = 588) or glipizide (N = 584) for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated by the investigator to a target FPG of < 6.11 mmol/L, without significant hypoglycaemia, over the next 18 weeks. A maximum dosage of 20 mg/day was allowed to optimise glycaemic control. Thereafter, the glipizide dose was to have been kept constant. The mean dose of glipizide after the titration period was 10.3 mg.

Both treatments resulted in a statistically significant improvement in glycaemic control from baseline. After 52 weeks, the reduction from baseline in HbA_{1c} was 0.67% for sitagliptin 100 mg daily and 0.67% for glipizide, confirming comparable efficacy of the two agents. The reduction in FPG was 0.56 mmol/L for sitagliptin and 0.42 mmol/L for glipizide. In a post-hoc analysis, patients with higher baseline HbA_{1c} (≥ 9%) in both groups had greater reductions from baseline in HbA_{1c} (sitagliptin, -1.68%; glipizide, -1.76%). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the sitagliptin group (4.9%) was significantly lower than that in the glipizide group (32.0%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

Sitagliptin Add-on Therapy in Patients Inadequately Controlled on Metformin and a Sulfonylurea

A total of 422 patients with type 2 diabetes inadequately controlled on combination therapy with metformin and a sulfonylurea participated in a randomised, double-blind, study designed to assess the efficacy of sitagliptin in combination with metformin and a sulfonylurea. The study consisted of a 24-week placebo-controlled phase followed by a 30-week active-controlled phase. All patients were on a stable dose of metformin (≥ 1500 mg/day) and either glimepiride (≥ 2 mg once daily) or gliclazide (≥ 60 mg [modified-release formulation] or ≥ 160 mg [non-modified-release formulation] once daily) prior to enrolment. Patients were randomised to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Glycaemic endpoints measured included HbA_{1c}, 2-hour PPG and fasting glucose. Another pre-specified secondary endpoint was the number of patients in each group who required therapeutic “rescue” with pioglitazone.

In combination with metformin and a sulfonylurea, sitagliptin provided significant improvements in HbA_{1c} compared to placebo with metformin and a sulfonylurea (see Table 7) after 24 weeks of treatment. The improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c}, type of sulfonylurea, gender, age, race, baseline BMI, or length of time since diagnosis of diabetes. There was no significant difference between sitagliptin and placebo in body weight change. Three of 210 patients (1%) randomised to sitagliptin and 15 of 212 patients (7%) randomised to placebo required pioglitazone “rescue”. After 54 weeks, treatment with sitagliptin, metformin and a sulfonylurea continued to provide clinically meaningful improvement in HbA_{1c} relative to baseline.

Table 7 Glycaemic Parameters and Body Weight at End of Phase A (24 Weeks) for Sitagliptin in Combination with Metformin and a Sulfonylurea† - Primary (HbA_{1c}) and Secondary Outcomes

	Sitagliptin 100 mg + Metformin + Sulfonylurea	Placebo + Metformin + Sulfonylurea
HbA_{1c} (%)	**N = 203**	**N = 202**
Baseline (mean)	8.39	8.36
Change from baseline (adjusted mean‡)	-0.84	-0.16
Difference from placebo + met + s/u (adjusted mean‡)	-0.68§	
Patients (%) achieving HbA_{1c} < 7%	59 (29.1)	28 (13.9)
FPG (mmol/L)	**N = 204**	**N = 203**
Baseline (mean)	9.30	9.26
Change from baseline (adjusted mean‡)	-0.73	0.30
Difference from placebo + met + s/u (adjusted mean‡)	-1.03§	
2-hour PPG (mmol/L)	**N = 184**	**N = 183**
Baseline (mean)	13.37	13.47
Change from baseline (adjusted mean‡)	-2.04	-0.19
Difference from placebo + met + s/u (adjusted mean‡)	-1.86§	
Body Weight (kg)ǁ	**N = 197**	**N = 178**
Baseline (mean)	78.7	75.3
Change from baseline (adjusted mean‡)	0.2	0.4
Difference from placebo + met + s/u (adjusted mean‡)	-0.2¶	

† Full Analysis Set Population (an intention-to-treat analysis).
‡ Least squares means adjusted for type of sulfonylurea and baseline value.
§ p<0.001 compared to placebo + metformin + sulfonylurea.
ǁ All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
¶ Not statistically significant (p≥0.05) compared to placebo + metformin + sulfonylurea

Sitagliptin Add-on Therapy in Patients Inadequately Controlled on the Combination of Metformin and Insulin

A total of 641 patients with type 2 diabetes participated in a 24 week, randomised, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin 100 mg once daily in combination with a stable dose of insulin. Approximately 75% of patients were also taking metformin. Patients on pre-mixed, long-acting or intermediate acting insulin (with or without metformin) were randomized to the addition of either 100 mg of sitagliptin or placebo. Patients with moderate or severe renal impairment and patients with NYHA Class II, III or IV congestive heart failure were not eligible for inclusion in the study. Glycaemic endpoints measured included HbA_{1c}, FPG and 2-hour PPG.

The combination of sitagliptin, metformin and insulin provided significant improvements in HbA_{1c}, FPG and 2-hour PPG compared to placebo (see Table 8). The improvement in HbA_{1c} compared to placebo was generally consistent across subgroups defined by gender, age, race, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). There was no meaningful change from baseline in body weight in either group.

Table 8 Glycaemic Parameters and Body Weight at Final Visit (24 Week Study) for Sitagliptin as Add-on Combination Therapy with Insulin plus a Stable Dose of Metformin†

	Sitagliptin 100 mg + Insulin + Metformin	Placebo + Insulin + Metformin
HbA_{1c} (%)	**N = 223**	**N = 229**
Baseline (mean)	8.73	8.60
Change from baseline (adjusted mean‡; 95%CI)	-0.66 (-0.78, -0.54)	-0.13 (-0.25, -0.01)
Difference from placebo (adjusted mean‡, §; 95%CI)	-0.53‖ (-0.69, -0.37)	
Patients (%) achieving HbA_{1c} < 7%	32 (14.3)	12 (5.2)
FPG (mmol/L)	**N = 225**	**N = 229**
Baseline (mean)	9.5	9.7
Change from baseline (adjusted mean‡; 95%CI)	-1.2 (-1.6, -0.8)	-0.2 (-0.6, 0.2)
Difference from placebo (adjusted mean‡; 95%CI)	-1.0‖ (-1.5, -0.5)	
2-hour PPG (mmol/L)	**N = 182**	**N = 189**
Baseline (mean)	15.4	15.4
Change from baseline (adjusted mean‡; 95%CI)	-2.1 (-2.7, -1.6)	0.1 (-0.5, 0.6)
Difference from placebo (adjusted mean‡; 95%CI)	-2.2‖ (-2.9, -1.5)	
Body Weight (kg)¶	**N = 201**	**N = 200**
Baseline (mean)	87.9	88.0
Change from baseline (adjusted mean‡; 95%CI)	-0.1 (-0.5, 0.3)	0.0 (-0.4, 0.4)
Difference from placebo (adjusted mean‡; 95%CI)	-0.1# (-0.6, 0.4)	

† All Patients Treated Population (an intention-to-treat analysis).
‡ Least squares means adjusted for metformin use at Visit 1 (yes/no), insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.
§ Treatment by insulin stratum interaction was not significant (p > 0.10).
‖ p<0.001 compared to placebo.
¶ All Patients as Treated (APaT) population, excluding data following glycaemic rescue therapy.
# Not statistically significant (p≥0.05) compared to placebo.

In another 24-week, randomized, double-blind, placebo-controlled study designed to assess the insulin-sparing efficacy of sitagliptin as add-on combination therapy, 660 patients with inadequate glycaemic control on insulin glargine with or without metformin (≥ 1500 mg per day) were randomized to the addition of either 100 mg of sitagliptin (N=330) or placebo (N=330), administered once daily while undergoing intensification of insulin therapy. Among patients taking metformin, baseline HbA_{1c} was 8.70% and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Glycaemic endpoints measured included HbA_{1c} and FPG.

Among patients taking metformin, at Week 24, the mean increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin (N=285) and 24 IU/day in patients treated with placebo (N=283). The reduction in HbA_{1c} for patients treated with sitagliptin, metformin, and insulin was -1.35% compared to -0.90% for patients treated with placebo, metformin, and insulin, a difference of -0.45% [95% CI: -0.62, -0.29]. The reduction in FPG for patients treated with sitagliptin, metformin, and insulin was -3.0 mmol/L compared to -2.4 mmol/L for patients treated with placebo, metformin, and insulin, a difference of -0.7 mmol/L [95% CI: -1.0, -0.3] The incidence of symptomatic hypoglycaemia was 24.9% for patients treated with sitagliptin, metformin, and insulin and 37.8% for patients treated with placebo, metformin and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.2 vs. 19.8 %). There was no difference in the incidence of severe hypoglycaemia.

Factorial study with ertugliflozin (STEGLATRO) and sitagliptin (JANUVIA) as add-on combination therapy with metformin
A total of 1,233 patients with type 2 diabetes participated in a randomised, double-blind, multi-centre, 26-week, active-controlled study to evaluate the efficacy and safety of STEGLATRO 5 mg or 15 mg in combination with JANUVIA 100 mg compared to the individual components. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (≥1,500 mg/day) were randomised to one of five active-treatment arms: STEGLATRO 5 mg or 15 mg, JANUVIA 100 mg, or JANUVIA 100 mg in combination with 5 mg or 15 mg STEGLATRO administered once daily in addition to continuation of background metformin therapy.

At Week 26, STEGLATRO 5 mg or 15 mg used in combination with JANUVIA 100 mg provided statistically significant improvement in HbA_{1c} and FPG compared to the individual components (see Table 9). More patients receiving STEGLATRO 5 mg or 15 mg in combination with JANUVIA 100 mg achieved an HbA_{1c} <7% compared to the individual components. Treatment with STEGLATRO 5 mg or 15 mg in combination with JANUVIA 100 mg also resulted in a statistically significant reduction in body weight and systolic blood pressure compared to JANUVIA 100 mg.

Table 9 Results at Week 26 from a Factorial Study with STEGLATRO and JANUVIA as Add-on Combination Therapy with Metformin Compared to Individual Components Alone*

	STEGLATRO 5 mg	STEGLATRO 15 mg	JANUVIA 100 mg	STEGLATRO 5 mg + JANUVIA 100 mg	STEGLATRO 15 mg + JANUVIA 100 mg
HbA_{1c} (%)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	8.57	8.57	8.50	8.56	8.56
Change from baseline (LS mean†)	-1.02	-1.08	-1.05	-1.49	-1.52
Difference from JANUVIA STEGLATRO 5 mg STEGLATRO 15 mg (LS mean†, 95% CI)				-0.43‡ (-0.60, -0.27) -0.46‡ (-0.63, -0.30)	-0.47‡ (-0.63, -0.30) -0.44‡ (-0.61, -0.27)
Patients [N (%)] with HbA_{1c} <7%	66 (26.4)	79 (31.9)	81 (32.8)	127§ (52.3)	120§ (49.2)
FPG (mmol/L)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	10.22	9.96	9.85	10.20	9.83
Change from baseline (LS mean†)	-1.98	-2.05	-1.42	-2.44	-2.70
Difference from JANUVIA STEGLATRO 5 mg STEGLATRO 15 mg (LS mean†, 95% CI)				-1.02‡ (-1.33, -0.71) - 0.46¶ (-0.77, -0.15)	-1.28‡ (-1.60, -0.97) -0.65‡ (-0.96, -0.35)
Body Weight (kg)	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	88.6	88.0	89.8	89.5	87.5
Change from baseline (LS mean†)	-2.7	-3.7	-0.7	-2.5	-2.9
Difference from JANUVIA (LS mean†, 95% CI)				-1.8‡ (-2.5, -1.2)	-2.3‡ (-2.9, -1.6)
Systolic Blood Pressure	**N = 250**	**N = 248**	**N = 247**	**N = 243**	**N = 244**
Baseline (mean)	129.7	128.9	128.3	130.2	129.1
Change from baseline (LS mean†)	-3.9	-3.7	-0.7	-3.4	-3.7
Difference from JANUVIA (LS mean†, 95% CI)				-2.8¶ (-4.7, -0.8)	-3.0¶ (-4.9, -1.1)
Efficacy in patients with high baseline HbA_{1c} (≥10%)					
HbA_{1c} (%)	**N = 25**	**N = 21**	**N = 26**	**N = 20**	**N = 22**
Baseline (mean)	10.66	10.51	10.46	10.46	10.39
Change from baseline (LS mean#)	-2.10	-1.30	-1.82	-2.35	-2.66
Difference from JANUVIA STEGLATRO 5 mg STEGLATRO 15 mg (LS mean#, 95% CI)				-0.53 (-1.08, -0.03) -0.24 (-0.80, -0.32)	-0.84 (-1.38, -0.30) -1.36 (-1.91, -0.81)

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, baseline eGFR and the interaction of time by treatment.
‡ p<0.001 compared to control group.
§ p<0.001 compared to corresponding dose of ertugliflozin or sitagliptin (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).
¶ p≤0.005 compared to control group.
# Obtained from a repeated measures ANCOVA model adjusted for baseline eGFR, baseline HbA_{1c}, treatment, subgroup, treatment-by-subgroup, and treatment-by-time-by-subgroup interactions.

Ertugliflozin (STEGLATRO) as add-on combination therapy with metformin and sitagliptin (JANUVIA)
A total of 463 patients with type 2 diabetes inadequately controlled on metformin (≥ 1,500 mg/day) and JANUVIA 100 mg once daily participated in a randomised, double-blind, multi-centre, 26-week, placebo-controlled study to evaluate the efficacy and safety of STEGLATRO. Patients were randomised to STEGLATRO 5 mg, STEGLATRO 15 mg, or placebo administered once daily in addition to continuation of background metformin and JANUVIA therapy.

At Week 26, treatment with STEGLATRO at 5 mg or 15 mg daily provided statistically significant improvements in HbA_{1c}, FPG, body weight, and systolic blood pressure compared to placebo. STEGLATRO also resulted in a greater proportion of patients achieving an HbA_{1c} <7% compared to placebo (see Table 10).

Table 10 Results at Week 26 from an Add-on Study of STEGLATRO in Combination with Metformin and JANUVIA*

	STEGLATRO 5 mg	STEGLATRO 15 mg	Placebo
HbA_{1c} (%)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	8.05	8.00	8.03
Change from baseline (LS mean†)	-0.78	-0.86	-0.09
Difference from placebo (LS mean†, 95% CI)	-0.69‡ (-0.87, -0.50)	-0.76‡ (-0.95, -0.58)	
Patients [N (%)] with HbA_{1c} <7%	50 (32.1)‡	61 (39.9)‡	26 (17.0)
FPG (mmol/L)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	9.31	9.53	9.41
Change from baseline (LS mean†)	-1.49	-1.83	-0.10
Difference from placebo (LS mean†, 95% CI)	-1.40‡ (-1.82, -0.97)	-1.74‡ (-2.16, -1.31)	
Body Weight (kg)	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	87.6	86.6	86.5
Change from baseline (LS mean†)	-3.3	-3.0	-1.3
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-2.6, -1.4)	-1.7‡ (-2.3, -1.1)	
Systolic Blood Pressure	**N = 156**	**N = 153**	**N = 153**
Baseline (mean)	132.1	131.6	130.2
Change from baseline (LS mean†)	-3.8	-4.8	-0.9
Difference from placebo (LS mean†, 95% CI)	-2.9§ (-5.4, -0.5)	-3.9§ (-6.4, -1.5)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, prior antihyperglycaemic medication.
‡ $p \leq 0.001$ compared to placebo.
§ $p < 0.05$ compared to placebo.

TECOS Cardiovascular Safety Study
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a randomized study in 14,671 patients in the intention-to-treat population with an HbA_{1c} of ≥ 6.5 to 8.0% with established CV disease who received JANUVIA (7,332) 100 mg daily (or 50 mg daily if the baseline estimated glomerular filtration rate (eGFR) was ≥ 30 and < 50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA_{1c} and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m^2 were not to be enrolled in the study.

The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

Over the course of the study, the overall estimated mean (SD) difference in HbA_{1c} between the sitagliptin and placebo groups was 0.29% (0.01), 95% CI (-0.32, -0.27); p< 0.001.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, JANUVIA, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without JANUVIA in patients with type 2 diabetes (see Table 11).

Table 11 Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	JANUVIA 100 mg		Placebo		Hazard Ratio (95% CI)	p-value†
	N (%)	Incidence Rate per 100 Patient-Years*	N (%)	Incidence Rate per 100 Patient-Years*		
Analysis in the Intention-to-Treat Population						
Number of Patients	7,332		7,339			
Primary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2	0.98 (0.89–1.08)	< 0.001
Secondary Composite Endpoint (Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	< 0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalisation for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalisation for heart failure‡	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

* Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥ 1 event during eligible exposure period per total patient-years of follow-up).
† Based on a Cox model stratified by region.
- For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3.
- For all other endpoints, the p-values correspond to a test of differences in hazard rates.

‡ The analysis of hospitalisation for heart failure was adjusted for a history of heart failure at baseline.

Sitagliptin Add-on Therapy in Paediatric Patients Inadequately Controlled on Metformin with or without Insulin

JANUMET and JANUMET XR are not indicated for use in paediatric patients.

The safety and efficacy of the addition of sitagliptin in 220 paediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycaemic control on metformin with or without insulin was assessed in two randomised, double-blind, placebo-controlled, parallel-group

studies over 54 weeks. The addition of sitagliptin (administered as JANUMET or JANUMET XR) was compared to the addition of placebo to metformin or metformin XR.

Results from the individual studies were inconsistent. In a pre-specified pooled analysis of these 2 studies, the treatment difference (JANUMET/JANUMET XR vs. metformin) for LS mean change from baseline in HbA1c at Week 20 was -0.49% (95% CI: -0.90, -0.09) (Treatment Effect estimand) and -0.33% (95% CI: -0.70, 0.05) (Treatment Policy estimand). Efficacy for JANUMET/JANUMET XR over metformin was not observed at Week 54. These results do not support use of JANUMET or JANUMET XR in paediatric subjects (10 to 17 years old) with type 2 diabetes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Metformin hydrochloride
The prospective randomised (UKPDS 34) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034.
- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017.
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021).
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01).

5.2 PHARMACOKINETIC PROPERTIES

JANUMET
The results of a definitive bioequivalence study in healthy subjects demonstrated that the JANUMET (sitagliptin phosphate monohydrate/metformin hydrochloride) 50 mg/500 mg and 50 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of sitagliptin phosphate monohydrate (JANUVIA®) and metformin hydrochloride as individual tablets.

Because bioequivalence is demonstrated at the lowest and highest combination tablet dose strengths available, bioequivalence is conferred to the (sitagliptin/metformin) 50 mg/850 mg fixed dose combination (FDC) tablet.

JANUMET XR
The results of a study in healthy subjects demonstrated that the JANUMET XR (sitagliptin phosphate monohydrate/metformin hydrochloride modified release) 50 mg/500 mg and 100 mg/1000 mg tablets and coadministration of corresponding doses of sitagliptin (JANUVIA) and metformin hydrochloride extended release (DIABEX XR®[3]) as individual tablets are bioequivalent.

[3] DIABEX in Australia is a registered trademark of Merck Sante.

Bioequivalence between two JANUMET XR 50 mg/500 mg tablets and one JANUMET XR 100 mg/1000 mg tablet was also demonstrated.

In a crossover study in healthy subjects, the total extent of exposure (AUC) and rate of absorption (C_{max}) for sitagliptin and AUC for metformin after administration of a single JANUMET XR 50 mg/500 mg tablet probe formulation and administration of a single JANUMET 50 mg/500 mg tablet were similar. After administration of a single JANUMET XR 50 mg/500 mg tablet probe formulation, the mean C_{max} value for metformin was 30% lower and the median T_{max} value occurred 4 hours later compared with corresponding values after administration of a single JANUMET 50 mg/500 mg tablet, which is consistent with the expected modified-release characteristics for metformin associated with the JANUMET XR formulation.

After administration of two JANUMET XR 50 mg/1000 mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady-state for sitagliptin and metformin was reached by Day 4 and 5, respectively. The median T_{max} values for sitagliptin and metformin at steady state were approximately 3 and 8 hours postdose, respectively. The median T_{max} values for sitagliptin and metformin after administration of a single tablet of JANUMET were 3 and 3.5 hours postdose, respectively.

Absorption

JANUMET
After administration of JANUMET tablets with a high-fat breakfast, the AUC, C_{max} and T_{max} for sitagliptin were not altered relative to the fasted state. After administration of JANUMET tablets with a high-fat breakfast, the AUC and C_{max} for metformin were decreased by 6% and 28%, respectively, and the T_{max} occurred approximately 1.5 hours later relative to the fasted state.

JANUMET XR
After administration of JANUMET XR tablets with a high-fat breakfast, the AUC for sitagliptin was not altered. The mean C_{max} was decreased by 17%, although the median T_{max} was unchanged relative to the fasted state. After administration of JANUMET XR with a high-fat breakfast, the AUC for metformin increased 62%, the C_{max} for metformin decreased by 9%, and the median T_{max} for metformin occurred 2 hours later relative to the fasted state.

Sitagliptin phosphate monohydrate
The absolute bioavailability of sitagliptin is approximately 87%. Coadministration of a high-fat meal had no effect on the pharmacokinetics of sitagliptin.

Metformin hydrochloride
The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 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, 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 with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin phosphate monohydrate
The mean volume of distribution at steady state following a single 100 mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

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

Metabolism

Sitagliptin phosphate monohydrate
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

Metformin hydrochloride
Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Excretion

Sitagliptin phosphate monohydrate
Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in faeces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Metformin hydrochloride
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug 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.

Characteristics in Patients

Type 2 Diabetes

Sitagliptin phosphate monohydrate

The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

Metformin hydrochloride

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Impairment

Sitagliptin phosphate monohydrate

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to < 45 mL/min/1.73 m^2, and an approximately 4-fold increase was observed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) including patients with end-stage renal disease (ESRD) on haemodialysis, as compared to subjects with normal renal function.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatic Impairment

Sitagliptin phosphate monohydrate

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin. These differences are not considered to be clinically meaningful.

There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Metformin hydrochloride

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

Gender

Sitagliptin phosphate monohydrate

Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analysed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycaemic effect of metformin was comparable in males and females.

Elderly
Sitagliptin phosphate monohydrate
Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Metformin hydrochloride
Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin 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 pharmacokinetics with aging is primarily accounted for by a change in renal function (see GLUCOPHAGE[4] US prescribing information: CLINICAL PHARMACOLOGY, Special Populations, Geriatrics).

Paediatric
The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to historical data from adult patients with type 2 diabetes for a 100 mg dose.

No studies with sitagliptin have been performed in paediatric patients < 10 years of age.

Race
Sitagliptin phosphate monohydrate
Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Metformin hydrochloride
No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycaemic effect was comparable in whites (n=249), blacks (n= 51), and Hispanics (n=24).

Body Mass Index (BMI)
Sitagliptin phosphate monohydrate
Body mass index (BMI) had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with the combined components of JANUMET or JANUMET XR.

Sitagliptin phosphate monohydrate
Sitagliptin was not mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity assay, a chromosome aberration assay in Chinese hamster ovary cells, an in vitro rat hepatocyte DNA alkaline elution assay (an assay

[4] **GLUCOPHAGE®** in the US is a registered trademark of Merck Sante S.A.S, an associate of Merck KGaA of Darmstadt, Germany. Licensed to Bristol-Meyers Squibb Company.

which measures the compound's ability to induce single strand breaks in DNA), and an *in vivo* mouse micronucleus assay.

Metformin hydrochloride
There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of JANUMET or JANUMET XR.

Sitagliptin phosphate monohydrate
A two-year carcinogenicity study was conducted in rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of preneoplastic lesions (altered hepatic foci) in both sexes at 150 and at 500 mg/kg/day, and hepatic adenomas and carcinomas in males and hepatic carcinomas in females at 500 mg/kg/day.

Systemic exposure in rats at 500 mg/kg/day is approximately 58 times that of humans at the recommended daily adult dose of 100 mg. This dose level was associated with hepatotoxicity in rats. The no-observed effect level for induction of hepatic neoplasia was 150 mg/kg/day, approximately 19-fold the human exposure at the 100 mg recommended dose. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. The clinical significance of these findings for humans is unknown.

In a two-year carcinogenicity study conducted in mice, sitagliptin did not increase tumour incidence at oral doses up to 500 mg/kg/day (approximately 68 times human exposure at the clinical dose of 100 mg/day).

Metformin hydrochloride
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumourigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

JANUMET
Tablet Core:
The film coated tablet contains the following inactive ingredients:
microcrystalline cellulose
povidone
sodium lauryl sulfate
sodium stearylfumarate

Film coating:
The film coating contains the following inactive ingredients:
polyvinyl alcohol
macrogol 3350
purified talc
titanium dioxide
iron oxide red
iron oxide black

JANUMET XR
Tablet Core:
All doses of JANUMET XR contain the following inactive ingredients:
povidone
colloidal anhydrous silica
hypromellose
sodium stearylfumarate
propyl gallate
macrogol 3350
kaolin

The JANUMET XR 50 mg/500 mg tablet contains the additional inactive ingredient:
microcrystalline cellulose

Film coating:
The film coating contains the following inactive ingredients:
hypromellose
hyprolose
titanium dioxide
indigo carmine
carnauba wax

The JANUMET XR 50 mg/1000 mg tablet contains the additional inactive Ingredient:
iron oxide yellow

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of these medicines.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

JANUMET is available in the following presentations:

JANUMET 50 mg/500 mg - in PVC/PE/PVDC/Aluminium blister packs of 14 (Starter Pack) and 56 tablets.

JANUMET 50 mg/850 mg - in PVC/PE/PVDC/Aluminium blister packs of 14 (Starter Pack) and 56 tablets.

JANUMET 50 mg/1000 mg - in PVC/PE/PVDC/Aluminium blister packs of 14 (Starter Pack) and 56 tablets.

JANUMET XR is available in the following presentations:

JANUMET XR 50 mg/500 mg[5] - in HDPE bottles of 14 (Starter Pack) and 56 tablets.

JANUMET XR 50 mg/1000 mg - in HDPE bottles of 14 (Starter Pack) and 56 tablets.

JANUMET XR 100 mg/1000 mg - in HDPE bottles of 7 (Starter Pack) and 28 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

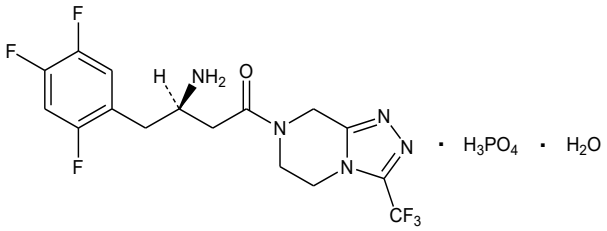
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

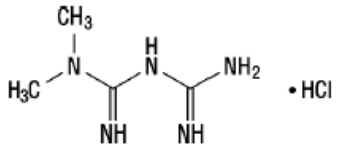
Chemical structure

Sitagliptin phosphate monohydrate
The chemical name of sitagliptin phosphate monohydrate is 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate.

The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Metformin hydrochloride
Metformin hydrochloride (*N*,*N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycaemic agents. The structural formula is as shown:



CAS number

Sitagliptin phosphate monohydrate
The CAS Registry Number is 654671-77-9.

[5] *Presentation not currently marketed in Australia.

Metformin hydrochloride
The CAS Registry Number is 1115-70-4.

Description

Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

The pH of a saturated water solution of sitagliptin phosphate monohydrate is 4.4. The partition coefficient is 1.8 and the pKa is 7.7.

Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1 Building A, 26 Talavera Road,
Macquarie Park NSW 2113
Australia
http://www.msd-australia.com.au/

9 DATE OF FIRST APPROVAL

20 April 2009

10 DATE OF REVISION

28 July 2026

Summary table of changes

Section changed	Summary of new information
4.4	Added warning for patients with mitochondrial diseases such as MELAS and MIDD, and hypothyroidism
4.5	Added Metformin and Levothyroxine drug-drug interaction
4.8	Added adverse effect for patients with hypothyroidism in the postmarketing experience section

RCN: 000028979-AU

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