SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

RISTABEN™ 25 Tablets

RISTABEN™ 50 Tablets

RISTABEN™ 100 Tablets

COMPOSITION

Each film-coated RISTABEN Tablet contains 32,13, 64,25 or 128,5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50 or 100 mg, respectively, of free base.

RISTABEN Tablets are sugar free.

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate and sodium stearyl fumarate.

In addition, the film-coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol (macrogol), talc, titanium dioxide, red iron oxide and yellow iron oxide.

PHARMACOLOGICAL CLASSIFICATION

A.21.2 Oral Hypoglycaemics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Incretin hormones physiologically regulate blood glucose levels by increasing insulin response from pancreatic beta cells and suppressing glucagon secretion from pancreatic alpha cells, when blood glucose levels are normal or elevated. These effects are not observed when blood glucose levels are low.

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 post-dose was 8,0 msec. This 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.

Pharmacokinetic properties

The pharmacokinetics of sitagliptin have been characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptin was absorbed with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8,52 micromolar hours, C_{max} was 950 nanomolar and apparent terminal half-life ($t_{1/2}$) was 12,4 hours. Plasma AUC of sitagliptin increased approximately 14 % following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5,8 % and 15,1 %). The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of sitagliptin is approximately 87 %. Co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics (see **DOSAGE AND DIRECTIONS FOR USE**).

Distribution

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 %).

Metabolism

Sitagliptin is primarily eliminated unchanged in urine (79 %) and metabolism is a minor pathway. Following a radioactively-labelled ^{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.

Elimination

Following administration of an oral radioactively-labelled ^{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 half-life ($t_{1/2}$) 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, ciclosporin a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Characteristics in Patients

Renal insufficiency: A single-dose, open-label study was conducted to evaluate the pharmacokinetics of sitagliptin (50 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to < 80 ml/min), moderate (30 to < 50 ml/min) and severe (< 30 ml/min), as well as patients with end-stage renal disease on haemodialysis. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:

$$CrCl = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \{\times 1,2\}}{[\text{serum creatinine (micromol/l)}]}$$

For female patients: 0,85 x value calculated for males

Compared to normal healthy control subjects, an approximate 1,6-fold increase in plasma AUC of sitagliptin was observed in patients with mild renal insufficiency. An approximately 2,3-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency, an approximately 3,8-fold increase was observed in patients with severe renal insufficiency and an approximately 4,5-fold increase was observed in patients with end-stage renal disease on haemodialysis, as compared to normal healthy control subjects. Sitagliptin was not meaningfully removed by haemodialysis (13,5 % over a 3- to 4-hour haemodialysis session

starting 4 hours post-dose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in end-stage renal disease patients requiring haemodialysis (see **DOSAGE AND DIRECTIONS FOR USE, Patients with renal insufficiency)**.

Hepatic insufficiency: In patients with moderate hepatic insufficiency (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 insufficiency (Child-Pugh score > 9) (see **CONTRAINDICATIONS**).

Elderly: 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.

Paediatric: No studies with sitagliptin have been performed in paediatric patients.

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

INDICATIONS

Monotherapy

RISTABEN is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Combination therapy

RISTABEN is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin, pioglitazone, a sulphonyl urea or combinations thereof or insulin when diet and exercise, plus the other therapies do not provide adequate glycaemic control.

CONTRAINDICATIONS

RISTABEN is contraindicated in:

- patients who are hypersensitive to any components of RISTABEN
- a history of hypersensitivity reactions, such as anaphylaxis and angioedema to RISTABEN or other gliptins (DPP-4)
- Type 1 diabetes mellitus
- Diabetes mellitus associated with ketoacidosis.

RISTABEN has not been studied in patients with severe hepatic insufficiency (see **PHARMACOLOGICAL ACTION, Pharmacokinetic properties, Hepatic insufficiency**).

WARNINGS AND SPECIAL PRECAUTIONS

Hypoglycaemia in combination with a sulphonylurea or with insulin

In clinical trials of RISTABEN as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia [i.e. metformin or a PPARγ agonist (thiazolidinedione)], rates of hypoglycaemia reported with RISTABEN were similar to rates in patients taking placebo. When RISTABEN was used in combination with a sulphonylurea or with insulin, the incidence of hypoglycaemia was increased over that of placebo (see **SIDE EFFECTS**). Therefore, to reduce the risk of sulphonylurea- or insulin-induced hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered (see **DOSAGE AND DIRECTIONS FOR USE**).

Renal insufficiency: A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with end-stage renal disease requiring haemodialysis or peritoneal dialysis (see **DOSAGE AND DIRECTIONS FOR USE, Patients with renal insufficiency**).

Pancreatitis: In post-marketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see **SIDE EFFECTS, Post-marketing experience**), in patients taking RISTABEN. Patients should be informed of the characteristic symptom of acute pancreatitis such as persistent, abdominal pain. Resolution of pancreatitis has been observed after discontinuation of RISTABEN. If pancreatitis is suspected, RISTABEN should be discontinued immediately.

Hypersensitivity Reactions: There have been post-marketing reports of serious hypersensitivity reactions in patients treated with RISTABEN. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions usually occurred within the first 3 months after initiation of treatment with RISTABEN, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue RISTABEN immediately and institute an alternative class of medicines for treatment for diabetes (see CONTRAINDICATIONS and SIDE EFFECTS, Post-marketing experience).

There have been post-marketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors such as RISTABEN. The time to onset of symptoms following initiation of RISTABEN therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of RISTABEN. A subset of patients experienced a recurrence of symptoms when restarting RISTABEN or a different DPP-4 inhibitor. Consider RISTABEN as a possible cause for severe joint pain and discontinue RISTABEN if appropriate.

Effects on ability to drive and use machinery

No studies of the effects of RISTABEN on the ability to drive and use machines have been performed.

INTERACTIONS

In interaction studies, RISTABEN did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin and

oral contraceptives. Based on these data, RISTABEN does not inhibit CYP isoenzymes CYP3A4, 2C8 or 2C9. Based on *in vitro* data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4. There is limited information on multiple dose co-administration of these agents.

There was an increase in the area under the curve (AUC, 11 %) and mean peak medicine concentration (C_{max} 18 %) of digoxin with the co-administration of sitagliptin. Patients receiving digoxin should be monitored appropriately.

The AUC and C_{max} of RISTABEN were increased approximately 29 % and 68 % respectively, in subjects with co-administration of a single 100 mg oral dose of RISTABEN and a single 600 mg oral dose of ciclosporin, a potent probe inhibitor of p-glycoprotein. The observed changes in RISTABEN pharmacokinetics are not considered likely to be clinically meaningful. No dosage adjustment for RISTABEN is recommended when co-administered with ciclosporin or other p-glycoprotein inhibitors (e.g. ketoconazole).

PREGNANCY AND LACTATION

Pregnancy

There are no studies in pregnant women; therefore, RISTABEN is not recommended for use in pregnancy.

Lactation

RISTABEN is secreted in the milk of lactating rats. It is not known whether RISTABEN is secreted in human milk. Therefore, RISTABEN should not be used by women who are breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE

RISTABEN can be taken with or without food.

The recommended dose of RISTABEN is 100 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, insulin (with or without metformin), a PPARγ agonist, metformin plus a sulphonylurea or metformin plus a PPARγ agonist.

When RISTABEN is used in combination with a sulphonylurea or with insulin, a lower dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see **WARNINGS AND SPECIAL PRECAUTIONS, Hypoglycaemia in combination with a sulphonylurea or with insulin)**.

If a dose of RISTABEN is missed, it should be taken as soon as the patient remembers. A double dose of RISTABEN should not be taken on the same day.

Patients with renal insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥ 50 ml/min, approximately corresponding to serum creatinine levels of ≤ 150 µmol/litre in men and ≤ 133 µmol/litre in women), no dosage adjustment for RISTABEN is required.

For patients with moderate renal insufficiency (CrCl ≥ 30 to < 50 ml/min, approximately corresponding to serum creatinine levels of > 150 µmol/litre to ≤ 265 µmol/litre in men and > 133 µmol/l to not ≤ 221 µmol/litre in women), the dose of RISTABEN is 50 mg once daily. This dose should be decreased if CrCl decreases to < 30ml/min.

For patients with severe renal insufficiency (CrCl < 30 ml/min, approximately corresponding to serum creatinine levels of > 265 µmol/litre in men and > 221 µmol/litre in women) or with end-stage renal disease requiring haemodialysis or peritoneal dialysis, the dose of RISTABEN is 25 mg once daily. RISTABEN may be administered without regard to the timing of dialysis.

Patients with hepatic insufficiency

No dosage adjustment is necessary for patients with mild to moderate hepatic insufficiency. RISTABEN has not been studied in patients with severe hepatic insufficiency.

Elderly

No dosage adjustment is necessary for elderly patients.

Paediatric population

There are no data available on the use of RISTABEN in patients younger than 18 years of age. Therefore, use of RISTABEN in paediatric patients is not recommended.

SIDE EFFECTS

Adverse reactions considered as medicine related reported in patients treated with sitagliptin occurring in excess (> 0,2 % and difference > 1 patient) of that in patients treated with placebo are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100); Rare (≥ 1/10 000, < 1/1 000); and Very rare (< 1/10 000).

Sitagliptin monotherapy

Infections and infestations

Common: upper respiratory tract infection, nasopharyngitis

Metabolism and nutrition disorders

Common: hypoglycaemia

Nervous system disorders

Common: headache

Uncommon: dizziness

Gastrointestinal disorders

Uncommon: constipation

Musculoskeletal and connective tissue disorders

Common: osteoarthritis, pain in extremity.

Sitagliptin with metformin

Metabolism and nutrition disorders

Common: hypoglycaemia

Nervous system disorders

Uncommon: somnolence

Gastrointestinal disorders

Common: nausea, flatulence, vomiting

Uncommon: diarrhoea, constipation, upper abdominal pain

Investigations

Uncommon: blood glucose.

Sitagliptin with sulphonylurea

Metabolism and nutrition disorders

Common: hypoglycaemia.

Sitagliptin with a sulphonylurea and metformin

Metabolism and nutrition disorders

Common: hypoglycaemia

Respiratory, thoracic and mediastinal disorders

Uncommon: rhinorrhoea

Gastrointestinal disorders

Uncommon: nausea.

Sitagliptin with a PPARγ agonist (pioglitazone)

Metabolism and nutrition disorders

Common: hypoglycaemia

Gastrointestinal disorders

Common: flatulence

General disorders and administration site conditions

Common: peripheral oedema

Investigations

Common: blood glucose.

Sitagliptin with a PPARγ agonist (pioglitazone) and metformin

Metabolism and nutrition disorders

Common: hypoglycaemia

General disorders and administration site conditions

Common: peripheral oedema

Sitagliptin with insulin (+/-) metformin

Infections and infestations

Common: influenza

Metabolism and nutrition disorders

Common: hypoglycaemia

Nervous system disorders

Common: headache

Gastrointestinal disorders

Uncommon: dry mouth, constipation.

In addition, in monotherapy studies of up to 24 weeks in duration of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions considered as medicine related reported in

patients treated with sitagliptin in excess (> 0,2 % and difference > 1 patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation and dizziness.

In addition to the medicine-related adverse experiences described above, adverse experiences reported regardless of causal relationship to medication and occurring in at least 5 % and more commonly in patients treated with RISTABEN included upper respiratory tract infection and nasopharyngitis. Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with RISTABEN (not reaching the 5 % level but occurring with an incidence of > 0,5 % higher with RISTABEN than that in the control group) included osteoarthritis and pain in extremity.

Post-marketing experience

During post-marketing experience the following additional side effects have been reported: hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliative skin conditions including Stevens-Johnson syndrome (see **WARNINGS AND SPECIAL PRECAUTIONS**); acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see **WARNINGS AND SPECIAL PRECAUTIONS, Pancreatitis**); worsening renal function, including acute renal failure (sometimes requiring dialysis); vomiting, headache, constipation, nasopharyngitis, upper respiratory tract infection, arthralgia, myalgia, pain in extremity, back pain.

Laboratory investigation

Across clinical studies, a small mean increase in uric acid (approximately 12 µmol/litre difference from placebo; mean baseline 297 to 327 µmol/litre) was found in patients treated with RISTABEN 100 or 200 mg daily. No increase in the incidence of gout was reported. A small mean decrease in total alkaline phosphatase (up to approximately 5 I.U./l difference from placebo; mean baseline approximately 56 to 62 I.U./l) was also observed, partly related to a small decrease in bone alkaline phosphatase. A small increase in white blood cell count (approximately 200 cells/µlitre) difference in WBC versus placebo; mean baseline WBC approximately 6600 cells/µlitre) was observed due to an increase in neutrophils. This observation was seen in most but not all studies. These changes in laboratory parameters are not considered to be clinically relevant.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

RISTABEN is not dialysable. In clinical studies, only about 13,5 % of the dose was removed over a 3 to 4 hour haemodialysis session. It is not known if RISTABEN is dialysable by peritoneal dialysis.

IDENTIFICATION

RISTABEN 25: A pink, round, biconvex film-coated tablet with 221 on one side and plain on the other.

RISTABEN 50: A light beige, round, biconvex film-coated tablet with 112 on one side and plain on the other.

RISTABEN 100: A beige, round, biconvex film-coated tablet with 277 on one side and plain on the other.

PRESENTATION

RISTABEN 25, 50 and100 is packaged in opaque PVDC/PE/PVC push-through blisters (referred to as PVDC blister) with push-through aluminium lidding. Packs contain 10, 14, 28 or 30 tablets with blisters of 10 or 14 tablets. The blisters are opened by pushing the tablets through the foil. 1 or 3 tablets of 10's or 2 blisters of 14 tablets are placed in a carton, with a package insert, to make packs of 10's, 28's or 30's tablets respectively.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from moisture.

Keep out of reach of children.

The blister should be kept in the carton until required for use.

REGISTRATION NUMBERS

RISTABEN 25: 48/21.2/1349

RISTABEN 50: 48/21.2/1350

RISTABEN 100: 42/21.2/1351

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

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