AUSTRALIAN PRODUCT INFORMATION – XELEVIA® (sitagliptin phosphate monohydrate)

1 NAME OF THE MEDICINE

sitagliptin phosphate monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

XELEVIA is available for oral use as film coated tablets containing sitagliptin phosphate monohydrate equivalent to 25, 50 or 100 mg of free base.

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

3 PHARMACEUTICAL FORM

XELEVIA 25 mg - a pink, round, film coated tablet with ”221” on one side and plain on the other.

XELEVIA 50 mg - a light beige, round, film coated tablet with ”112” on one side and plain on the other.

XELEVIA 100 mg - a beige, round, film coated tablet with ”277” on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

XELEVIA (sitagliptin phosphate monohydrate) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as:

- monotherapy when metformin is considered inappropriate due to intolerance; or
- in combination with other anti-hyperglycaemic agents, including insulin

[see 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials, 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for available data on different add-on combination therapies].

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose of XELEVIA is 100 mg once daily as monotherapy, or as combination therapy with metformin, or a sulfonylurea (clinical experience is with glimepiride as dual therapy), insulin (with or without metformin), a thiazolidinedione (clinical experience is with pioglitazone as dual therapy), or combination therapy with metformin and a sulfonylurea (clinical experience is with addition of sitagliptin to glimepiride or gliclazide and metformin as triple therapy). XELEVIA can be taken with or without food.

When XELEVIA is used in combination with a sulfonylurea or with insulin, reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of sulfonylurea- or insulin-induced hypoglycaemia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Hypoglycaemia in Combination with a Sulfonylurea or with Insulin*).

Patients with Renal Impairment
Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of XELEVIA and periodically thereafter.

For patients with eGFR ≥ 45 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2, no dosage adjustment for XELEVIA is required.

For patients with eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2, the dose of XELEVIA is 50 mg once daily.

For patients with eGFR ≥ 15 mL/min/1.73 m^2 to < 30 mL/min/1.73 m^2 or with ESRD (eGFR < 15 mL/min/1.73 m^2), including those requiring haemodialysis or peritoneal dialysis, the dose of XELEVIA is 25 mg once daily. XELEVIA may be administered without regard to the timing of dialysis.

The use of XELEVIA in combination with insulin has not been studied in patients with moderate or severe renal impairment.

4.3 CONTRAINDICATIONS

XELEVIA is contraindicated in patients who are hypersensitive to any components of this product (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Hypersensitivity Reactions* and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), *Postmarketing Experience*.).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

XELEVIA 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, XELEVIA and other potentially suspect medicinal products should be discontinued.

Use in renal impairment

Because XELEVIA is renally excreted, to achieve plasma concentrations of XELEVIA similar to those in patients with normal renal function, lower dosages are recommended in patients with eGFR< 45 mL/min/1.73 m^2, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, *Patients with Renal Impairment*). Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of XELEVIA and periodically thereafter. The use of XELEVIA in combination with other antihyperglycaemic agents (i.e. metformin, sulfonylureas, thiazolidinediones or insulin) has not been studied in patients with moderate or severe renal impairment.

Hypoglycaemia in Combination with a Sulfonylurea or with Insulin

In clinical trials of XELEVIA as monotherapy and XELEVIA as part of combination therapy with metformin or pioglitazone, rates of hypoglycaemia reported with XELEVIA were similar to rates in patients taking placebo.

As typical with other antihyperglycaemic agents used in combination with sulfonylurea or with insulin, hypoglycaemia has been observed when XELEVIA was 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, reduction in the 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 XELEVIA. 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 XELEVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue XELEVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes (See Section 4.3 CONTRAINDICATIONS and Section 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 XELEVIA. If bullous pemphigoid is suspected, XELEVIA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Use in the elderly

In clinical studies, the safety and effectiveness of XELEVIA in the elderly (≥ 65 years) were comparable to those seen in younger patients (< 65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal impairment; as with other patients, dosage adjustment may be required in the presence of significant renal impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, *Patients with Renal impairment*).

Paediatric use

Safety and effectiveness of XELEVIA in paediatric patients under 18 years have not been established.

XELEVIA should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

XELEVIA has not been studied in paediatric patients under 10 years of age.

Effects on laboratory tests

The incidence of laboratory adverse experiences was similar in patients treated with XELEVIA 100 mg compared to patients treated with placebo. Across clinical 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 an 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

***In vitro* Assessment of Drug Interactions**

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6 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**

Effects 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.

Metformin: Coadministration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport.

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 XELEVIA 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.

Effects 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.

Metformin: Coadministration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

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 XELEVIA 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, but not restricted to, cholesterol-lowering agents (including statins, fibrates, ezetimibe), anti-platelet agents (including clopidogrel), antihypertensives (including ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (including naproxen, diclofenac, celecoxib), anti-depressants (including bupropion, fluoxetine, sertraline), antihistamines (including cetirizine), proton-pump inhibitors (including omeprazole, lansoprazole), and medications for erectile dysfunction (including sildenafil).

Use with other antidiabetic agents

The safety and efficacy of sitagliptin in combination with GLP-1 mimetics, or alpha-glucosidase inhibitors has not been established.

Other Drugs

Sitagliptin has not been studied in combination with orlistat.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No adverse effects on fertility were observed in male and female rats given sitagliptin orally at doses up to 1000 mg/kg/day (approximately 100 times the AUC in humans at the clinical dose of 100 mg/day) prior to and throughout mating.

Use in Pregnancy (Category B3)

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 AUC in humans at the clinical dose of 100 mg/day). A slight increase in the incidence of foetal rib abnormalities (absent, hypoplastic and wavy ribs) was observed among foetuses of rats given sitagliptin at 1000 mg/kg/day (approximately 100 times the AUC in humans at 100 mg/day). Pups of rats administered sitagliptin at 1000 mg/kg/day from gestation day 6 to lactation day 20 showed reduced birth weight and postnatal body weight gain (observed prior to and after weaning). No functional or behavioural toxicity was observed in the offspring of treated rats.

Sitagliptin crosses the placenta in rats and rabbits.

There are no adequate and well-controlled studies with XELEVIA in pregnant women. XELEVIA, like other oral antihyperglycaemic agents, is not recommended for use in pregnancy.

Use in Lactation

Treatment of rats with sitagliptin during pregnancy and lactation caused decreased pup body weight gain (see Use in Pregnancy). Sitagliptin is excreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk. Therefore, XELEVIA 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 XELEVIA on the ability to drive and use machines have been performed. However, XELEVIA is not expected to affect the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

In controlled clinical studies as both monotherapy and combination therapy with metformin or pioglitazone, the overall incidence of adverse reactions, hypoglycaemia, and discontinuation of therapy due to clinical adverse reactions with XELEVIA were similar to placebo (discontinuation rates: XELEVIA monotherapy, 24-week study, 2.1% vs placebo 1.6%, 18-week study 2% vs placebo 2.7%; XELEVIA add-on to metformin 2.4% vs placebo and metformin 3%; XELEVIA add-on to pioglitazone 5.7% vs placebo and pioglitazone 1.1%).

In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with XELEVIA was higher than with placebo, in part related to a higher incidence of hypoglycaemia (see Table 1); the incidence of discontinuation due to clinical adverse reactions was similar to placebo (discontinuation rates: XELEVIA add-on to glimepiride, with or without metformin, 2.3% vs placebo and glimepiride, with or without metformin, 1.4%; XELEVIA add-on to metformin and a sulfonylurea, at 54 weeks, 1.4% vs placebo/pioglitazone, metformin and a sulfonylurea 3.8%). In combination with stable-dose insulin, with or without metformin, the overall incidence of clinical adverse reactions with XELEVIA was higher than placebo, in part related to a higher incidence of hypoglycaemia

(see Table 1); the incidence of discontinuation due to clinical adverse reactions was slightly higher than placebo (discontinuation rates: XELEVIA add-on to insulin, with or without metformin, 3.4% vs placebo and insulin, with or without metformin, 1.3%).

Monotherapy and Add-On Combination Therapy

Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with XELEVIA 100 mg daily, XELEVIA 200 mg daily, and placebo. Five 24-week, placebo-controlled add-on combination therapy studies, one with metformin, one with pioglitazone, one with glimepiride with or without metformin, one with metformin and a sulfonylurea (glimepiride or gliclazide) and one with stable-dose insulin with or without metformin were also conducted. In addition to a stable dose of metformin, pioglitazone, glimepiride, glimepiride and metformin, gliclazide and metformin, insulin, or insulin and metformin, patients whose diabetes was not adequately controlled were given either XELEVIA 100 mg daily or placebo. The adverse reactions, reported regardless of investigator assessment of causality in ≥ 5% of patients treated with XELEVIA 100 mg daily as monotherapy, XELEVIA in combination with pioglitazone, XELEVIA in combination with glimepiride, with or without metformin, or XELEVIA in combination with metformin and a sulfonylurea, or XELEVIA in combination with insulin, with or without metformin, and more commonly than in patients treated with placebo, are shown in Table 1.

Table 1 Placebo-Controlled Clinical Studies of XELEVIA Monotherapy* or Add-on Combination Therapy with Pioglitazone or Glimepiride +/- Metformin or Metformin + Sulfonylurea or Insulin +/- Metformin: Adverse Reactions Reported in ≥ 5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

Body System/Adverse Reactions	**Number of Patients (%)**	
	XELEVIA 100 mg	**Placebo**
	N = 443	N = 363
Infections and Infestations		
Nasopharyngitis	23 (5.2)	12 (3.3)
	XELEVIA 100 mg + Pioglitazone	**Placebo + Pioglitazone**
	N = 175	N = 178
Infections and Infestations		
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Nervous System Disorders		
Headache	9 (5.1)	7 (3.9)
	XELEVIA 100 mg + Glimepiride (+/- Metformin)	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Metabolism and Nutrition disorders		
Hypoglycaemia	27 (12.2)	4 (1.8)
Infections and Infestations		
Nasopharyngitis	14 (6.3)	10 (4.6)
Nervous System Disorders		
Headache	13 (5.9)	5 (2.3)
	XELEVIA 100 mg + Metformin + Sulfonylurea	**Placebo + Metformin + Sulfonylurea**
	N = 210	N = 212
Metabolism and Nutrition Disorders		
Hypoglycaemia	31 (14.8)‡	10 (4.7)‡
	XELEVIA 100 mg + Insulin (+/- Metformin)	**Placebo + Insulin (+/- Metformin)**
	N = 322	N = 319
Metabolism and Nutrition disorders		
Hypoglycaemia	50 (15.5)	25 (7.8)

† Intent to treat population
* Overall, the safety profile of the 200 mg daily dose was similar to that of the 100 mg daily dose.
‡ Weeks 0-24.

In the study of patients receiving XELEVIA as monotherapy compared to metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥ 5% of patients and more commonly than in patients given placebo. In another 24-week study of patients receiving XELEVIA as add-on therapy while undergoing insulin intensification (with or without metformin), there were no drug-related adverse reactions reported that occurred with an incidence of ≥ 1% in patients treated with XELEVIA 100 mg and more

commonly than in patients treated with placebo.

The adverse reactions, reported regardless of investigator assessment of causality in ≥ 5% of patients treated with XELEVIA 100 mg daily or patients treated with metformin as monotherapy are shown in Table 2.

Table 2 Initial Therapy with Sitagliptin or Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Mono Therapy all patients "as treated"

Number of patients (%)		
	Sitagliptin	**Metformin**
	N = 528	**N = 522**
Diarrhoea	**19 (3.6)**	**57 (10.9)**

When XELEVIA was added to metformin and a sulfonylurea, over the 54-week study duration hypoglycaemia was reported in 38 (18.1%) patients treated with XELEVIA + 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 XELEVIA + 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 XELEVIA in these studies and at least 2 fold more commonly than in patients treated with placebo are listed below:

XELEVIA monotherapy (24-week study)
Gastrointestinal Disorders: Constipation
Infections and Infestations: Pharyngitis
Vascular Disorders: Hypertension

XELEVIA monotherapy (18-week study)
Musculoskeletal and Connective Tissue Disorders**:** Back Pain, Osteoarthritis, Pain in Extremity

XELEVIA with metformin
Musculoskeletal and Connective Tissue Disorders**:** Arthralgia

XELEVIA with pioglitazone
Psychiatric Disorders: Depression

XELEVIA with glimepiride (with or without metformin)
Gastrointestinal Disorders: Abdominal Pain Upper, Constipation, Dyspepsia
Infections and Infestations: Bronchitis, Gastroenteritis, Influenza
Musculoskeletal and Connective Tissue Disorders: Back Pain, Pain in Extremity

XELEVIA with metformin and a sulfonylurea (with or without metformin)
Infections and Infestations: Influenza, Nasopharyngitis
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity

XELEVIA with insulin (with or without metformin)
Nervous system disorders: Headache

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

XELEVIA monotherapy versus metformin (24-week study)
Vascular Disorders: Hypertension

Initial Combination Therapy
In an additional, 24-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 3.

Table 3 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 (XELEVIA) 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 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.

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 XELEVIA in this study and at least 2 fold more commonly than in patients treated with placebo/active comparator are listed below:

Initial therapy with XELEVIA
Gastrointestinal Disorders: Abdominal Pain Upper, Constipation
Infections and Infestations: Gastroenteritis
Musculoskeletal and Connective Tissue Disorders: Arthralgia

Sitagliptin in Combination with Ertugliflozin
The safety of sitagliptin used in combination with the SGLT2 inhibitor ertugliflozin has been evaluated in 990 patients with type 2 diabetes mellitus treated for 26 weeks in three studies. The incidence and type of adverse reactions in these three studies were consistent with that observed in studies with the individual components, sitagliptin and ertugliflozin.

Pooled Analysis
In the pre specified pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse experiences of hypoglycaemia in patients treated with XELEVIA 100 mg was similar to placebo (1.2% vs. 0.9%). Adverse experiences of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidence of selected gastrointestinal adverse reactions in patients treated with XELEVIA or placebo was as follows: abdominal pain (XELEVIA, 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), vomiting (0.8%, 0.9%), and diarrhoea (3.0%, 2.3%).

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with XELEVIA.

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.)

TECOS Cardiovascular Safety Study
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with XELEVIA, 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 XELEVIA 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 XELEVIA-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 XELEVIA-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in XELEVIA-treated patients and 0.2% in placebo-treated patients.

Postmarketing Experience

Additional adverse reactions have been identified during postmarketing use of XELEVIA as monotherapy 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*).

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 13 11 26 (Australia).

During controlled clinical trials in healthy subjects, single doses of up to 800 mg XELEVIA 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 XELEVIA (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 XELEVIA with doses of up to 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Sitagliptin is a member of a class of oral anti-hyperglycaemic 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 physiological 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. 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 secretion is markedly enhanced as glucose rises above normal concentrations. 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 where insulin is released even when glucose levels are low, which 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*.

Clinical trials

Results from long-term studies of XELEVIA on overall morbidity and mortality outcomes are not available.

There were 4911 patients with type 2 diabetes randomised in eight double-blind, placebo-controlled Phase III clinical studies conducted to evaluate the effects of sitagliptin on glycaemic control as monotherapy and in combination with metformin, pioglitazone, glimepiride, glimepiride+metformin and insulin (with or without metformin). Co-morbid diseases were common in the patients studied in a pooled analysis of five of these studies: 58% of patients had hypertension, 54% had dyslipidaemia, and more than 50% were obese (BMI $\geq$ 30 kg/m^2). The majority of patients (51.6% to 65.8%) met National Cholesterol Education Program (NCEP) criteria for metabolic syndrome. In these studies, the mean age of patients was 55.0 years, and 62% of patients were white, 18% were Hispanic, 6% were black, 9% were Asian, and 4% were of other racial groups. The studies that support registration in general used the reduction in haemoglobin A1c (HbA_{1c}) as the primary outcome variable. Pre-specified secondary endpoints included FPG and 2-hour PPG.

An additional double-blind, placebo-controlled clinical study was conducted in 91 patients with type 2 diabetes and moderate to severe renal impairment.

An active (glipizide)-controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycaemic control on metformin. In patients with type 2 diabetes, treatment with XELEVIA produced statistically significant improvements in haemoglobin A_{1c} (HbA_{1c}). Clinically significant improvements in HbA_{1c} were maintained for 52 weeks. Treatment with XELEVIA showed suggestions of improvement in measures of beta cell function (see Section 5.1 PHARMACODYNAMIC PROPERTICS, Mechanism of action).

Clinical Studies Monotherapy

A total of 1262 patients with type 2 diabetes participated in two double-blind, placebo-controlled studies, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of XELEVIA monotherapy. Patients with inadequate glycaemic control (HbA_{1c} 7%

to 10%) were randomized to receive a 100 mg (443 patients) or 200 mg dose (456 patients) of XELEVIA or placebo (363 patients) once daily. XELEVIA as monotherapy is indicated for use when metformin cannot be used (see Section 4.1 THERAPEUTIC INDICATIONS).

Treatment with XELEVIA at 100 mg daily provided significant improvements in HbA_{1c}, FPG, and 2-hour PPG compared to placebo (see Table 4 and Table 5). These studies included patients with a wide range of baseline HbA_{1c}. The improvement in HbA1c compared to placebo was not affected by gender, age, race, prior antihyperglycaemic therapy, baseline BMI, presence of metabolic syndrome, or a standard index of insulin resistance (HOMA-IR). Patients with a shorter length of time since diagnosis of diabetes (< 3 years) or with higher baseline HbA_{1c} had greater reductions in HbA_{1c}. In the 18- and 24-week studies, among patients who were not on an antihyperglycaemic agent at study entry, the reduction from baseline in HbA_{1c} was -0.67% (95% CI -0.87, -0.48) and -0.85% (95% CI -1.02, -0.68), respectively, for those given XELEVIA and -0.10% (95% CI -0.39, 0.19) and -0.18% (95% CI -0.35, -0.02), respectively, for those given placebo. In both studies, XELEVIA provided a significant reduction compared with placebo in FPG (-1.07 mmol/L in the 18-week study and -0.88 mmol/L in the 24-week study) at 3 weeks, the first time point at which FPG was measured. Overall, the 200 mg daily dose did not provide greater glycaemic efficacy than the 100 mg daily dose. The effect of XELEVIA on lipid endpoints was similar to placebo. Body weight did not increase from baseline with XELEVIA therapy in either study, compared to a small reduction in patients given placebo. The observed incidence of hypoglycaemia in patients treated with XELEVIA was similar to placebo.

Table 4 HbA_{1c} Results in 18- and 24-Week Placebo-Controlled Studies of XELEVIA in Patients with Type 2 Diabetes†, including Stratification by Baseline HbA_{1c} Category

	18-Week Study		24-Week Study	
	XELEVIA 100 mg	**Placebo**	**XELEVIA 100 mg**	**Placebo**
HbA_{1c} (%)	N = 193	N = 103	N = 229	N = 244
Baseline (mean)	8.04	8.05	8.01	8.03
Change from Baseline (adjusted mean‡ (95% CI))	-0.48 (-0.61, -0.35)	0.12 (-0.05, 0.30)	-0.61 (-0.74, -0.49)	0.18 (0.06, 0.30)
Difference from Placebo (adjusted mean‡ (95% CI))	-0.60§ (-0.82, -0.39)		-0.79§ (-0.96, -0.62)	
Patients (%) achieving HbA_{1c} < 7%	69 (35.8)	16 (15.5)	93 (40.6)	41 (16.8)
Baseline HbA_{1c} Category				
HbA_{1c} (%) ≥ 9% at Baseline	N = 27	N = 20	N = 37	N = 35
Baseline (mean)	9.48	9.48	9.59	9.46
Change from Baseline (adjusted mean‡)	-0.83	0.37	-1.27	0.25
Difference from Placebo (adjusted mean‡)	-1.20		-1.52	
HbA_{1c} (%) ≥ 8% to < 9% at Baseline	N = 70	N = 25	N = 62	N = 82
Baseline (mean)	8.40	8.38	8.36	8.41
Change from Baseline (adjusted mean‡)	-0.42	0.19	-0.64	0.16
Difference from Placebo (adjusted mean‡)	-0.61		-0.80	
HbA_{1c} (%) < 8% at Baseline	N = 96	N = 58	N = 130	N = 127
Baseline (mean)	7.37	7.41	7.39	7.39
Change from Baseline (adjusted mean‡)	-0.42	0.02	-0.40	0.17
Difference from Placebo (adjusted mean‡)	-0.44		-0.57	

† 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.

Table 5 Additional Glycaemic Parameters in 18- and 24-Week Placebo-Controlled Studies of XELEVIA in Patients with Type 2 Diabetes†

	18-Week Study		24-Week Study	
	XELEVIA 100 mg	**Placebo**	**XELEVIA 100 mg**	**Placebo**
FPG (mmol/L)	N = 201	N = 107	N = 234	N = 247
Baseline (mean)	9.98	10.19	9.46	9.78
Change from baseline (adjusted mean‡)	-0.70	0.39	-0.69	0.26
Difference from Placebo (adjusted mean‡)	-1.09§		-0.95§	
2-hour PPG (mmol/L)	%	%	N = 201	N = 204
Baseline (mean)			14.28	15.03
Change from baseline (adjusted mean‡)			-2.71	-0.12
Difference from Placebo (adjusted mean‡)			-2.59§	

† 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.
% Data not available.
¶ All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
# Not statistically significant (p≥0.05) compared to placebo.
†† p<0.01 compared to placebo.

These two studies were extended to examine the efficacy and safety of sitagliptin monotherapy long-term. In the 24 week study, patients receiving placebo were redistributed (1:1) between the 2 sitagliptin doses (100 mg q.d. or 200 mg q.d.) for an 80-week single-blind (blind to dose) treatment period. Patients in the sitagliptin treatment groups in Phase A continued on the same dose of sitagliptin during the single-blind treatment period (Phase B).

In the 18 week study, patients receiving placebo were started on therapy with pioglitazone at a dose of 30 mg q.d. for a 36-week active-controlled double-blind treatment period. Patients in a sitagliptin treatment group continued on the same dose of sitagliptin during the active-controlled, double-blind treatment period. Patients in the placebo/pioglitazone arm showed a -0.87% reduction in HbA_{1c} at Week 54, compared to -0.28% and -0.19% for the sitagliptin 100 mg and 200 mg groups, respectively.

Treatment with sitagliptin 100 mg q.d. and 200 mg q.d. provided similar reductions in glycaemic parameters over the duration of each study.

Active-Controlled Study with Metformin
The efficacy of XELEVIA compared to that of metformin was evaluated in a 24-week, double-blind, metformin-controlled trial in patients with type 2 diabetes and inadequate glycaemic control on diet and exercise and who were not on antihyperglycaemic therapy (patients who were treated with oral antihyperglycaemic therapy at enrolment discontinued all antihyperglycaemic therapy for at least 4 months before beginning study therapy). In this study, patients were randomized to receive either XELEVIA 100 mg daily (N=528) or metformin (N=522) for 24 weeks. Patients receiving metformin were given an initial dosage of 500 mg/day and then titrated by the investigator to a dose of 1500 to 2000 mg/day over a period of up to 5 weeks based on tolerability.

The mean dose of metformin after the titration period was approximately 1900 mg/day. Glycaemic endpoints measured included HbA_{1c} and fasting glucose.

Both treatments resulted in a statistically significant improvement in glycaemic control from baseline. The mean baseline HbA_{1c} was 7.2% in the per protocol population. At 24 weeks, the least squares means adjusted reduction from baseline in HbA_{1c} were -0.43% (95%CI -0.48, -0.38) for XELEVIA 100 mg daily and -0.57% (95%CI -0.62, -0.51) for metformin group, with a difference of 0.14% (95% CI 0.06, 0.21). The difference met the pre-specified criterion for confirming comparable efficacy of the two agents. In a pre-defined subgroup analysis, patients with baseline HbA_{1c} ≥ 8% also had similar reductions in both groups (XELEVIA, -1.13%; metformin, -1.24%).

The reduction in FPG was -0.64 mmol/L for XELEVIA and -1.08 mmol/L for metformin. Standard indices of insulin resistance (HOMA-IR) and insulin secretion (HOMA-β) showed similar improvements in both groups. Slightly smaller proportions of patients in the XELEVIA group relative to the metformin group had an HbA_{1c} value < 6.5% (33.6% vs. 39.2%) and < 7.0% (68.8% vs. 75.9%) at Week 24. Slight increases were also observed in the XELEVIA group relative to the metformin group for LDL-C, non-HDL-C and total-C. Both the XELEVIA and metformin treatment groups exhibited a decrease in fasting insulin, fasting proinsulin and the proinsulin to insulin ratio, with a greater reduction observed for the metformin group in fasting proinsulin, which resulted in a larger reduction in the proinsulin to insulin ratio. A smaller increase in 1,5-anhydroglucitol at Week 24 was observed in the XELEVIA group compared to the metformin group.

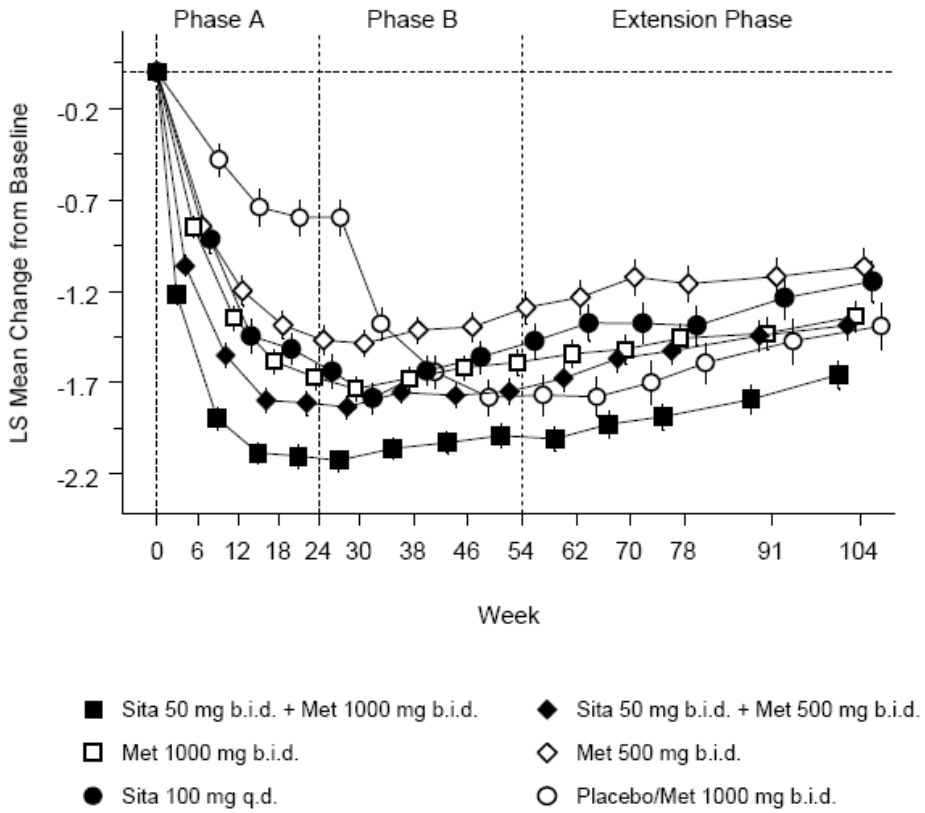
The overall incidence of gastrointestinal adverse reactions in patients treated with XELEVIA was 11.6% compared with 20.7% in patients treated with metformin. The incidence of selected gastrointestinal adverse experiences was: diarrhoea (XELEVIA, 3.6%; metformin, 10.9%), nausea (1.1%, 3.1%), abdominal pain (2.1%, 3.8%), and vomiting (0.4%, 1.3%). The incidence of hypoglycaemia was not significantly different between the treatment groups (XELEVIA, 1.7%; metformin, 3.4%). Body weight decreased from baseline in both treatment groups (XELEVIA, -0.6 kg; metformin -1.9 kg).

XELEVIA 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, randomized, 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 randomized 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 randomized. 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 randomized 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 provides sustained improvements in HbA_{1c} and FPG and 2-hour PPG compared with either corresponding monotherapy dose over 104 weeks; (see Table 6 and Figure 1). 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, -1.11%.

Figure 1 LS Mean Change from Baseline for HbA_{1c} over Time (LS Mean ± SE) by Treatment Group – All-Patients-Treated in the Extension Phase*



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

Table 6 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)
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)[%]	**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.
% 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.

Add-on Therapy to Metformin
A total of 701 patients with type 2 diabetes with inadequate glycaemic control on metformin alone participated in a 24-week, randomised, double-blind, placebo-controlled study designed to assess the efficacy of XELEVIA in combination with metformin (HbA_{1c} 7% to 10%). All patients were started on metformin monotherapy and the dose increased to at least 1500 mg per day. Patients were randomised to the addition of either 100 mg of XELEVIA or placebo, administered once daily.

In combination with metformin, XELEVIA provided significant improvements in HbA_{1c} (the primary endpoint), FPG, and 2-hour PPG compared to placebo with metformin (see Table 7). A pre-specified secondary endpoint was the number of patients in each group who required therapeutic "rescue" with pioglitazone. Twenty-one of 464 patients (5%) randomised to XELEVIA and 32 of 237 patients (14%) randomised to placebo required pioglitazone "rescue".

The improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c}, prior anti-hyperglycaemic 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 XELEVIA demonstrated slight decreases in total cholesterol, non-HDL cholesterol and triglycerides. A similar decrease in body weight was observed in both treatment groups.

Table 7 Glycaemic Parameters and Body Weight at Final Visit (24-Week Study for XELEVIA in Combination with Metformin† - Primary (HbA_{1c}) and Secondary Outcomes

	XELEVIA 100 mg + 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 patients given glycaemic rescue therapy.
¶ Not statistically significant (p≥0.05) compared to placebo + metformin.

Active- Controlled Study Against Glipizide as Add-on Therapy to Metformin
Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes. Patients with inadequate glycaemic control on metformin at ≥ 1500 mg/day were randomized to treatment with XELEVIA 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 over the next 18 weeks, to a maximum dosage of 20 mg/day as needed 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. The objective of the study was to test whether sitagliptin was not inferior to glipizide, at a non-inferiority margin of 0.3%. After 52 weeks, both treatments resulted in a statistically significant improvement in glycaemic control from baseline. The reduction from baseline in HbA_{1c} (primary endpoint) was 0.67% for XELEVIA 100 mg daily and 0.67% for glipizide, confirming the noninferiority of XELEVIA compared to glipizide.

With respect to other analyses, the reduction in FPG was 0.56 mmol/L for XELEVIA 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} (XELEVIA, -1.68%; glipizide, -1.76%). The incidence of hypoglycaemia in the XELEVIA group (4.9%) was significantly lower than that in the glipizide group (32.0%). Patients treated with XELEVIA 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).

Add-on Therapy to Pioglitazone
A total of 353 patients with type 2 diabetes inadequately controlled on pioglitazone alone participated in a 24-week, randomised, double-blind, placebo-controlled study designed to assess the efficacy of XELEVIA in combination with pioglitazone. All patients were started on pioglitazone monotherapy at a dose of 30-45 mg per day. Patients were randomised to the addition of either 100 mg of XELEVIA or placebo, administered once daily. Glycaemic endpoints measured included HbA_{1c} and fasting glucose. Another pre-specified secondary endpoint was the number of patients in each group who required therapeutic “rescue” with metformin.

In combination with pioglitazone, XELEVIA provided significant improvements in HbA_{1c} and FPG compared to placebo with pioglitazone (see Table 8). The improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c}, prior anti-hyperglycaemic therapy, 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). Compared to patients taking placebo, patients taking XELEVIA demonstrated a slight decrease in triglycerides. There was no significant difference between XELEVIA and placebo in body weight change. Twelve of 175 patients (7%) randomised to XELEVIA and 25 of 178 patients (14%) randomised to placebo required metformin “rescue”.

Table 8 Glycaemic Parameters and Body Weight at Final Visit (24-Week Study) for XELEVIA in Combination with Pioglitazone† - Primary (HbA_{1c}) and Secondary Outcomes

	XELEVIA 100 mg + Pioglitazone	Placebo + Pioglitazone
HbA_{1c} (%)	**N = 163**	**N = 174**
Baseline (mean)	8.05	8.00
Change from baseline (adjusted mean‡)	-0.85	-0.15
Difference from placebo + pioglitazone (adjusted mean‡)	-0.70§	
Patients (%) achieving HbA1c < 7%	74 (45.4)	40 (23.0)
FPG (mmol/L)	**N = 163**	**N = 174**
Baseline (mean)	9.34	9.19
Change from baseline (adjusted mean‡)	-0.93	0.06
Difference from placebo + pioglitazone (adjusted mean‡)	-0.98§	
Body Weight (kg)%	**N = 133**	**N = 136**
Baseline (mean)	90.0	85.6
Change from baseline (adjusted mean‡)	1.8	1.5
Difference from placebo + pioglitazone (adjusted mean‡)	0.2¶	

† 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 + pioglitazone.
% All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
¶ Not statistically significant (p≥0.05) compared to placebo + pioglitazone.

Add-on Therapy to 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 XELEVIA 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 XELEVIA 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, XELEVIA provided significant improvements in HbA_{1c} compared to placebo with metformin and a sulfonylurea (see Table 9) 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 XELEVIA and placebo in body weight change. Three of 210 patients (1%) randomised to XELEVIA and 15 of 212 patients (7%) randomised to placebo required pioglitazone “rescue”. After 54 weeks, treatment with XELEVIA, metformin and a sulfonylurea continued to provide clinically meaningful improvement in HbA_{1c} relative to baseline.

Table 9 Glycaemic Parameters and Body Weight at End of Phase A (24 Weeks) for XELEVIA in Combination with Metformin and a Sulfonylurea† - Primary (HbA_{1c}) and Secondary Outcomes

	XELEVIA 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)%	**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.
% All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.
¶ Not statistically significant ($p\geq0.05$) compared to placebo + metformin + sulfonylurea.

Add-on Combination Therapy with Insulin (with or without Metformin)

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 XELEVIA as add-on combination therapy with stable dose of insulin (with or without metformin). Patients on pre-mixed, long-acting, or intermediate-acting insulin with or without metformin (≥ 1500 mg per day) were randomized to the addition of either 100 mg of XELEVIA or placebo, administered once daily. 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}, fasting glucose, and 2-hour post-prandial glucose.

In combination with insulin (with or without metformin), XELEVIA provided significant improvements in HbA_{1c}, FPG, and 2 hour PPG compared to placebo (see Table 10). 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, and standard indices of insulin resistance (HOMA-IR) and insulin secretion (HOMA-β). There was no significant difference between XELEVIA and placebo in body weight change.

Table 10 Glycaemic Parameters and Body Weight at Final Visit (24 Week Study) for XELEVIA as Add-on Combination Therapy with a Stable Dose of Insulin (with or without Metformin)†

	XELEVIA 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
HbA_{1c} (%)	**N = 305**	**N = 312**
Baseline (mean)	8.72	8.64
Change from baseline (adjusted mean‡; 95%CI)	-0.59 (-0.70, -0.48)	-0.03 (-0.14, 0.08)
Difference from placebo (adjusted mean‡, §; 95% CI)	-0.56% (-0.70, -0.42)	
Patients (%) achieving HbA_{1c} < 7%	39 (12.8)	16 (5.1)
FPG (mmol/L)	**N = 310**	**N = 313**
Baseline (mean)	9.7	9.8
Change from baseline (adjusted mean‡; 95% CI)	-1.0 (-1.4, -0.7)	-0.2 (-0.6, 0.2)
Difference from placebo (adjusted mean‡; 95% CI)	-0.8% (-1.3, -0,4)	
2-hour PPG (mmol/L)	**N = 240**	**N = 257**
Baseline (mean)	16.0	16.1
Change from baseline (adjusted mean‡; 95% CI)	-1.7 (-2.2, -1.2)	0.3 (-0.2, 0.8)
Difference from placebo (adjusted mean‡; 95% CI)	-2.0% (-2.6, -1.4)	
Body Weight (kg)¶	**N = 266**	**N = 266**
Baseline (mean)	86.6	87.4
Change from baseline (adjusted mean‡; 95% CI)	0.1 (-0.2, 0.4)	0.1 (-0.3, 0.4)
Difference from placebo (adjusted mean‡; 95% CI)	0.0# (-0.4, 0.5)	

† 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 stratum interaction was not significant (p>0.10) for metformin stratum and for insulin stratum.
% 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.

A 24-week placebo-controlled study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Baseline HbA_{1c} was 8.74 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values.

At Week 24, the mean increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin, and 24 IU/day in patients treated with placebo. The mean reduction in HbA_{1c} in patients treated with sitagliptin and insulin (with or without metformin) was -1.31 % compared to -0.87 % in patients treated with placebo and insulin (with or without metformin), a difference of -0.45 % [95 % CI: -0.60, -0.29]. The mean reduction in FPG in patients treated with sitagliptin and insulin (with or without metformin) was -3.1 mmol/L compared to -2.5 mmol/L in patients treated with placebo and insulin (with or without metformin), a difference of -0.6 mmol/L [95 % CI: -1.0, -0.2]. The incidence of symptomatic hypoglycaemia was 25.2% in patients treated with sitagliptin and insulin (with or without metformin) and 36.8 % in patients treated with placebo and insulin (with or without metformin). The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs. 19.2 %). There was no difference in the incidence of severe hypoglycaemia.

Factorial study with ertugliflozin (STEGLATRO) and XELEVIA 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 XELEVIA 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, XELEVIA 100 mg, or XELEVIA 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 XELEVIA 100 mg provided statistically significant improvement in HbA_{1c} and FPG compared to the individual components (see Table 11). More patients receiving STEGLATRO 5 mg or 15 mg in combination with XELEVIA 100 mg achieved an HbA_{1c} <7% compared to the individual components. Treatment with STEGLATRO 5 mg or 15 mg in combination with XELEVIA 100 mg also resulted in a statistically significant reduction in body weight and systolic blood pressure compared to XELEVIA 100 mg.

Table 11 Results at Week 26 from a Factorial Study with STEGLATRO and XELEVIA as Add-on Combination Therapy with Metformin Compared to Individual Components Alone*

	STEGLATRO 5 mg	STEGLATRO 15 mg	XELEVIA 100 mg	STEGLATRO 5 mg + XELEVIA 100 mg	STEGLATRO 15 mg + XELEVIA 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 XELEVIA 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 XELEVIA 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 XELEVIA (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 XELEVIA (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 XELEVIA 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 XELEVIA

A total of 463 patients with type 2 diabetes inadequately controlled on metformin (≥1,500 mg/day) and XELEVIA 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 XELEVIA 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 HbA1c <7% compared to placebo (see Table 12).

Table 12 Results at Week 26 from an Add-on Study of STEGLATRO in Combination with Metformin and XELEVIA *

	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<0.001 compared to placebo.
§ p<0.05 compared to placebo.

Initial combination therapy of ertugliflozin (STEGLATRO) and XELEVIA
A total of 291 patients with type 2 diabetes inadequately controlled on diet and exercise participated in a randomised, double-blind, multi-centre, placebo-controlled 26-week study to evaluate the efficacy and safety of STEGLATRO in combination with XELEVIA. These patients, who were not receiving any background antihyperglycaemic treatment, were randomised to STEGLATRO 5 mg or STEGLATRO 15 mg in combination with XELEVIA (100 mg) or to placebo once daily.

At Week 26, treatment with STEGLATRO 5 mg and 15 mg in combination with XELEVIA at 100 mg daily provided significant improvements in HbA_{1c}, FPG, body weight, 2-hour PPG, and systolic blood pressure compared to placebo. STEGLATRO 5 mg and 15 mg in combination with XELEVIA at 100 mg daily also resulted in a significantly higher proportion of patients achieving an HbA_{1c} <7% compared with placebo (see Table 13).

Table 13 Results at Week 26 from an Initial combination Therapy Study of STEGLATRO and XELEVIA *

	STEGLATRO 5 mg + XELEVIA 100 mg	**STEGLATRO 15 mg + XELEVIA 100 mg**	**Placebo**
HbA_{1c} (%)	**N = 98**	**N = 96**	**N = 96**
Baseline (mean)	8.90	8.98	8.95
Change from baseline (LS mean†)	-1.60	-1.68	-0.44
Difference from placebo (LS mean†, 95% CI)	-1.16‡ (-1.49, -0.84)	-1.24‡ (-1.57, -0.91)	
Patients [N (%)] with HbA_{1c} <7%	35 (35.7)§	30 (31.3)§	8 (8.3)
FPG (mmol/L)	**N = 98**	**N = 96**	**N = 96**
Baseline (mean)	10.99	10.42	11.52
Change from baseline (LS mean†)	-2.68	-3.07	-0.52
Difference from placebo (LS mean†, 95% CI)	-2.16‡ (-2.77, -1.55)	-2.56‡ (-3.17, -1.94)	
2-hour PPG (mmol/L)	**N = 97**	**N = 95**	**N = 91**
Baseline (mean)	15.61	15.63	15.95
Change from baseline (LS mean†)	-4.60	-5.00	-1.13
Difference from placebo (LS mean†, 95% CI)	-3.46‡ (-4.47, -2.46)	-3.87‡ (-4.87, -2.86)	
Body Weight (kg)	**N = 98**	**N = 96**	**N = 97**
Baseline (mean)	90.8	91.3	95.0
Change from baseline (LS mean†)	-2.9	-3.0	-0.9
Difference from placebo (LS mean†, 95% CI)	-2.0‡ (-3.0, -1.0)	-2.1‡ (-3.1, -1.1)	
Systolic Blood Pressure (mmHg)	**N = 98**	**N = 96**	**N = 97**
Baseline (mean)	130.7	129.2	127.4
Change from baseline (LS mean†)	-2.0	-4.0	2.4
Difference from placebo (LS mean†, 95% CI)	-4.4¶ (-7.9, -1.0)	-6.4‡ (-9.8, -3.0)	

* N includes all patients who received at least one dose of study medication and had at least one measurement of the outcome variable.
† Least squares means adjusted for treatment, time, antihyperglycaemic medication wash-off status, baseline eGFR, and the interaction of time by treatment.
‡ p<0.001 compared to placebo.
§ p<0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).
¶ p=0.011 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 XELEVIA (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, XELEVIA, 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 XELEVIA in patients with type 2 diabetes (see Table 14).

Table 14 Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	XELEVIA 100 mg		Placebo			
	N (%)	Incidence Rate per 100 Patient-Years*	N (%)	Incidence Rate per 100 Patient-Years*	Hazard Ratio (95% CI)	p-value†
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.

Clinical Studies in Patients with Renal Impairment
A study comparing sitagliptin at 25 or 50 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in patients with moderate to severe renal impairment. In this study, 277 patients with chronic renal impairment were included in the Per-protocol population (135 patients on XELEVIA: moderate [n=98], severe [n=37]; and 142 patients on glipizide: moderate [n=106], severe [n=36]). After 54 weeks, the mean reduction from baseline in HbA_{1c} was -0.76% with sitagliptin and -0.64% with glipizide (Per-Protocol Analysis). In this study, the efficacy and safety profile of sitagliptin at 25 or 50 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia in the sitagliptin group (6.2%) was significantly lower than that in the glipizide group (17.0%), while the incidence of severe hypoglycaemia was not significantly different between the two treatment groups (sitagliptin, 1.4%; glipizide, 2.8%).

Another study comparing sitagliptin at 25 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in 129 patients with ESRD who were on dialysis (64 patients on XELEVIA; and 65 patients on glipizide). After 54 weeks, the mean reduction from baseline in HbA_{1c} was -0.72% with sitagliptin and -0.87% with glipizide. In this study, the efficacy and safety profile of sitagliptin at 25 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 6.3%; glipizide, 10.8%), whereas the incidence of severe hypoglycaemia was significantly lower in the sitagliptin group (0.0%) compared to the glipizide group (7.7%).

A multinational, randomised, double-blind, placebo-controlled study was also conducted to assess the safety and tolerability of XELEVIA in 91 patients with type 2 diabetes and chronic renal impairment (creatinine clearance < 50 mL/min). Patients with moderate renal impairment received 50 mg daily of XELEVIA and those with severe renal impairment or with ESRD on haemodialysis or peritoneal dialysis received 25 mg daily. In this study, the safety and tolerability of XELEVIA were generally similar to placebo. (See Section 5.2 PHARMACOKINETIC PROPERTIES, Characteristics in Patients*, Renal Impairment*).

XELEVIA in Paediatric Patients with Type 2 Diabetes and Inadequate Glycaemic Control
XELEVIA is not indicated for use in paediatric patients.

A 54-week, double-blind study was conducted to evaluate the efficacy and safety of XELEVIA 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti-hyperglycaemic therapy for at least 12 weeks (with HbA_{1c} 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA_{1c} 7% to 10%). Patients were randomised to XELEVIA 100 mg or placebo once daily for 20 weeks.

Mean baseline HbA_{1c} was 7.5%. Treatment with XELEVIA 100 mg did not provide significant improvement in HbA_{1c} at 20 weeks. The reduction in HbA_{1c} in patients treated with XELEVIA (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3). The profile of adverse reactions was comparable to that observed in adults (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

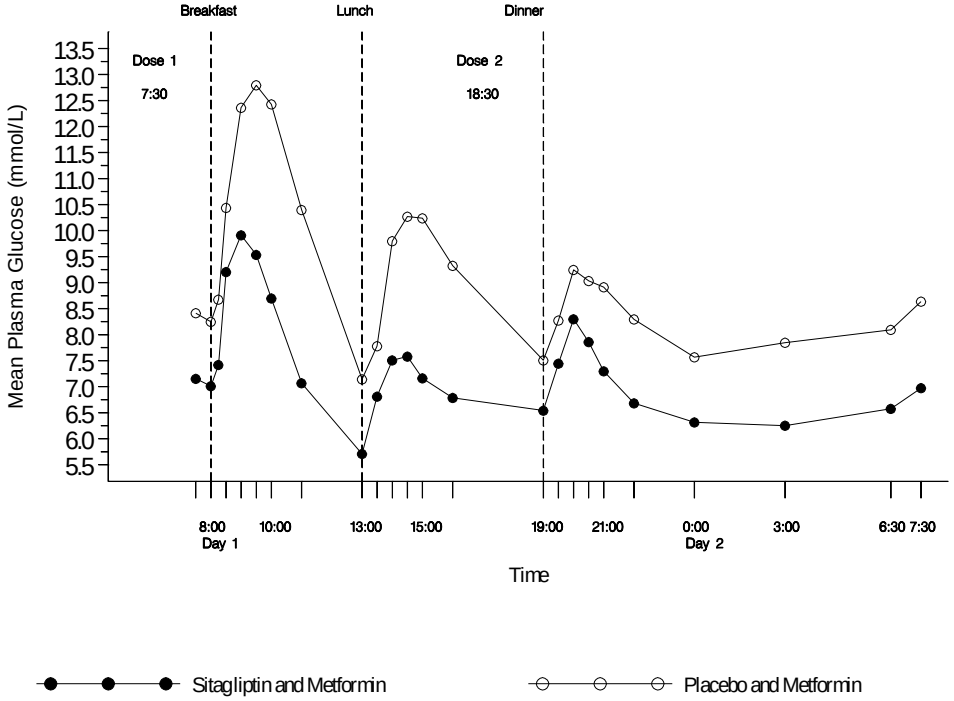
Long Term Efficacy of XELEVIA
Improvements in glycaemic control with sitagliptin have been demonstrated over periods of up to 2 years in both the Phase II studies and Phase III studies. Importantly, the effect size and the durability of these improvements over 104-106 weeks were similar to those observed in the active-comparator groups. The observed reduction in glycaemic efficacy after initial improvement is believed to be a consequence of the natural history of the disease with continued loss of β-cell function, and/or an additional increase in insulin resistance, and/or diminishing compliance with diet and exercise, and is similar to that observed with

other classes of antihyperglycaemic therapies.

General
In patients with type 2 diabetes, administration of single oral doses of XELEVIA 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 a study of patients with type 2 diabetes inadequately controlled on metformin monotherapy, glucose levels monitored throughout the day were significantly lower in patients who received sitagliptin 100 mg per day (50 mg twice daily) in combination with metformin compared with patients who received placebo with metformin (see Figure 2).

Figure 2 24-hour Plasma Glucose Profile after 4-Week Treatment with Sitagliptin 50 mg BID with Metformin or Placebo with Metformin



In Phase III clinical studies of 18- and 24-week duration, treatment with XELEVIA 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. There are no clinical studies that demonstrate that sitagliptin alters the natural history of impaired glucose tolerance or type 2 diabetes mellitus. The durability of efficacy requires further study.

In Phase II studies, XELEVIA 50 mg twice daily provides no additional glycaemic efficacy compared to 100 mg once daily.

In studies with healthy subjects, XELEVIA did not lower blood glucose or cause hypoglycaemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, *Hypoglycaemia in Combination with a Sulfonylurea or with Insulin.* See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) in respect of use with sulfonylureas or insulin).

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 XELEVIA was generally well tolerated. In these patients, XELEVIA had a modest blood pressure lowering effect; 100 mg per day of XELEVIA 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. As per good medical practice, hypertensive patients who receive XELEVIA should continue to have their blood pressure monitored.

Cardiac Electrophysiology
In a randomised, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of XELEVIA 100 mg, XELEVIA 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 small increase was not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11-fold higher than the peak concentrations following a 100 mg dose.

In patients with type 2 diabetes administered XELEVIA 100 mg (N=81) or XELEVIA 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.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of sitagliptin have been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly 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 μM•hr, C_{max} was 950 nM, 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%. Since coadministration of a high-fat meal with XELEVIA had no effect on the pharmacokinetics, XELEVIA may be administered with or without food.

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, 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.

Excretion

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, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Characteristics in Patients

Renal Impairment
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of XELEVIA (50 mg dose) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with end stage renal disease (ESRD) on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2) and patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2), and approximately 4-fold in patients with severe renal impairment (eGFR< 30 mL/min/1.73 m^2), including patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5% over a 3- to 4-hour haemodialysis session starting 4 hours postdose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with eGFR<45 mL/min/1.73 m^2 (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, *Patients with Renal Impairment*).

Hepatic Impairment
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 XELEVIA. These differences are not considered to be clinically meaningful. No dosage adjustment for

XELEVIA is necessary for patients with mild or moderate hepatic impairment.

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.

Elderly Patients
No dosage adjustment is required based on age. 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 Patients
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.

Sex
No dosage adjustment is necessary based on sex of the patient. The sex of the subject 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.

Race
No dosage adjustment is necessary based on race. 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.

Body Mass Index
No dosage adjustment is necessary based on BMI. Body mass index 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.

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

5.3 PRECLINICALSAFETY DATA

Genotoxicity

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

Carcinogenicity

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 focal eosinophilic cellular alterations in the liver in both sexes at 150 mg/kg/day and at 500 mg/kg/day. There was an

increased incidence of basophilic cellular alterations in females at 500 mg/kg/day. Eosinophilic and basophilic cellular alterations are regarded as preneoplastic lesions. There was an increase in hepatic adenomas and carcinomas in males, and hepatic carcinomas in females at 500 mg/kg/day. Systemic exposure in rats at 150 and 500 mg/kg/day are 19 and 58 times, respectively, that of humans at 100 mg/day. The no-observed effect level for induction of hepatic neoplasia in rats was 150 mg/kg/day, producing exposure approximately 19-fold higher than the human exposure at the 100 mg/day clinical dose. The increased incidence of hepatic tumours 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).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet Core:
The tablet contains the following inactive ingredients:
calcium hydrogen phosphate
croscarmellose sodium
magnesium stearate
microcrystalline cellulose
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 yellow

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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 30°C. Store in original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

XELEVIA is available in the following presentations:

XELEVIA 25 mg - in PVC / Aluminium blister packs of 28 tablets.

XELEVIA 50 mg - in PVC / Aluminium blister packs of 28 tablets.

XELEVIA 100 mg - in PVC / Aluminium blister packs 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.

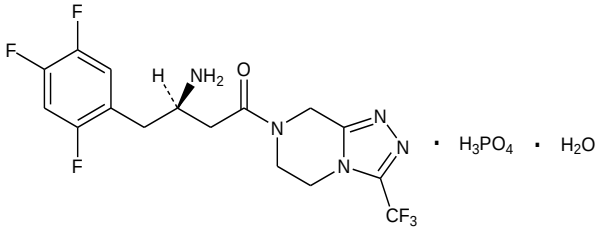
6.7 PHYSICOCHEMICAL PROPERTIES

XELEVIA (sitagliptin phosphate monohydrate) is an orally-active inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferators-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

Chemical structure

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:



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.

CAS number

The CAS Registry Number is 654671-77-9.

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

14 January 2008

10 DATE OF REVISION

22 October 2021

Summary table of changes

Section changed	Summary of new information
4.4	Update paediatric use to include data not supporting the use in patients between 10 and 17 years
5.1	Added paediatric study description and results
5.2	Added paediatric pharmacokinetic data
Throughout	Format HbA_{1C} consistently; minor editorial changes to spelling, grammar and punctuation

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