SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Incresync 25 mg/45 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Incresync 25 mg/45 mg film-coated tablets
Each tablet contains alogliptin benzoate and pioglitazone hydrochloride equivalent to 25 mg alogliptin and 45 mg pioglitazone.

Excipient(s) with known effect
Each tablet contains 105 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Incresync 25 mg/45 mg film-coated tablets
Red, round (approximately 8.7 mm in diameter), biconvex, film-coated tablets with both “A/P” and “25/45” printed in grey ink on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Incresync is indicated as a second or third line treatment in adult patients aged 18 years and older with type 2 diabetes mellitus:

- as an adjunct to diet and exercise to improve glycaemic control in adult patients (particularly overweight patients) inadequately controlled on pioglitazone alone, and for whom metformin is inappropriate due to contraindications or intolerance.

- in combination with metformin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients (particularly overweight patients) inadequately controlled on their maximal tolerated dose of metformin and pioglitazone.

In addition, Incresync can be used to replace separate tablets of alogliptin and pioglitazone in those adult patients aged 18 years and older with type 2 diabetes mellitus already being treated with this combination.

After initiation of therapy with Incresync, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, Incresync should be discontinued. In light of potential risks with prolonged pioglitazone therapy, prescribers should confirm at subsequent routine reviews that the benefit of Incresync is maintained (see section 4.4).

4.2 Posology and method of administration

Posology

For the different dose regimens Incresync is available in strengths of 25 mg/30 mg, 25 mg/45 mg and 12.5 mg/30 mg film-coated tablets.

Adults (≥ 18 years old)
The dose should be individualised on the basis of the patient's current treatment regimen

For patients intolerant to metformin or for whom metformin is contraindicated, inadequately controlled on pioglitazone alone, the recommended dose of Incresync is one tablet of 25 mg/30 mg or 25 mg/45 mg once daily, depending on the dose of pioglitazone already being taken.

For patients inadequately controlled on dual therapy with pioglitazone and a maximally tolerated dose of metformin, the dose of metformin should be maintained, and Incresync administered concomitantly. The recommended dose is one tablet of 25 mg/30 mg or 25 mg/45 mg once daily, depending on the dose of pioglitazone already being taken.

Caution should be exercised when alogliptin is used in combination with metformin and a thiazolidinedione as an increased risk of hypoglycaemia has been observed with this triple therapy (see section 4.4). In case of

hypoglycaemia, a lower dose of the thiazolidinedione or metformin may be considered.

For patients switching from separate tablets of alogliptin and pioglitazone, both alogliptin and pioglitazone should be dosed at the daily dose already being taken.

Maximum daily dose
The maximum recommended daily dose of 25 mg alogliptin and 45 mg pioglitazone should not be exceeded.

Special populations
Elderly (≥ 65 years old)
No dose adjustment is necessary based on age (see section 4.4). However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function in this population.

Renal impairment
For patients with mild renal impairment (creatinine clearance (CrCl) > 50 to ≤ 80 mL/min), no dose adjustment of Incresync is necessary (see section 5.2).

For patients with moderate renal impairment (CrCl ≥ 30 to ≤ 50 mL/min), one-half of the recommended dose of alogliptin should be administered. Therefore, one tablet of 12.5 mg/30 mg once daily is recommended in patients with moderate renal impairment (see section 5.2).

Incresync is not recommended for patients with severe renal impairment (CrCl < 30 mL/min) or end-stage renal disease requiring dialysis.

Appropriate assessment of renal function is recommended prior to initiation of Incresync and periodically thereafter (see section 4.4).

Hepatic impairment
Incresync must not be used in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of Incresync in children and adolescents < 18 years old have not been established. No data are available.

Method of administration

Oral use.

Incresync should be taken once daily with or without food. The tablets should be swallowed whole with water.

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

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl-peptidase-4 (DPP-4) inhibitor (see sections 4.4 and 4.8)
- Cardiac failure or history of cardiac failure (NYHA stages I to IV; see section 4.4)
- Hepatic impairment (see section 4.4)
- Diabetic ketoacidosis
- Current bladder cancer or a history of bladder cancer (see section 4.4)
- Uninvestigated macroscopic haematuria (see section 4.4)

4.4 Special warnings and precautions for use

General

Incresync should not be used in patients with type 1 diabetes mellitus.
Incresync is not a substitute for insulin in insulin-requiring patients.
Fluid retention and cardiac failure

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. When treating patients who have at least one risk factor for development of congestive heart failure (e.g. prior myocardial infarction or symptomatic coronary artery disease or the elderly), physicians should start pioglitazone therapy with the lowest available dose and increase the dose gradually. Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve. There have been post-marketing cases of cardiac failure reported when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure. Patients should be observed for signs and symptoms of heart failure, weight gain and oedema when pioglitazone is used in combination with insulin. Since insulin and pioglitazone are both associated with fluid retention, concomitant administration may increase the risk of oedema. Post marketing cases of peripheral oedema and cardiac failure have also been reported in patients with concomitant use of pioglitazone and nonsteroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors. Incresync should be discontinued if any deterioration in cardiac status occurs.

A cardiovascular outcome study of pioglitazone has been performed in patients under 75 years with type 2 diabetes mellitus and pre-existing major macrovascular disease. Pioglitazone or placebo was added to existing anti-diabetic and cardiovascular therapy for up to 3.5 years. This study showed an increase in reports of heart failure, however this did not lead to an increase in mortality in this study.

Elderly patients

In light of age-related risks (especially bladder cancer, fractures and heart failure associated with the pioglitazone component), the balance of benefits and risks should be considered carefully both before and during Incresync treatment in the elderly.

Bladder cancer

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical studies with pioglitazone (19 cases from 12,506 patients, 0.15%) than in control groups (7 cases from 10,212 patients, 0.07%) HR = 2.64 (95% CI 1.11-6.31, P = 0.029). After excluding patients in whom exposure to the medicinal product was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Epidemiological studies have also suggested a small increased risk of bladder cancer in diabetic patients treated with pioglitazone, although not all studies identified a statistically significant increased risk.

Risk factors for bladder cancer should be assessed before initiating Incresync treatment (risks include age, smoking history, exposure to some occupational or chemotherapy medicinal products e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting therapy.

Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

Monitoring of liver function

There have been rare reports of hepatocellular dysfunction during post-marketing experience with pioglitazone (see section 4.8). Postmarketing reports of hepatic dysfunction including hepatic failure have been received for alogliptin. It is recommended, therefore, that patients treated with Incresync undergo periodic monitoring of liver enzymes. Liver enzymes should be checked prior to the initiation of therapy in all patients. Therapy with Incresync should not be initiated in patients with increased baseline liver enzyme levels (ALT > 2.5 x upper limit of normal) or with any other evidence of liver disease.

Following initiation of therapy with Incresync, it is recommended that liver enzymes be monitored periodically based on clinical judgement. If ALT levels are increased to 3 x upper limit of normal during therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 x the upper limit of normal, therapy should be discontinued. If any patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. The decision whether to continue the patient on therapy with Incresync should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, the medicinal product should be discontinued.

Renal impairment

As there is a need for dose adjustment of alogliptin in patients with moderate or severe renal impairment, or end-stage renal disease requiring dialysis, appropriate assessment of renal function is recommended prior to initiation of Incresync and periodically thereafter (see section 4.2).

Incresync is not recommended for patients with severe renal impairment or end-stage renal disease requiring dialysis. No information is available on pioglitazone and alogliptin use in dialysed patients and, therefore, co-administered alogliptin plus pioglitazone should not be used in such patients (see sections 4.2 and 5.2).

Weight gain

In clinical studies with pioglitazone, there was evidence of dose-related weight gain, which may be due to fat accumulation and, in some cases, associated with fluid retention. In some cases, weight increase may be a symptom of cardiac failure, therefore weight should be closely monitored. Part of the treatment of diabetes is dietary control. Patients should be advised to adhere strictly to a calorie-controlled diet.

Haematology

There was a small reduction in mean haemoglobin (4% relative reduction) and haematocrit (4.1% relative reduction) during therapy with pioglitazone, consistent with haemodilution. Similar changes were seen in metformin- (haemoglobin 3-4% and haematocrit 3.6-4.1% relative reductions) and to a lesser extent sulphonylurea- and insulin- (haemoglobin 1-2% and haematocrit 1-3.2% relative reductions) treated patients in comparative-controlled studies with pioglitazone.

Use with other antihyperglycaemic medicinal products and hypoglycaemia

Due to the increased risk of hypoglycaemia in combination with metformin, a lower dose of metformin or the pioglitazone component may be considered to reduce the risk of hypoglycaemia when this combination is used (see section 4.2).

Combinations not studied

The efficacy and safety of Incresync as triple therapy with a sulphonylurea has not been established and thus use is not recommended.

Incresync should not be used in combination with insulin, as the safety and efficacy of this combination have not been established.

Eye disorders

Post-marketing reports of new-onset or worsening diabetic macular oedema with decreased visual acuity have been reported with thiazolidinediones, including pioglitazone. Many of these patients reported concurrent peripheral oedema. It is unclear whether or not there is a direct association between pioglitazone and macular oedema but prescribers should be alert to the possibility of macular oedema if patients on Incresync report disturbances in visual acuity; an appropriate ophthalmological referral should be considered.

Hypersensitivity reactions

Hypersensitivity reactions, including anaphylactic reactions, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome and erythema multiforme have been observed for DPP-4 inhibitors and have been spontaneously reported for alogliptin in the post-marketing setting. In clinical studies of alogliptin, anaphylactic reactions were reported with a low incidence.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. In a pooled analysis of the data from 13 studies, the overall rates of pancreatitis reports in patients treated with 25 mg alogliptin, 12.5 mg alogliptin, active control or placebo were 2, 1, 1 or 0 events per 1,000 patient years, respectively. In the cardiovascular outcomes study the rates of pancreatitis reports in patients treated with alogliptin or placebo were 3 or 2 events per 1,000 patient years, respectively. There have been spontaneously reported adverse reactions of acute pancreatitis in the post-marketing setting. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain, which may radiate to the back. If pancreatitis is suspected, Incresync should be discontinued; if acute pancreatitis is confirmed, Incresync should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Bullous Pemphigoid

There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including alogliptin. If bullous pemphigoid is suspected, alogliptin should be discontinued.

Others

An increased incidence in bone fractures in women was seen in a pooled analysis of adverse reactions of bone fracture from randomised, controlled, double-blind clinical studies in over 8,100 pioglitazone- and 7,400 comparator-treated patients, on treatment for up to 3.5 years.

Fractures were observed in 2.6% of women taking pioglitazone compared to 1.7% of women treated with a comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%).

The fracture incidence calculated was 1.9 fractures per 100 patient years in women treated with pioglitazone and 1.1 fractures per 100 patient years in women treated with a comparator. The observed excess risk of fractures for women in this dataset on pioglitazone is, therefore, 0.8 fractures per 100 patient years of use.

In the 3.5 year cardiovascular risk PROactive study, 44/870 (5.1%; 1.0 fractures per 100 patient years) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%; 0.5 fractures per 100 patient years) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%).

Some epidemiological studies have suggested a similarly increased risk of fracture in both men and women. The risk of fractures should be considered in the long-term care of patients treated with Incresync (see section 4.8).

As a consequence of enhancing insulin action, pioglitazone treatment in patients with polycystic ovarian syndrome may result in resumption of ovulation. These patients may be at risk of pregnancy. Patients should, therefore, be made aware of the risk of pregnancy and if a patient wishes to become pregnant or if pregnancy occurs, Incresync treatment should be discontinued (see section 4.6).

Incresync should be used with caution during concomitant administration of cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin). Glycaemic control should be monitored closely. Pioglitazone dose adjustment within the recommended posology or changes in diabetic treatment should be considered (see section 4.5).

Incresync tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of 25 mg alogliptin once daily and 45 mg pioglitazone once daily for 12 days in healthy subjects had no clinically relevant effects on the pharmacokinetics of alogliptin, pioglitazone or their active metabolites.

Specific pharmacokinetic drug interaction studies have not been performed with Incresync. The following section outlines the interactions observed with the individual components of Incresync (alogliptin/pioglitazone) as reported in their respective Summary of Product Characteristics.

Interactions with pioglitazone

Co-administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) is reported to result in a 3-fold increase in AUC for pioglitazone. Since there is a potential for an increase in dose-related adverse reactions, a decrease in the dose of pioglitazone may be needed when gemfibrozil is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4).

Co-administration of pioglitazone with rifampicin (an inducer of cytochrome P450 2C8) is reported to result in a 54% decrease in AUC for pioglitazone. The pioglitazone dose may need to be increased when rifampicin is concomitantly administered. Close monitoring of glycaemic control should be considered (see section 4.4).

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon or metformin. Co-administration of pioglitazone with sulphonylureas does not appear to affect the pharmacokinetics of the sulphonylurea. Studies in man suggest no induction of the main inducible cytochrome P450, 1A, 2C8/9 and 3A4. *In vitro* studies have shown no inhibition of any subtype of cytochrome P450. Interactions with substances metabolised by these enzymes, e.g. oral contraceptives, cyclosporin, calcium channel blockers and HMGCoA reductase inhibitors, are not to be expected.

Effects of other medicinal products on alogliptin

Alogliptin is primarily excreted unchanged in the urine and metabolism by the cytochrome (CYP) P450 enzyme system is negligible (see section 5.2). Interactions with CYP inhibitors are thus not expected and have not been shown.

Results from clinical interaction studies also demonstrate that there are no clinically relevant effects of gemfibrozil (a CYP2C8/9 inhibitor), fluconazole (a CYP2C9 inhibitor), ketoconazole (a CYP3A4 inhibitor), cyclosporine (a p-glycoprotein inhibitor), voglibose (an alpha-glucosidase inhibitor), digoxin, metformin, cimetidine, pioglitazone or atorvastatin on the pharmacokinetics of alogliptin.

Effects of alogliptin on other medicinal products

In vitro studies suggest that alogliptin does not inhibit nor induce CYP 450 isoforms at concentrations achieved with the recommended dose of 25 mg alogliptin (see section 5.2). Interaction with substrates of CYP 450 isoforms are thus not expected and have not been shown. In studies *in vitro*, alogliptin was found to be neither a substrate nor an inhibitor of key transporters associated with disposition of the active substance in the kidney: organic anion transporter-1, organic anion transporter-3 or organic cationic transporter-2 (OCT2). Furthermore, clinical data do not suggest interaction with p-glycoprotein inhibitors or substrates.

In clinical studies, alogliptin had no clinically relevant effect on the pharmacokinetics of caffeine, (R)-warfarin, pioglitazone, glyburide, tolbutamide, (S)-warfarin, dextromethorphan, atorvastatin, midazolam, an oral contraceptive (norethindrone and ethinyl oestradiol), digoxin, fexofenadine, metformin, or cimetidine, thus providing *in vivo* evidence of a low propensity to cause interaction with substrates of CYP1A2, CYP3A4, CYP2D6, CYP2C9, p-glycoprotein, and OCT2.

In healthy subjects, alogliptin had no effect on prothrombin time or International Normalised Ratio (INR) when administered concomitantly with warfarin.

Combination of alogliptin with other anti-diabetic medicinal products

Results from alogliptin studies with metformin, pioglitazone (thiazolidinedione), voglibose (alpha-glucosidase inhibitor) and glyburide (sulphonylurea) have shown no clinically relevant pharmacokinetic interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Incresync in pregnant women. Studies in animals with alogliptin plus pioglitazone as combination treatment have shown reproductive toxicity (slight augmentation of pioglitazone-related foetal

growth retardation and foetal visceral variations, see section 5.3). Incresync should not be used during pregnancy.

Risk related to alogliptin
There are no data from the use of alogliptin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Risk related to pioglitazone
There are no adequate human data to determine the safety of pioglitazone during pregnancy. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy, thereby reducing the availability of metabolic substrates for foetal growth. The relevance of such a mechanism in humans is unclear.

Breast-feeding

No studies in lactating animals have been conducted with the combined active substances of Incresync. In studies performed with the individual active substances, both alogliptin and pioglitazone were excreted in the milk of lactating rats. It is unknown whether alogliptin and pioglitazone are excreted in human milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Incresync therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of Incresync on fertility in humans has not been studied. No adverse effects on fertility were observed in animal studies conducted with alogliptin (see section 5.3). In animal fertility studies conducted with pioglitazone there was no effect on copulation, impregnation or fertility index.

4.7 Effects on ability to drive and use machines

Incresync has no or negligible influence on the ability to drive and use machines. However, patients who experience visual disturbance should be cautious when driving or using machines. Patients should be alerted to the risk of hypoglycaemia when Incresync is used in combination with other anti-diabetic medicinal products known to cause hypoglycaemia.

4.8 Undesirable effects

Summary of the safety profile

Acute pancreatitis is a serious adverse reaction and is attributed to the alogliptin component of Incresync (see section 4.4). Hypersensitivity reactions, including Stevens-Johnson syndrome, anaphylactic reactions, and angioedema are serious and are attributed to the alogliptin component of Incresync (see section 4.4). Other reactions such as upper respiratory tract infections, sinusitis, headache, hypoglycaemia, nausea, weight increase and oedema may occur commonly (≥ 1/100 to < 1/10).

Clinical studies conducted to support the efficacy and safety of Incresync involved the co-administration of alogliptin and pioglitazone as separate tablets. However, the results of bioequivalence studies have demonstrated that Incresync film-coated tablets are bioequivalent to the corresponding doses of alogliptin and pioglitazone co-administered as separate tablets.

The information provided is based on a total of 3,504 patients with type 2 diabetes mellitus, including 1,908 patients treated with alogliptin and pioglitazone, who participated in 4 phase 3 double-blind, placebo- or active-controlled clinical studies. These studies evaluated the effects of co-administered alogliptin and pioglitazone on glycaemic control and their safety as initial combination therapy, as dual therapy in patients initially treated with pioglitazone alone (with or without metformin or a sulphonylurea), and as add-on therapy to metformin.

Tabulated list of adverse reactions

The adverse reactions are listed by system organ class and frequency. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data).

Table 1: Adverse reactions

System organ class **Adverse reaction**	**Frequency of adverse reactions**		
	Alogliptin	**Pioglitazone**	**Incresync**
Infections and infestations			
upper respiratory tract infections	common	common	common
nasopharyngitis	common		
sinusitis		uncommon	common
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
bladder cancer		uncommon	
Immune system disorders			
hypersensitivity	not known		
hypersensitivity and allergic reactions		not known	
Metabolism and nutrition disorders			
hypoglycaemia	common		common
Nervous system disorders			
headache	common		common
hypoaesthesia		common	
insomnia		uncommon	
Eye disorders			
visual disturbance		common	
macular oedema		not known	
Gastrointestinal disorders			
abdominal pain	common		common
gastroesophageal reflux disease	common		
diarrhoea	common		
dyspepsia			common
nausea			common
acute pancreatitis	not known		
Hepatobiliary disorders			
hepatic dysfunction including hepatic failure	not known		
Skin and subcutaneous tissue disorders			
pruritus	common		common
rash	common		
exfoliative skin conditions including Stevens-Johnson syndrome	not known		
erythema multiforme	not known		
angioedema	not known		
urticaria	not known		
bullous pemphigoid	not known		
Musculoskeletal and connective tissues disorders			
myalgia			common
fracture bone		common	
General disorders and administration site conditions			
oedema peripheral			common

System organ class Adverse reaction	Frequency of adverse reactions		
	Alogliptin	**Pioglitazone**	**Incresync**
weight increased			common
Renal and urinary disorders			
interstitial nephritis	not known		
Investigations			
weight increased		common	
alanine aminotransferase increased		not known	

Description of selected adverse reactions

Post-marketing spontaneous reports of hypersensitivity reactions in patients treated with pioglitazone include anaphylaxis, angioedema, and urticaria.

Visual disturbance has been reported mainly early in treatment and is related to changes in blood glucose due to temporary alteration in the turgidity and refractive index of the lens as seen with other hypoglycaemic treatments.

Oedema was reported in 6-9% of patients treated with pioglitazone over one year in controlled clinical studies. The oedema rates for comparator groups (sulphonylurea, metformin) were 2-5%. The reports of oedema were generally mild to moderate and usually did not require discontinuation of treatment.

A pooled analysis was conducted of adverse reactions of bone fractures from randomised, comparator-controlled, double-blind clinical studies in over 8,100 patients in the pioglitazone-treated groups and 7,400 in the comparator-treated groups of up to 3.5 years duration. A higher rate of fractures was observed in women taking pioglitazone (2.6%) versus comparator (1.7%). No increase in fracture rates was observed in men treated with pioglitazone (1.3%) versus comparator (1.5%). In the 3.5 year PROactive study, 44/870 (5.1%) of pioglitazone-treated female patients experienced fractures compared to 23/905 (2.5%) of female patients treated with comparator. No increase in fracture rates was observed in men treated with pioglitazone (1.7%) versus comparator (2.1%). Post-marketing, bone fractures have been reported in both male and female patients (see section 4.4).

In active comparator-controlled studies, mean weight increase with pioglitazone given as monotherapy was 2-3 kg over one year. This is similar to that seen in a sulphonylurea active comparator group. In combination studies, pioglitazone added to metformin resulted in mean weight increase over one year of 1.5 kg and added to a sulphonylurea of 2.8 kg. In comparator groups, addition of sulphonylurea to metformin resulted in a mean weight gain of 1.3 kg and addition of metformin to a sulphonylurea a mean weight loss of 1.0 kg.

In clinical studies with pioglitazone, the incidence of elevations of ALT greater than three times the upper limit of normal was equal to placebo but less than that seen in metformin or sulphonylurea comparator groups. Mean levels of liver enzymes decreased with treatment with pioglitazone. Rare cases of elevated liver enzymes and hepatocellular dysfunction have occurred in post-marketing experience. Although in very rare cases, fatal outcome has been reported, causal relationship has not been established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No data are available with regard to overdose of Incresync.

Alogliptin

The highest doses of alogliptin administered in clinical studies were single doses of 800 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type 2 diabetes mellitus (equivalent to 32 times and 16 times the recommended daily dose of 25 mg alogliptin, respectively).

Pioglitazone

In clinical studies, patients have taken pioglitazone at higher than the recommended highest dose of 45 mg daily. The maximum reported dose of 120 mg/day for four days, then 180 mg/day for seven days was not associated with any symptoms.

Hypoglycaemia may occur in combination with sulphonylureas or insulin.

Management

In the event of an overdose, appropriate supportive measures should be employed as dictated by the patient's clinical status.

Minimal quantities of alogliptin are removed by haemodialysis (approximately 7% of the substance was removed during a 3-hour haemodialysis session). Therefore, haemodialysis is of little clinical benefit in overdose. It is not known if alogliptin is removed by peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes; combinations of oral blood glucose lowering drugs.

ATC code: A10BD09.

Mechanism of action and pharmacodynamic effects

Incresync combines two antihyperglycaemic medicinal products with complementary and distinct mechanisms of action to improve glycaemic control in patients with type 2 diabetes mellitus: alogliptin, a dipeptidyl-peptidase-4 (DPP-4) inhibitor, and pioglitazone, a member of the thiazolidinedione class. Studies in animal models of diabetes showed that concomitant treatment with alogliptin and pioglitazone produced both additive and synergistic improvements in glycaemic control, increased pancreatic insulin content and normalised pancreatic beta-cell distribution.

Alogliptin
Alogliptin is a potent and highly selective inhibitor of DPP-4, > 10,000-fold more selective for DPP-4 than other related enzymes including DPP-8 and DPP-9. DPP-4 is the principal enzyme involved in the rapid degradation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and GIP (glucose-dependent insulinotropic polypeptide), which are released by the intestine and levels are increased in response to a meal. GLP-1 and GIP increases insulin biosynthesis and secretion from pancreatic beta cells, while GLP-1 also inhibits glucagon secretion and hepatic glucose production. Alogliptin therefore improves glycaemic control via a glucose-dependent mechanism, whereby insulin release is enhanced and glucagon levels are suppressed when glucose levels are high.

Pioglitazone
Pioglitazone effects may be mediated by a reduction of insulin resistance. Pioglitazone appears to act via activation of specific nuclear receptors (peroxisome proliferator activated receptor gamma) leading to increased insulin sensitivity of liver, fat and skeletal muscle cells in animals. Treatment with pioglitazone has been shown to reduce hepatic glucose output and to increase peripheral glucose disposal in the case of insulin resistance.

Fasting and postprandial glycaemic control is improved following treatment with pioglitazone in patients with type 2 diabetes mellitus. The improved glycaemic control is associated with a reduction in both fasting and postprandial plasma insulin concentrations.

HOMA analysis shows that pioglitazone improves beta-cell function as well as increasing insulin sensitivity. Two-year clinical studies have shown maintenance of this effect.

In one-year clinical studies, pioglitazone consistently gave a statistically significant reduction in the albumin/creatinine ratio compared to baseline.

The effect of pioglitazone (45 mg monotherapy vs. placebo) was studied in a small 18-week study in type 2 diabetics. Pioglitazone was associated with significant weight gain. Visceral fat was significantly decreased while there was an increase in extra-abdominal fat mass. Similar changes in body fat distribution on pioglitazone have been accompanied by an improvement in insulin sensitivity. In most clinical studies, reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels were observed as compared to placebo with small, but not clinically significant, increases in LDL-cholesterol levels.

In clinical studies of up to two years duration, pioglitazone reduced total plasma triglycerides and free fatty acids, and increased HDL-cholesterol levels compared to placebo, metformin or gliclazide. Pioglitazone did not cause statistically significant increases in LDL-cholesterol levels compared to placebo whilst reductions were observed with metformin and gliclazide. In a 20-week study, as well as reducing fasting triglycerides, pioglitazone reduced postprandial hypertriglyceridaemia through an effect on both absorbed and hepatically synthesised triglycerides. These effects were independent of pioglitazone’s effects on glycaemia and were statistically significantly different to glibenclamide.

Clinical efficacy

Clinical studies conducted to support the efficacy of Incresync involved the co-administration of alogliptin and pioglitazone as separate tablets. However, the results of bioequivalence studies have demonstrated that Incresync film-coated tablets are bioequivalent to the corresponding doses of alogliptin and pioglitazone co-administered as separate tablets.

The co-administration of alogliptin and pioglitazone has been studied as dual therapy in patients initially treated with pioglitazone alone (with or without metformin or a sulphonylurea) and as add-on therapy to metformin.

Administration of 25 mg alogliptin to patients with type 2 diabetes mellitus produced peak inhibition of DPP-4 within 1 to 2 hours and exceeded 93% both after a single 25 mg dose and after 14 days of once-daily dosing. Inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing. When the 4-hour postprandial glucose concentrations were averaged across breakfast, lunch and dinner, 14 days of treatment with 25 mg alogliptin resulted in a mean placebo-corrected reduction from baseline of -35.2 mg/dL.

Both 25 mg alogliptin alone and in combination with 30 mg pioglitazone demonstrated significant decreases in postprandial glucose and postprandial glucagon whilst significantly increasing postprandial active GLP-1 levels at Week 16 compared to placebo ($p < 0.05$). In addition, 25 mg alogliptin alone and in combination with 30 mg pioglitazone produced statistically significant ($p < 0.001$) reductions in total triglycerides at Week 16 as measured by postprandial incremental $AUC_{(0-8)}$ change from baseline compared to placebo.

A total of 3,504 patients with type 2 diabetes mellitus, including 1,908 patients treated with alogliptin and pioglitazone, participated in 4 phase 3 double-blind, placebo- or active-controlled clinical studies conducted to evaluate the effects of co-administered alogliptin and pioglitazone on glycaemic control and their safety. In these studies, 312 alogliptin/pioglitazone-treated patients were ≥ 65 years old. The studies included 1,269 patients with mild renal impairment and 161 patients with moderate renal impairment treated with alogliptin/pioglitazone.

Overall, treatment with the recommended daily dose of 25 mg alogliptin in combination with pioglitazone improved glycaemic control. This was determined by clinically relevant and statistically significant reductions in glycosylated haemoglobin (HbA1c) and fasting plasma glucose compared to control from baseline to study endpoint. Reductions in HbA1c were similar across different subgroups including renal impairment, age, gender and body mass index, while differences between races (e.g. White and non-White) were small. Clinically meaningful reductions in HbA1c compared to control were also observed regardless of baseline background medicinal product dose. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Generally, the effects of alogliptin on body weight and lipids were neutral.

Alogliptin as add-on therapy to pioglitazone
The addition of 25 mg alogliptin once daily to pioglitazone therapy (mean dose = 35.0 mg, with or without metformin or a sulphonylurea) resulted in statistically significant improvements from baseline in HbA1c and fasting plasma glucose at Week 26 when compared to the addition of placebo (Table 2). Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin or sulphonylurea therapy. Significantly more patients receiving 25 mg alogliptin (49.2%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving placebo (34.0%) at Week 26 ($p = 0.004$).

Alogliptin as add-on therapy to pioglitazone with metformin

The addition of 25 mg alogliptin once daily to 30 mg pioglitazone in combination with metformin hydrochloride therapy (mean dose = 1,867.9 mg) resulted in improvements from baseline in HbA1c at Week 52 that were both non-inferior and statistically superior to those produced by 45 mg pioglitazone in combination with metformin hydrochloride therapy (mean dose = 1,847.6 mg, Table 3). The significant reductions in HbA1c observed with 25 mg alogliptin plus 30 mg pioglitazone and metformin were consistent over the entire 52-week treatment period compared to 45 mg pioglitazone and metformin ($p < 0.001$ at all time points). In addition, mean change from baseline in fasting plasma glucose at Week 52 for 25 mg alogliptin plus 30 mg pioglitazone and metformin was significantly greater than that for 45 mg pioglitazone and metformin ($p < 0.001$). Significantly more patients receiving 25 mg alogliptin plus 30 mg pioglitazone and metformin (33.2%) achieved target HbA1c levels of ≤ 7.0% compared to those receiving 45 mg pioglitazone and metformin (21.3%) at Week 52 ($p < 0.001$).

Table 2: Change in HbA1c (%) from baseline with alogliptin 25 mg at Week 26 by placebo-controlled study (FAS, LOCF)

Study	**Mean baseline HbA1c (%) (SD)**	**Mean change from baseline in HbA1c (%)† (SE)**	**Placebo-corrected change from baseline in HbA1c (%)† (2-sided 95% CI)**
Add-on combination therapy placebo-controlled studies			
Alogliptin 25 mg once daily with pioglitazone ± metformin or a sulphonylurea (n = 195)	8.01 (0.837)	-0.80 (0.056)	-0.61* (-0.80, -0.41)

FAS = full analysis set
LOCF = last observation carried forward
† Least squares means adjusted for prior antihyperglycaemic therapy status and baseline values
* $p < 0.001$ compared to placebo or placebo+combination treatment

Table 3: Change in HbA1c (%) from baseline with alogliptin 25 mg by active-controlled study (PPS, LOCF)			
Study	**Mean baseline HbA1c (%) (SD)**	**Mean change from baseline in HbA1c (%)† (SE)**	**Treatment-corrected change from baseline in HbA1c (%)† (1-sided CI)**
Add-on combination therapy studies			
Alogliptin 25 mg once daily with pioglitazone + metformin vs titrating pioglitazone + metformin			
Change at Week 26 (n = 303)	8.25 (0.820)	-0.89 (0.042)	-0.47* (-infinity, -0.35)
Change at Week 52 (n = 303)	8.25 (0.820)	-0.70 (0.048)	-0.42* (-infinity, -0.28)

PPS = per protocol set
LOCF = last observation carried forward
* Non inferiority and superiority statistically demonstrated
† Least squares means adjusted for prior antihyperglycaemic therapy status and baseline values

Patients with renal impairment
Incresync is not recommended for patients with severe renal impairment or end-stage renal disease requiring dialysis (see section 4.2).

Elderly (≥ 65 years old)
The efficacy and safety of the recommended doses of alogliptin and pioglitazone in a subgroup of patients with type 2 diabetes mellitus and ≥ 65 years old were reviewed and found to be consistent with the profile obtained in patients < 65 years old.

Clinical safety

Cardiovascular Safety
In a pooled analysis of the data from 13 studies, the overall incidences of cardiovascular death, non fatal myocardial infarction and non-fatal stroke were comparable in patients treated with 25 mg alogliptin, active control or placebo.

In addition, a prospective randomised cardiovascular outcomes safety study was conducted with 5,380 patients with high underlying cardiovascular risk to examine the effect of alogliptin compared with placebo (when added to

standard of care) on major adverse cardiovascular events (MACE) including time to the first occurrence of any event in the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke in patients with a recent (15 to 90 days) acute coronary event. At baseline, patients had a mean age of 61 years, mean duration of diabetes of 9.2 years, and mean HbA1c of 8.0%.

The study demonstrated that alogliptin did not increase the risk of having a MACE compared to placebo [Hazard Ratio: 0.96; 1-sided 99% Confidence Interval: 0-1.16]. In the alogliptin group, 11.3% of patients experienced a MACE compared to 11.8% of patients in the placebo group.

Table 4. MACE Reported in cardiovascular outcomes study

	Number of Patients (%)	
	Alogliptin 25 mg	**Placebo**
	N = 2,701	N = 2,679
Primary Composite Endpoint [First Event of CV Death, Nonfatal MI and Nonfatal Stroke]	**305 (11.3)**	**316 (11.8)**
Cardiovascular Death*	89 (3.3)	111 (4.1)
Nonfatal Myocardial Infarction	187 (6.9)	173 (6.5)
Nonfatal Stroke	29 (1.1)	32 (1.2)
*Overall there were 153 subjects (5.7%) in the alogliptin group and 173 subjects (6.5%) in the placebo group who died (all-cause mortality)		

There were 703 patients who experienced an event within the secondary MACE composite endpoint (first event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and urgent revascularization due to unstable angina). In the alogliptin group, 12.7% (344 subjects) experienced an event within the secondary MACE composite endpoint, compared with 13.4% (359 subjects) in the placebo group [Hazard Ratio = 0.95; 1-sided 99% Confidence Interval: 0-1.14].

In controlled clinical studies, the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonylurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo when added to therapy that included insulin. However, this did not lead to an increase in mortality in this study. Heart failure has been reported rarely with marketing use of pioglitazone, but more frequently when pioglitazone was used in combination with insulin or in patients with a history of cardiac failure.

In PROactive, a cardiovascular outcome study, 5,238 patients with type 2 diabetes mellitus and pre-existing major macrovascular disease were randomised to pioglitazone or placebo in addition to existing anti-diabetic and cardiovascular therapy, for up to 3.5 years. The study population had an average age of 62 years; the average duration of diabetes was 9.5 years. Approximately one third of patients were receiving insulin in combination with metformin and/or a sulphonylurea. To be eligible, patients had to have had one or more of the following: myocardial infarction, stroke, percutaneous cardiac intervention or coronary artery bypass graft, acute coronary syndrome, coronary artery disease, or peripheral arterial obstructive disease. Almost half of the patients had a previous myocardial infarction and approximately 20% had had a stroke. Approximately half of the study population had at least two of the cardiovascular history entry criteria. Almost all subjects (95%) were receiving cardiovascular medicinal products (beta blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II antagonists, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates).

Although the study failed regarding its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.

Hypoglycaemia
In a pooled analysis of the data from 12 studies, the overall incidence of any episode of hypoglycaemia was lower in patients treated with 25 mg alogliptin than in patients treated with 12.5 mg alogliptin, active-control or placebo (3.6%, 4.6%, 12.9% and 6.2%, respectively). The majority of these episodes were mild to moderate in intensity. The overall incidence of episodes of severe hypoglycaemia was comparable in patients treated with 25 mg alogliptin or 12.5 mg alogliptin, and lower than the incidence in patients treated with active-control or placebo (0.1%, 0.1%, 0.4% and 0.4%, respectively). In the prospective randomised controlled cardiovascular outcomes study, investigator reported events of hypoglycemia were similar in patients receiving placebo (6.5%) and patients receiving alogliptin (6.7%) in addition to standard of care.

A clinical study of alogliptin as add-on therapy to pioglitazone demonstrated that there was no clinically relevant increase in hypoglycaemia rate compared to placebo. The incidence of hypoglycaemia was greater when alogliptin was used as triple therapy with pioglitazone and metformin (compared to active-control). This has also been observed with other DPP-4 inhibitors.

Patients (≥ 65 years old) with type 2 diabetes mellitus are considered more susceptible to episodes of hypoglycaemia than patients < 65 years old. In a pooled analysis of the data from 12 studies, the overall incidence of any episode of hypoglycaemia was similar in patients ≥ 65 years old treated with 25 mg alogliptin (3.8%) to that in patients < 65 years old (3.6%).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Incresync in all subsets of the paediatric population in the treatment of type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The results of bioequivalence studies in healthy subjects demonstrated that Incresync film-coated tablets are bioequivalent to the corresponding doses of alogliptin and pioglitazone co-administered as separate tablets.

Co-administration of 25 mg alogliptin once daily and 45 mg pioglitazone once daily for 12 days in healthy subjects had no clinically relevant effects on the pharmacokinetics of alogliptin, pioglitazone or their active metabolites.

Administration of Incresync with food resulted in no change in overall exposure to alogliptin or pioglitazone. Incresync may, therefore, be administered with or without food.

The following section outlines the pharmacokinetic properties of the individual components of Incresync (alogliptin/pioglitazone) as reported in their respective Summary of Product Characteristics.

Alogliptin

The pharmacokinetics of alogliptin has been shown to be similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption
The absolute bioavailability of alogliptin is approximately 100%.

Administration with a high-fat meal resulted in no change in total and peak exposure to alogliptin. Alogliptin may, therefore, be administered with or without food.

After administration of single, oral doses of up to 800 mg in healthy subjects, alogliptin was rapidly absorbed with peak plasma concentrations occurring 1 to 2 hours (median T_{max}) after dosing.

No clinically relevant accumulation after multiple dosing was observed in either healthy subjects or in patients with type 2 diabetes mellitus.

Total and peak exposure to alogliptin increased proportionately across single doses of 6.25 mg up to 100 mg alogliptin (covering the therapeutic dose range). The inter-subject coefficient of variation for alogliptin AUC was small (17%).

Distribution
Following a single intravenous dose of 12.5 mg alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L indicating that the active substance is well distributed into tissues.

Alogliptin is 20-30% bound to plasma proteins.

Biotransformation
Alogliptin does not undergo extensive metabolism, 60-70% of the dose is excreted as unchanged active substance in the urine.

Two minor metabolites were detected following administration of an oral dose of [^{14}C] alogliptin, N-demethylated alogliptin, M-I (< 1% of the parent compound), and N-acetylated alogliptin, M-II (< 6% of the parent compound). M-I is an active metabolite and is a highly selective inhibitor of DPP-4 similar to alogliptin; M-II does not display any inhibitory activity towards DPP-4 or other DPP-related enzymes. *In vitro* data indicate that CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

In vitro studies indicate that alogliptin does not induce CYP1A2, CYP2B6 and CYP2C9 and does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at concentrations achieved with the recommended dose of 25 mg alogliptin. Studies *in vitro* have shown alogliptin to be a mild inducer of CYP3A4, but alogliptin has not been shown to induce CYP3A4 in studies in vivo.

In studies *in vitro*, alogliptin was not an inhibitor of the following renal transporters; OAT1, OAT3 and OCT2.

Alogliptin exists predominantly as the (R)-enantiomer (> 99%) and undergoes little or no chiral conversion *in vivo* to the (S)-enantiomer. The (S)-enantiomer is not detectable at therapeutic doses.

Elimination
Alogliptin was eliminated with a mean terminal half-life ($T_{1/2}$) of approximately 21 hours.

Following administration of an oral dose of [^{14}C] alogliptin, 76% of total radioactivity was eliminated in the urine and 13% was recovered in the faeces.

The average renal clearance of alogliptin (170 mL/min) was greater than the average estimated glomerular filtration rate (approx. 120 mL/min), suggesting some active renal excretion.

Time-dependency
Total exposure ($AUC_{(0\text{-}inf)}$) to alogliptin following administration of a single dose was similar to exposure during one dose interval ($AUC_{(0\text{-}24)}$) after 6 days of once daily dosing. This indicates no time-dependency in the kinetics of alogliptin after multiple dosing.

Special populations
Renal impairment
A single dose of 50 mg alogliptin was administered to 4 groups of patients with varying degrees of renal impairment (CrCl using the Cockcroft-Gault formula): mild (CrCl = > 50 to ≤ 80 mL/min), moderate (CrCl = ≥ 30 to ≤ 50 mL/min), severe (CrCl = < 30 mL/min) and end-stage renal disease on haemodialysis.

An approximate 1.7-fold increase in AUC for alogliptin was observed in patients with mild renal impairment. However, as the distribution of AUC values for alogliptin in these patients was within the same range as control subjects, no dose adjustment of alogliptin for patients with mild renal impairment is necessary (see section 4.2).

In patients with moderate or severe renal impairment, or end-stage renal disease on haemodialysis, an increase in systemic exposure to alogliptin of approximately 2- and 4-fold was observed, respectively. (Patients with end-stage renal disease underwent haemodialysis immediately after alogliptin dosing. Based on mean dialysate concentrations, approximately 7% of the active substance was removed during a 3-hour haemodialysis session. Therefore, in order to maintain systemic exposures to alogliptin that are similar to those observed in patients with normal renal function, lower doses of alogliptin should be used in patients with moderate or severe renal impairment, or end-stage renal disease requiring dialysis (see above and section 4.2).

Hepatic impairment
Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment compared to control subjects. The magnitude of these reductions was not considered to be clinically relevant. Therefore, no dose adjustment of alogliptin is necessary for patients with mild to moderate hepatic impairment (Child-Pugh scores of 5 to 9). Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9).

Age, gender, race, body weight
Age (65-81 years old), gender, race (white, black and Asian) and body weight did not have any clinically relevant effect on the pharmacokinetics of alogliptin. No dose adjustment is necessary (see section 4.2).

Paediatric population
The pharmacokinetics of alogliptin in children and adolescents < 18 years old has not been established. No data are available (see section 4.2).

Pioglitazone

Absorption
Following oral administration, pioglitazone is rapidly absorbed and peak serum concentrations of unchanged pioglitazone are usually achieved 2 hours after administration. Proportional increases of the serum concentration were observed for doses from 2-60 mg. Steady-state is achieved after 4-7 days of dosing. Repeated dosing does not result in accumulation of the compound or metabolites. Absorption is not influenced by food intake. Absolute bioavailability is greater than 80%.

Distribution
The estimated volume of distribution in humans is 19 L.

Pioglitazone and all active metabolites are extensively bound to plasma protein (> 99%).

Biotransformation
Pioglitazone undergoes extensive hepatic metabolism by hydroxylation of aliphatic methylene groups. This is predominantly via cytochrome P450 2C8 although other isoforms may be involved to a lesser degree. Three of the six identified pioglitazone metabolites are active (M-II, M-III, and M-IV). When activity, concentrations and protein binding are taken into account, pioglitazone and metabolite M-III contribute equally to efficacy. On this basis, M-IV contribution to efficacy is approximately 3-fold that of pioglitazone whilst the relative efficacy of M-II is minimal.

In vitro studies have shown no evidence that pioglitazone inhibits any subtype of cytochrome P450. There is no induction of the main inducible P450 isoenzymes 1A, 2C8/9 and 3A4 in man.

Interaction studies have shown that pioglitazone has no relevant effect on either the pharmacokinetics or pharmacodynamics of digoxin, warfarin, phenprocoumon or metformin. Concomitant administration of pioglitazone with gemfibrozil (an inhibitor of cytochrome P450 2C8) or with rifampicin (an inducer of cytochrome P450 2C8) is reported to increase or decrease, respectively, the serum concentration of pioglitazone (see section 4.5).

Elimination
Following oral administration of radiolabelled pioglitazone to man, recovered label was mainly in faeces (55%) and a lesser amount in urine (45%). In animals, only a small amount of unchanged pioglitazone can be detected in either urine or faeces. The mean serum elimination half-life of unchanged pioglitazone in man is 5 to 6 hours and for its total active metabolites 16 to 23 hours.

Special populations
Renal impairment
In patients with renal impairment, serum concentrations of pioglitazone and its metabolites are lower than those seen in subjects with normal renal function, but oral clearance of parent substance is similar. Thus, free (unbound) pioglitazone concentration is unchanged (see section 4.2).

Hepatic impairment
Total serum concentration of pioglitazone is unchanged, but with an increased volume of distribution. Intrinsic clearance is, therefore, reduced coupled with a higher unbound fraction of pioglitazone (see section 4.2).

Elderly (≥ 65 years old)
Steady-state pharmacokinetics is similar in patients aged 65 years and over and young subjects (see section 4.2).

Paediatric population
The pharmacokinetics of pioglitazone in children and adolescents < 18 years old has not been established. No data are available (see section 4.2).

Incresync

Special populations
Renal impairment
For patients with moderate renal impairment, Incresync 12.5 mg/30 mg should be administered once daily. Incresync is not recommended for patients with severe renal impairment or end-stage renal disease requiring dialysis. No dose adjustment of Incresync for patients with mild renal impairment is necessary (see section 4.2).

Hepatic impairment
Due to its pioglitazone component, Incresync should not be used in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Animal studies of up to 13-weeks duration have been conducted with the combined substances in Incresync.

Concomitant treatment with alogliptin and pioglitazone did not produce new toxicities, nor did it exacerbate any pioglitazone-related findings. No effects on the toxicokinetics of either compound were observed.

Combination treatment with alogliptin and pioglitazone to pregnant rats slightly augmented pioglitazone-related foetal effects of growth retardation and visceral variations, but did not induce embryo-foetal mortality or teratogenicity.

The following data are findings from studies performed with alogliptin or pioglitazone individually.

Alogliptin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and toxicology.

The no-observed-adverse-effect level (NOAEL) in the repeated dose toxicity studies in rats and dogs up to 26- and 39-weeks in duration, respectively, produced exposure margins that were approximately 147- and 227-fold, respectively, the exposure in humans at the recommended daily dose of 25 mg alogliptin.

Alogliptin was not genotoxic in a standard battery of *in vitro* and *in vivo* genotoxicity studies.

Alogliptin was not carcinogenic in 2-year carcinogenicity studies conducted in rats and mice. Minimal to mild simple transitional cell hyperplasia was seen in the urinary bladder of male rats at the lowest dose used (27 times the human exposure) without establishment of a clear NOEL (no observed effect level).

No adverse effects of alogliptin were observed upon fertility, reproductive performance, or early embryonic development in rats up to a systemic exposure far above the human exposure at the recommended dose. Although fertility was not affected, a slight, statistical increase in the number of abnormal sperm was observed in males at an exposure far above the human exposure at the recommended dose.

Placental transfer of alogliptin occurs in rats.

Alogliptin was not teratogenic in rats or rabbits with a systemic exposure at the NOAELs far above the human exposure at the recommended dose. Higher doses of alogliptin were not teratogenic but resulted in maternal toxicity, and were associated with delayed and/or lack of ossification of bones and decreased foetal body weights.

In a pre- and postnatal development study in rats, exposures far above the human exposure at the recommended dose did not harm the developing embryo or affect offspring growth and development. Higher doses of alogliptin decreased offspring body weight and exerted some developmental effects considered secondary to the low body weight.

Studies in lactating rats indicate that alogliptin is excreted in milk.

No alogliptin-related effects were observed in juvenile rats following repeat-dose administration for 4 and 8 weeks.

Pioglitazone

In toxicology studies, plasma volume expansion with haemodilution, anaemia and reversible eccentric cardiac hypertrophy was consistently apparent after repeated dosing of mice, rats, dogs and monkeys. In addition, increased fatty deposition and infiltration were observed. These findings were observed across species at plasma concentrations $\leq$ 4 times the clinical exposure. Foetal growth restriction was apparent in animal studies with pioglitazone. This was attributable to the action of pioglitazone in diminishing the maternal hyperinsulinaemia and increased insulin resistance that occurs during pregnancy thereby reducing the availability of metabolic substrates for foetal growth.

Pioglitazone was devoid of genotoxic potential in a comprehensive battery of *in vivo* and *in vitro* genotoxicity assays. An increased incidence of hyperplasia (males and females) and tumours (males) of the urinary bladder epithelium was apparent in rats treated with pioglitazone for up to 2 years.

The formation and presence of urinary calculi with subsequent irritation and hyperplasia was postulated as the mechanistic basis for the observed tumourigenic response in the male rat. A 24-month mechanistic study in male rats demonstrated that administration of pioglitazone resulted in an increased incidence of hyperplastic changes in the bladder. Dietary acidification significantly decreased but did not abolish the incidence of tumours. The presence of microcrystals exacerbated the hyperplastic response but was not considered to be the primary cause of hyperplastic changes. The relevance to humans of the tumourigenic findings in the male rat cannot be excluded.

There was no tumourigenic response in mice of either sex. Hyperplasia of the urinary bladder was not seen in dogs or monkeys treated with pioglitazone for up to 12 months.

In an animal model of familial adenomatous polyposis, treatment with two other thiazolidinediones increased tumour multiplicity in the colon. The relevance of this finding is unknown.

Environmental Risk Assessment (ERA)

No environmental impact is anticipated from the clinical use of pioglitazone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate
Lactose monohydrate

Film-coating

12.5 mg/30 mg film-coated tablets	**25 mg/30 mg film-coated tablets**	**25 mg/45 mg film-coated tablets**
Hypromellose	Hypromellose	Hypromellose
Talc	Talc	Talc
Titanium dioxide (E171)	Titanium dioxide (E171)	Titanium dioxide (E171)
Macrogol 8000	Macrogol 8000	Macrogol 8000
Iron oxide red (E172)	Iron oxide red (E172)	Iron oxide red (E172)
Iron oxide yellow (E172)	Iron oxide yellow (E172)	

Printing ink

12.5 mg/30 mg film-coated tablets	**25 mg/30 mg film-coated tablets**	**25 mg/45 mg film-coated tablets**
Shellac	Shellac	Shellac
Iron oxide red (E172)	Iron oxide black (E172)	Iron oxide black (E172)
Carnauba wax		
Glycerol mono-oleate		

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Nylon/aluminium/polyvinyl chloride (PVC) blisters with push through aluminium lidding foil. Pack sizes of 10, 14, 28, 30, 56, 60, 90, 98 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15475/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/01/2021