

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Onglyza 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg saxagliptin (as hydrochloride).

Excipients:

Each tablet contains 99 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pink, biconvex, round, film-coated tablet, with “5” printed on one side and “4215” printed on the other side, in blue ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Add-on combination therapy

Onglyza is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control:

- in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control;
- in combination with a sulphonylurea, when the sulphonylurea alone, with diet and exercise, does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate.
- in combination with a thiazolidinedione, when the thiazolidinedione alone with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate.

4.2 Posology and method of administration

Posology

Add-on combination therapy

The recommended dose of Onglyza is 5 mg once daily as add-on combination therapy with metformin, a thiazolidinedione or a sulphonylurea.

The safety and efficacy of saxagliptin as triple oral therapy in combination with metformin and a thiazolidinedione, or with metformin and a sulphonylurea, has not been established.

Special populations

Renal impairment

No dose adjustment is recommended for patients with mild renal impairment. Clinical study experience with Onglyza in patients with moderate to severe renal impairment is limited. Therefore, use of Onglyza is not recommended in this patient population (see sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment (see section 5.2). Saxagliptin should be used with caution in patients with moderate hepatic impairment, and is not recommended for use in patients with severe hepatic impairment (see section 4.4).

Elderly (≥ 65 years)

No dose adjustment is recommended based solely on age. Experience in patients aged 75 years and older is very limited and caution should be exercised when treating this population (see also sections 4.4, 5.1 and 5.2).

Paediatric population

Onglyza is not recommended for use in children and adolescents due to lack of data on safety and efficacy.

Method of administration

Onglyza can be taken with or without a meal at any time of the day. 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 substance or to any of the excipients.

4.4 Special warnings and precautions for use

General

Onglyza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Saxagliptin has not been studied in combination with insulin.

Renal impairment

Clinical study experience with saxagliptin in patients with moderate to severe renal impairment is limited. Therefore, use of Onglyza is not recommended in this patient population (see sections 4.2 and 5.2).

Hepatic impairment

Saxagliptin should be used with caution in patients with moderate hepatic impairment, and is not recommended for use in patients with severe hepatic impairment (see section 4.2).

Use with sulphonylureas

Sulphonylureas are known to cause hypoglycaemia. Therefore, a lower dose of sulphonylurea may be required to reduce the risk of hypoglycaemia when used in combination with Onglyza.

Hypersensitivity reactions

Onglyza should not be used in patients who have had any serious hypersensitivity reaction to a dipeptidyl peptidase 4 (DPP4) inhibitor.

Elderly patients

Experience in patients aged 75 years and older is very limited and caution should be exercised when treating this population (see sections 5.1 and 5.2).

Skin disorders

Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3). Although skin lesions were not observed at an increased incidence in clinical trials, there is limited experience in patients with diabetic skin complications. Postmarketing reports of rash have been described in the DPP4 inhibitor class. Rash is also noted as an adverse event

(AE) for Onglyza (section 4.8). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.

Cardiac failure

Experience in NYHA class I-II is limited, and there is no experience in clinical studies with saxagliptin in NYHA class III-IV.

Immunocompromised patients

Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome, have not been studied in the Onglyza clinical program. Therefore, the efficacy and safety profile of saxagliptin in these patients has not been established.

Use with potent CYP 3A4 inducers

Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin may reduce the glycaemic lowering effect of Onglyza (see section 4.5).

Lactose

The tablet contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical data described below suggest that the risk for clinically meaningful interactions with co-administered medicinal products is low.

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4. In studies conducted in healthy subjects, neither the pharmacokinetics of saxagliptin and its major metabolite, were meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, omeprazole, antacids or famotidine. In addition, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem or ketoconazole.

Concomitant administration of saxagliptin with the moderate inhibitor of CYP3A4/5 diltiazem, increased the C_{max} and AUC of saxagliptin by 63% and 2.1-fold, respectively, and the corresponding values for the active metabolite were decreased by 44 and 34%, respectively.

Concomitant administration of saxagliptin with the potent inhibitor of CYP3A4/5 ketoconazole, increased the C_{max} and AUC of saxagliptin by 62% and 2.5-fold, respectively, and the corresponding values for the active metabolite were decreased by 95% and 88%, respectively.

Concomitant administration of saxagliptin with the potent CYP3A4/5 inducer rifampicin, reduced C_{max} and AUC of saxagliptin by 53% and 76%, respectively. The exposure of the active metabolite and the plasma DPP4 activity inhibition over a dose interval were not influenced by rifampicin (see section 4.4).

The co-administration of saxagliptin and CYP3A4/5 inducers, other than rifampicin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) have not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metabolite. Glycaemic control should be carefully assessed when saxagliptin is used concomitantly with a potent CYP3A4 inducer.

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of saxagliptin have not been specifically studied.

4.6 Pregnancy and lactation

Pregnancy

There are no data from the use of saxagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Onglyza should not be used during pregnancy unless clearly necessary.

Lactation

It is unknown whether saxagliptin is excreted in human breast milk. Animal studies have shown excretion of saxagliptin and/or metabolite in milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy to the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that dizziness has been reported with saxagliptin.

4.8 Undesirable effects

There were 4,148 patients with type 2 diabetes, including 3,021 patients treated with Onglyza, randomised in six double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control.

In a pooled analysis, the overall incidence of adverse events in patients treated with saxagliptin 5 mg was similar to placebo. Discontinuation of therapy due to adverse events was higher in patients who received saxagliptin 5 mg as compared to placebo (3.3% as compared to 1.8%).

Adverse reactions reported (regardless of investigator assessment of causality) in $\geq 5\%$ of patients treated with saxagliptin 5 mg and more commonly than in patients treated with placebo or that were reported in $\geq 2\%$ of patients treated with saxagliptin 5 mg and $\geq 1\%$ more frequently compared to placebo are shown in Table 1.

The adverse reactions are listed by system organ class and absolute frequency. Frequencies are defined as Very common ($\geq 1/10$), Common ($\geq 1/100$ to $<1/10$), Uncommon ($\geq 1/1,000$ to $1/100$), Rare ($\geq 1/10,000$ to $1/1,000$), or Very rare ($<1/10,000$), not known (cannot be estimated from the available data).

Table 1 Frequency of adverse reactions by system organ class

System organ class Adverse Reaction	Frequency of adverse reactions by treatment regimen			
	Saxagliptin monotherapy	Saxagliptin with metformin ¹	Saxagliptin with a sulphonylurea (glibenclamide)	Saxagliptin with a thiazolidinedione
Infections and infestations				
Upper respiratory infection	Common	Common	Common	Common
Urinary tract infection	Common	Common	Common	Common
Gastroenteritis	Common	Common	Common	Common
Sinusitis	Common	Common	Common	Common
Nasopharyngitis		Common ²		
Metabolism and nutrition disorders				
Hypoglycaemia			Very common ³	
Nervous system disorders				
Headache	Common	Common	Common	Common
Gastrointestinal disorders				
Vomiting	Common	Common	Common	Common
General disorders				
Oedema peripheral				Common ⁴

¹Includes saxagliptin in add-on to metformin and initial combination with metformin.

²Only in the initial combination therapy.

³There was no statistically significant difference compared to placebo. The incidence of confirmed hypoglycaemia was uncommon for Onglyza 5 mg (0.8%) and placebo (0.7%).

⁴All of the reported adverse drug reactions of peripheral oedema were of mild to moderate intensity and none resulted in study drug discontinuation.

In addition to the adverse reactions described above, adverse events reported regardless of causal relationship to the medicinal product and occurring more commonly in patients treated with Onglyza include hypersensitivity (0.6% vs. 0%) and rash (1.4% vs. 1.0%) as compared with placebo.

Adverse events, considered by the investigator to be at least possibly drug-related and reported in at least two more patients treated with saxagliptin 5 mg compared to control, are described below by treatment regimen.

As monotherapy: dizziness (common) and fatigue (common).

As add-on to metformin: dyspepsia (common) and myalgia (common).

As add-on to sulphonylurea (glibenclamide): fatigue (uncommon), dyslipidemia (uncommon) and hypertriglyceridemia (uncommon).

As initial combination with metformin: gastritis (common), arthralgia (uncommon), myalgia (uncommon), and erectile dysfunction (uncommon).

Laboratory tests

Across clinical studies, the incidence of laboratory adverse events was similar in patients treated with saxagliptin 5 mg compared to patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2,200 cells/ μ l, a mean decrease of approximately 100 cells/ μ l relative to placebo was observed in the placebo-controlled-pooled analysis. Mean absolute lymphocyte counts remained stable with daily dosing up to 102 weeks in duration. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The clinical significance of this decrease in lymphocyte count relative to placebo is not known.

4.9 Overdose

Onglyza has been shown to be safe and well-tolerated with no clinically meaningful effect on QTc interval or heart rate at oral doses up to 400 mg daily for 2 weeks (80 times the recommended dose). In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite can be removed by haemodialysis (23% of dose over 4 hours).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group; Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH03

Mechanism of action

Saxagliptin is a highly potent (K_i : 1.3 nM), selective, reversible, competitive, DPP-4 inhibitor. In patients with type 2 diabetes, administration of saxagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load, this DPP-4 inhibition resulted in a 2-to 3-fold increase in circulating levels of active incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C-peptide concentrations. The rise in insulin from pancreatic beta-cells and the decrease in glucagon from pancreatic alpha-cells were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. Saxagliptin improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes.

Clinical safety and efficacy

A total of 4,148 patients with type 2 diabetes, including 3,021 patients treated with, saxagliptin were randomised in 6 double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control. In these studies 634 patients were 65 years and older, while 59 patients were 75 years and older. Treatment with saxagliptin 5 mg once daily produced clinically relevant and statistically significant improvements in haemoglobin A1c (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG) compared to placebo in monotherapy, in combination with metformin (initial or add-on therapy), in combination with a sulphonylurea, and in combination with a thiazolidinedione (see Table 2). There was also no apparent change in body weight associated with saxagliptin. Reductions in HbA1c were seen across subgroups including gender, age, race, and baseline body mass index (BMI) and higher baseline HbA1c was associated with a greater adjusted mean change from baseline with saxagliptin.

Saxagliptin as monotherapy

Two double-blind, placebo-controlled studies of 24-week duration were conducted to evaluate the efficacy and safety of saxagliptin monotherapy in patients with type 2 diabetes. In both studies, once-daily treatment with saxagliptin provided significant improvements in HbA1c.

Saxagliptin add-on to metformin therapy

An add-on to metformin placebo-controlled study of 24-week duration was conducted to evaluate the efficacy and safety of saxagliptin in combination with metformin in patients with inadequate glycaemic control (HbA1c 7-10%) on metformin alone. Saxagliptin provided significant improvements in HbA1c, FPG and PPG compared to placebo.

Controlled long-term study extension

Patients who completed all visits during the initial 24-week study period without need for hyperglycaemia rescue therapy were eligible to enter a controlled long-term study extension. Patients who received saxagliptin plus metformin in the initial 24-week study period maintained the same dose of saxagliptin in the long-term extension. Treatment with saxagliptin 5 mg plus metformin was associated with a greater reduction in HbA1c than in the placebo plus metformin group, and this effect was sustained up to Week 102. The HbA1c change for saxagliptin 5 mg plus metformin compared to placebo plus metformin was – 0.7% at Week 102.

Saxagliptin in combination with metformin as initial therapy

A 24-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin as initial combination therapy in treatment-naïve patients with inadequate glycaemic control (HbA1c 8-12%). Initial therapy with the combination of saxagliptin 5 mg plus metformin provided significant improvements in HbA1c, FPG and PPG compared to with either saxagliptin or metformin alone as initial therapy. Reductions in HbA1c from baseline to Week 24 were observed in all evaluated subgroups defined by baseline HbA1c, with greater reductions observed in patients with a baseline HbA1c $\geq 10\%$ (see Table 2).

Saxagliptin add-on to glibenclamide therapy

An add-on placebo-controlled study of 24-week duration was conducted to evaluate the efficacy and safety of saxagliptin in combination with glibenclamide in patients with inadequate glycaemic control at enrolment (HbA1c 7.5-10%) on a sub-maximal dose of glibenclamide alone. Saxagliptin in combination with a fixed, intermediate dose of a sulphonylurea (glibenclamide 7.5 mg) was compared to titration to a higher dose of glibenclamide (approximately 92% of patients in the placebo plus glibenclamide group were up-titrated to a final total daily dose of 15 mg). Saxagliptin provided significant improvements in HbA1c, FPG and PPG compared to titration to a higher dose of glibenclamide.

Saxagliptin add-on to thiazolidinedione therapy

A placebo-controlled study of 24-week duration was conducted to evaluate the efficacy and safety of saxagliptin in combination with a thiazolidinedione (TZD) in patients with inadequate glycaemic control (HbA1c 7-10.5%) on TZD alone. Saxagliptin provided significant improvements in HbA1c, FPG and PPG compared to placebo.

Table 2. Key efficacy results of Onglyza 5 mg per day in placebo-controlled monotherapy trials and in add-on combination therapy trials

	Mean baseline HbA _{1c} (%)	Mean change ² from baseline HbA _{1c} (%) at Week 24	Placebo-corrected mean change in HbA _{1c} (%) at Week 24 (95% CI)
MONOTHERAPY STUDIES			
• Study CV181011 (n=103)	8.0	-0.5	-0.6 (-0.9, -0.4) ³
• Study CV181038 (n=69)	7.9	-0.7 (morning)	-0.4 (-0.7, -0.1) ⁴
(n=70)	7.9	-0.6 (evening)	-0.4 (-0.6, -0.1) ⁵
ADD-ON/COMBINATION STUDIES			
• Study CV181014: add-on to metformin (n=186)	8.1	-0.7	-0.8 (-1.0, -0.6) ³
• Study CV181040: add-on to SU ¹ (n=250)	8.5	-0.6	-0.7 (-0.9, -0.6) ³
• Study CV181013: add-on to TZD (n=183)	8.4	-0.9	-0.6 (-0.8, -0.4) ³
• Study CV181039: initial combination with metformin ⁶			
Overall population (n=306)	9.4	-2.5	-0.5 (-0.7, -0.4) ⁷
Baseline HbA _{1c} ≥10% strata (n=107)	10.8	-3.3	-0.6 (-0.9, -0.3) ⁸

n=Randomized patients (primary efficacy-intention-to-treat analysis).

¹Placebo group had uptitration of glibenclamide from 7.5 to 15 mg total daily dose.

² Adjusted mean change from baseline adjusted for baseline value (ANCOVA).

³ p<0.0001 compared to placebo.

⁴p=0.0059 compared to placebo.

⁵p=0.0157 compared to placebo.

⁶ Metformin was uptitrated from 500 to 2000 mg per day as tolerated.

⁷ Mean HbA_{1c} change is the difference between the saxagliptin+metformin and metformin alone groups (p<0.0001).

⁸ Mean HbA_{1c} change is the difference between the saxagliptin+metformin and metformin alone groups.

5.2 Pharmacokinetic properties

The pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Absorption

Saxagliptin was rapidly absorbed after oral administration in the fasted state, with maximum plasma concentrations (C_{max}) of saxagliptin and its major metabolite attained within 2 and 4 hours (T_{max}), respectively. The C_{max} and AUC values of saxagliptin and its major metabolite increased proportionally with the increment in the saxagliptin dose, and this dose-proportionality was observed in doses up to 400 mg. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its major metabolite were 78 ng·h/ml and 214 ng·h/ml, respectively. The corresponding plasma C_{max} values were 24 ng/ml and 47 ng/ml, respectively. The intra-subject coefficients of variation for saxagliptin C_{max} and AUC were less than 12%.

The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site.

Interaction with food

Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with food (a high-fat meal) resulted in no change in saxagliptin C_{max} and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach C_{max} (T_{max}) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

Distribution

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is negligible. Thus, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Biotransformation

The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

Elimination

The mean plasma terminal half-life ($t_{1/2}$) values for saxagliptin and its major metabolite are 2.5 hours and 3.1 hours respectively, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of 14 C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its major metabolite, and total radioactivity respectively. The average renal clearance of saxagliptin (~230 ml/min) was greater than the average estimated glomerular filtration rate (~120 ml/min), suggesting some active renal excretion. For the major metabolite, renal clearance values were comparable to estimated glomerular filtration rate. A total of 22% of the administered radioactivity was recovered in faeces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed medicinal product from the gastrointestinal tract.

Linearity

The C_{max} and AUC of saxagliptin and its major metabolite increased proportionally to the saxagliptin dose. No appreciable accumulation of either saxagliptin or its major metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg.

Special populations

Renal impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a 10 mg oral dose of saxagliptin in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. In subjects with mild (>50 to ≤ 80 ml/min), moderate (≥ 30 to ≤ 50 ml/min), or severe (19-30 ml/min) renal impairment the exposures to saxagliptin were 1.2-, 1.4- and 2.1-fold higher, respectively, and the exposures to BMS-510849 were 1.7-, 2.9-, and 4.5-fold higher, respectively, than those observed in subjects with normal renal function (>80 ml/min).

Hepatic impairment

In subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment the exposures to saxagliptin were 1.1-, 1.4- and 1.8-fold higher, respectively, and the exposures to BMS-510849 were 22%, 7%, and 33% lower, respectively, than those observed in healthy subjects.

Elderly patients (≥ 65 years)

Elderly (65-80 years) had about 60% higher saxagliptin AUC than young patients (18-40 years). This is not considered clinically meaningful, therefore, no dose adjustment for Onglyza is recommended on the basis of age alone.

5.3 Preclinical safety data

In cynomolgus monkeys saxagliptin produced reversible skin lesions (scabs, ulcerations and necrosis) in extremities (tail, digits, scrotum and/or nose) at doses ≥ 3 mg/kg/day. The no effect level (NOEL)

for the lesions is 1 and 2 times the human exposure or saxagliptin and the major metabolite respectively, at the recommended human dose of 5 mg/day (RHD). The clinical relevance of the skin lesions is not known, however clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

Immune related findings of minimal, nonprogressive, lymphoid hyperplasia in spleen, lymph nodes and bone marrow with no adverse sequelae have been reported in all species tested at exposures starting from 7 times the RHD.

Saxagliptin produced gastrointestinal toxicity in dogs, including bloody/mucoid faeces and enteropathy at higher doses with a NOEL 4 and 2 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD.

Saxagliptin was not genotoxic in a conventional battery of genotoxicity studies *in vitro* and *in vivo*. No carcinogenic potential was observed in two-year carcinogenicity assays with mice and rats.

Effects on fertility were observed in male and female rats at high doses producing overt signs of toxicity. Saxagliptin was not teratogenic at any doses evaluated in rats or rabbits. At high doses in rats, saxagliptin caused reduced ossification (a developmental delay) of the foetal pelvis and decreased foetal body weight (in the presence of maternal toxicity), with a NOEL 303 and 30 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD. In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (NOEL 158 and 224 times the human exposure for saxagliptin and the major metabolite, respectively at RHD). In a pre- and postnatal developmental study in rats, saxagliptin caused decreased pup weight at maternally toxic doses, with NOEL 488 and 45 times the human exposure for saxagliptin and the major metabolite, respectively at RHD. The effect on offspring body weights were noted until postnatal day 92 and 120 in females and males, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Cellulose microcrystalline (E460i)
Croscarmellose sodium (E468)
Magnesium stearate

Film coating:

Polyvinyl alcohol
Macrogol/3350
Titanium dioxide (E171)
Talc (E553b)
Iron oxide red (E172)

Printing ink:

Shellac
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu/Alu blister.

Pack sizes of 14, 28, 56 and 98 film-coated tablets in non-perforated blisters.

Pack sizes of 14, 28, 56 and 98 film-coated tablets in non-perforated calendar blisters.

Pack sizes of 30x1 and 90x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu/>.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Onglyza 5 mg film-coated tablets
Saxagliptin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg saxagliptin (as hydrochloride).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablets
56 film-coated tablets
90x1 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onglyza 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PERFORATED/NON-PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

Onglyza 5 mg tablets
Saxagliptin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTERS (NON-PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

Onglyza 5 mg tablets
Saxagliptin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Onglyza 5 mg film-coated tablets Saxagliptin

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse, or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Onglyza is and what it is used for
2. Before you take Onglyza
3. How to take Onglyza
4. Possible side effects
5. How to store Onglyza
6. Further information

1. WHAT ONGLYZA IS AND WHAT IT IS USED FOR

Onglyza contains the active substance saxagliptin, which belongs to a group of medicines called ‘oral anti-diabetics’. They work by helping to control the level of sugar in your blood.

Onglyza is used for ‘type 2 diabetes’, if the disease cannot be adequately controlled with one oral anti-diabetic medicine, diet and exercise. Onglyza is used together with another oral anti-diabetic medicine.

It is important to keep following the advice about diet and exercise that you have been given by your doctor or nurse.

2. BEFORE YOU TAKE ONGLYZA

Do not take Onglyza

- if you are allergic (hypersensitive) to saxagliptin or any of the other ingredients of Onglyza (listed in Section 6, ‘What Onglyza contains’).

Take special care with Onglyza

Check with your doctor or pharmacist before taking Onglyza if you:

- have type 1 diabetes (your body does not produce any insulin) or diabetic ketoacidosis (a complication of diabetes with high blood sugar, rapid weight loss, nausea or vomiting). Onglyza should not be used to treat these conditions;
- are taking an anti-diabetic medicine known as ‘sulphonylurea’, your doctor may want to reduce your dose of sulphonylurea when you take it together with Onglyza in order to avoid low blood sugar;
- have had allergic reactions to any other medicines that you take to control the amount of sugar in your blood;
- have a disease or take a medicine that can reduce your defense against infections;
- suffer from heart failure;
- have moderate to severe kidney problems, then Onglyza is not recommended for you;
- have moderate or severe liver problems. If you have severe liver problems, then Onglyza is not recommended for you

Diabetic skin lesions are a common complication of diabetes. Rash has been seen with Onglyza and with certain anti-diabetic medicines in the same class as Onglyza. You are advised to follow the recommendations for skin and foot care that you are given by your doctor or nurse.

Onglyza is not recommended for children and adolescents under 18 years.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription.

In particular, you should tell your doctor if you are using medicines containing any of the following active substances:

- Carbamazepine, phenobarbital or phenytoin. These may be used to control fits (seizures) or chronic pain.
- Dexamethasone – a steroid medicine. This may be used to treat inflammation in different body parts and organs.
- Rifampicin. This is an antibiotic used to treat infections such as tuberculosis
- Ketoconazole. This may be used to treat fungal infections.
- Diltiazem. This is a medicine used to lower blood pressure.

Taking Onglyza with food and drink

You can take Onglyza with or without food.

Pregnancy and breast-feeding

Talk to your doctor before you take Onglyza if you are pregnant or plan to become pregnant. You should not use Onglyza if you are pregnant.

Talk to your doctor if you want to breast-feed while taking this medicine. It is not known if Onglyza passes into human breast milk.

Driving and using machines

If you feel dizzy while taking Onglyza, do not drive or use any tools or machines.

Important information about some of the ingredients of Onglyza

Onglyza contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ONGLYZA

Always take Onglyza exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose of Onglyza is one 5 mg tablet once a day.

Your doctor will prescribe Onglyza together with another oral anti-diabetic medicine. Remember to take this other medicine as directed by your doctor to achieve the best results for your health.

How to take Onglyza

Swallow the tablet whole with some water. You can take the tablet with or without food. The tablet can be taken at any time of the day, however try to take your tablet at the same time each day. This will help you to remember to take it.

If you take more Onglyza than you should

If you take more Onglyza tablets than you should, talk to a doctor straight away.

If you forget to take Onglyza

- If you forget to take a dose of Onglyza, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose. Never take two doses on the same day.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Onglyza can cause side effects, although not everybody gets them.

Some symptoms need immediate medical attention:

You should stop taking Onglyza and see your doctor immediately if you experience the following symptoms of low blood sugar: trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change, vagueness or confusion (hypoglycaemia).

Side effects below may occur with certain frequencies, which are defined as follows:

- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000
- Not known: frequency cannot be estimated from the available data

Some patients have had the following side effects while taking Onglyza and metformin:

- Common: infection of the upper airways, infection of the urinary tract, inflamed stomach or gut usually caused by an infection (gastroenteritis), infection of the upper airways with a feeling of pain and fullness behind your cheeks and eyes (sinusitis), inflamed nose or throat (nasopharyngitis) (signs of this may include a cold or a sore throat), headache, muscle pain (myalgia) vomiting, inflammation of the stomach (gastritis) and indigestion (dyspepsia).
- Uncommon: joint pain (arthralgia) and difficulties in getting or maintaining an erection (erectile dysfunction).

Some patients have had the following side effects while taking Onglyza and a sulphonylurea:

- Very common: low blood sugar (hypoglycaemia)
- Common: infection of the upper airways, infection of the urinary tract, inflamed stomach or gut usually caused by an infection (gastroenteritis), infection of the upper airways with a feeling of pain and fullness behind your cheeks and eyes (sinusitis), headache and vomiting.
- Uncommon: fatigue, abnormal lipid (fatty acids) levels (dyslipidemia, hypertriglyceridemia).

Some patients have had the following side effects while taking Onglyza and a thiazolidinedione:

- Common: infection of the upper airways, infection of the urinary tract, inflamed stomach or gut usually caused by an infection (gastroenteritis), infection of the upper airways with a feeling of pain and fullness behind your cheeks and eyes (sinusitis), headache, vomiting, swelling of the hands, ankles or feet (peripheral oedema).

Some patients have had the following additional side effect while taking Onglyza alone: Common: dizziness.

Some patients have had a small reduction in the number of one type of white blood cells (lymphocytes) shown in a blood test. In addition, some patients have reported rash and skin reactions (hypersensitivity) while taking Onglyza.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ONGLYZA

Keep out of the reach and sight of children.

Do not use Onglyza after the expiry date which is stated on the blister and the carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not use Onglyza if the package is damaged or shows signs of tampering.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Onglyza contains

- The active substance is saxagliptin.

Each Onglyza film-coated tablet contains 5 mg saxagliptin (as hydrochloride).

- The other ingredients are

Tablet core: lactose monohydrate, cellulose microcrystalline (E460i), croscarmellose sodium (E468), magnesium stearate.

Film-coating: polyvinyl alcohol, macrogol/3350, titanium dioxide (E171) and talc (E553b). Onglyza tablets also contain iron oxide red (E172).

Printing ink: shellac, indigo carmine aluminium lake (E132).

What Onglyza looks like and contents of the pack

- Onglyza 5 mg film-coated tablets are pink, biconvex, round. They have “5” printed on one side and “4215” printed on the other side, in blue ink.
- Onglyza is available in aluminium foil blister. The pack sizes are 14, 28, 56, or 98 film-coated tablets in non-perforated blisters, 14, 28, 56, or 98 film-coated tablets in non-perforated calendar blisters and 30x1 or 90x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

Manufacturer
Bristol-Myers Squibb Company
Contrada Fontana del Ceraso
03012 Anagni (FR)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
BRISTOL-MYERS SQUIBB BELGIUM
S.A./N.V.
Tél/Tel: + 32 2 352 74 60

Luxembourg/Luxemburg
BRISTOL-MYERS SQUIBB BELGIUM
S.A./N.V.
Tél/Tel: + 32 2 352 74 60

България
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Тел.: + 359 800 12 400

Magyarország
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel.: + 36 1 301 9700

Česká republika
BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 420 221 016 111

Malta
BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

Danmark
BRISTOL-MYERS SQUIBB
Tlf: + 45 45 93 05 06

Nederland
BRISTOL-MYERS SQUIBB BV
Tel: + 31 34 857 42 22

Deutschland
BRISTOL-MYERS SQUIBB GMBH & CO.
KGAA
Tel: + 49 89 121 42 0

Norge
BRISTOL-MYERS SQUIBB NORWAY LTD
Tlf: + 47 67 55 53 50

Eesti
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 372 640 1301

Österreich
BRISTOL-MYERS SQUIBB GESMBH
Tel: + 43 1 60 14 30

Ελλάδα
BRISTOL-MYERS SQUIBB A.E.
Τηλ: + 30 210 6074300

Polska
BRISTOL-MYERS SQUIBB POLSKA SP. Z
O.O.
Tel.: + 48 22 5796666

España
BRISTOL-MYERS SQUIBB, S.A.
Tel: + 34 91 456 53 00

Portugal
BRISTOL-MYERS SQUIBB FARMACÊUTICA
PORTUGUESA, S.A.
Tel: + 351 21 440 70 00

France
BRISTOL-MYERS SQUIBB SARL
Tél: + 33 (0)810 410 500

România
BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 40 (0)21 272 16 00

Ireland
BRISTOL-MYERS SQUIBB

Slovenija
BRISTOL-MYERS SQUIBB SPOL. S R.O.

PHARMACEUTICALS LTD
Tel: + 353 (1 800) 749 749

Tel: + 386 1 236 47 00

Ísland

VISTOR HFSími:
+ 354 535 7000

Slovenská republika

BRISTOL-MYERS SQUIBB SPOL. S R.O.
Tel: + 421 2 59298411

Italia

BRISTOL-MYERS SQUIBB S.R.L.
Tel: + 39 06 50 39 61

Suomi/Finland

OY BRISTOL-MYERS SQUIBB (FINLAND)
ABPuh/
Tel: + 358 9 251 21 230

Κύπρος

ΑΚΗΣ ΠΑΝΑΓΙΩΤΟΥ & ΥΙΟΣ Ε.Π.Ε.
Τηλ: + 357 22 677038

Sverige

BRISTOL-MYERS SQUIBB AB
Tel: + 46 8 704 71 00

Latvija

BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 371 750 21 85

United Kingdom

BRISTOL-MYERS SQUIBB
PHARMACEUTICALS LTD
Tel: + 44 (0800) 731 1736

Lietuva

BRISTOL-MYERS SQUIBB
GYÓGYSZERKERESKEDELMI KFT.
Tel: + 370 5 2790 762

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Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu>