8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD. When administered to rats in combination with metformin, saxagliptin was not teratogenic nor embryolethal at exposures 21 times the saxagliptin MRHD. Combination administration of metformin with a higher dose of saxagliptin (109 times the saxagliptin MRHD) was associated with craniorachischisis (a rare neural tube defect characterized by incomplete closure of the skull and spinal column) in two fetuses from a single dam. Metformin exposures in each combination were 4 times the human exposure of 2000 mg daily.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

8.3 Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many

drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of ONGLYZA in pediatric patients have not been established.

8.5 Geriatric Use

In the six, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, 634 (15.3%) of the 4148 randomized patients were 65 years and over, and 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between patients ≥65 years old and the younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. [See *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3).*]

10 OVERDOSAGE

In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

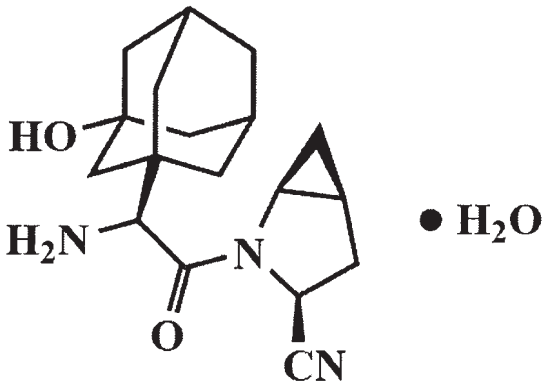
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

11 DESCRIPTION

Saxagliptin is an orally-active inhibitor of the DPP4 enzyme.

Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.$1^{3,7}$]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-

azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is $C_{18}H_{25}N_3O_2 \bullet H_2O$ and the molecular weight is 333.43. The structural formula is:



Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).

Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the dipeptidyl peptidase-4 (DPP4) enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their

bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

12.2 Pharmacodynamics

In patients with type 2 diabetes mellitus, administration of ONGLYZA inhibits DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, ONGLYZA was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the MRHD).

12.3 Pharmacokinetics

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin were similar in healthy subjects and in patients with type 2 diabetes mellitus. The C_{max} and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active 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 average variability (%CV) for AUC and C_{max} for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

Absorption

The median time to maximum concentration (T_{max}) following the 5 mg once daily dose was 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. ONGLYZA may be administered with or without food.

Distribution

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

Metabolism

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite. [See *Drug Interactions (7)*.]

Excretion

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 active 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. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of ONGLYZA 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Specific Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment (N=8 per group) compared to subjects with normal renal function. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease on hemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

The degree of renal impairment did not affect the C_{max} of saxagliptin or its active metabolite. In subjects with mild renal impairment, the AUC values of saxagliptin and its active metabolite were 20% and 70% higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not considered to be clinically relevant, dosage adjustment in patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment, the AUC values of saxagliptin and its active metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. To achieve plasma exposures of saxagliptin and its active metabolite similar to those in patients with normal renal function, the recommended dose is 2.5 mg once daily in patients with moderate and severe renal impairment, as well as in patients with end-stage renal disease requiring hemodialysis. Saxagliptin is removed by hemodialysis.

Hepatic Impairment

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The corresponding C_{max} and AUC of the active metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful. No dosage adjustment is recommended for patients with hepatic impairment.

Body Mass Index

No dosage adjustment is recommended based on body mass index (BMI) which was not identified as a significant covariate on the apparent clearance of saxagliptin or its active metabolite in the population pharmacokinetic analysis.

Gender

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the active metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Geriatric

No dosage adjustment is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for saxagliptin than young subjects (18-40 years). Differences in active metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the active metabolite in young and elderly subjects is likely due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Pediatric

Studies characterizing the pharmacokinetics of saxagliptin in pediatric patients have not been performed.

Race and Ethnicity

No dosage adjustment is recommended based on race. The population pharmacokinetic analysis compared the pharmacokinetics of saxagliptin and its active metabolite in 309 Caucasian subjects with 105 non-Caucasian subjects (consisting of six racial groups). No significant

difference in the pharmacokinetics of saxagliptin and its active metabolite were detected between these two populations.

Drug-Drug Interactions

In Vitro Assessment of Drug Interactions

The metabolism of saxagliptin is primarily mediated by CYP3A4/5.

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate but is not a significant inhibitor or inducer of P-gp.

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Thus, protein binding would not have a meaningful influence on the pharmacokinetics of saxagliptin or other drugs.

In Vivo Assessment of Drug Interactions

Effects of Saxagliptin on Other Drugs

In studies conducted in healthy subjects, as described below, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, or ketoconazole.

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an hOCT-2 substrate, did not alter the pharmacokinetics of metformin in healthy subjects. Therefore, ONGLYZA is not an inhibitor of hOCT-2-mediated transport.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, increased the plasma C_{max} of glyburide by 16%; however, the AUC of glyburide was unchanged. Therefore, ONGLYZA does not meaningfully inhibit CYP2C9-mediated metabolism.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 substrate, increased the plasma C_{max} of pioglitazone by 14%; however, the AUC of pioglitazone was unchanged.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of digoxin. Therefore, ONGLYZA is not an inhibitor or inducer of P-gp-mediated transport.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, did not alter the pharmacokinetics of simvastatin. Therefore, ONGLYZA is not an inhibitor or inducer of CYP3A4/5-mediated metabolism.

Diltiazem: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the plasma C_{max} of diltiazem by 16%; however, the AUC of diltiazem was unchanged.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and multiple doses of ketoconazole (200 mg every 12 hours at steady state), a strong inhibitor of CYP3A4/5 and P-gp, decreased the plasma C_{max} and AUC of ketoconazole by 16% and 13%, respectively.

Effects of Other Drugs on Saxagliptin

Metformin: Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an hOCT-2 substrate, decreased the C_{max} of saxagliptin by 21%; however, the AUC was unchanged.

Glyburide: Coadministration of a single dose of saxagliptin (10 mg) and glyburide (5 mg), a CYP2C9 substrate, increased the C_{max} of saxagliptin by 8%; however, the AUC of saxagliptin was unchanged.

Pioglitazone: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of saxagliptin.

Digoxin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of saxagliptin.

Simvastatin: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, increased the C_{max} of saxagliptin by 21%; however, the AUC of saxagliptin was unchanged.

Diltiazem: Coadministration of a single dose of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the C_{max} of saxagliptin by 63% and the AUC by 2.1-fold. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 44% and 36%, respectively.

Ketoconazole: Coadministration of a single dose of saxagliptin (100 mg) and ketoconazole (200 mg every 12 hours at steady state), a strong inhibitor of CYP3A4/5 and P-gp, increased the C_{max} for saxagliptin by 62% and the AUC by 2.5-fold. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 95% and 91%, respectively.

In another study, coadministration of a single dose of saxagliptin (20 mg) and ketoconazole (200 mg every 12 hours at steady state), increased the C_{max} and AUC of saxagliptin by 2.4-fold and 3.7-fold, respectively. This was associated with a corresponding decrease in the C_{max} and AUC of the active metabolite by 96% and 90%, respectively.

Rifampin: Coadministration of a single dose of saxagliptin (5 mg) and rifampin (600 mg QD at steady state) decreased the C_{max} and AUC of saxagliptin by 53% and 76%, respectively, with a corresponding increase in C_{max} (39%) but no significant change in the plasma AUC of the active metabolite.

Omeprazole: Coadministration of multiple once-daily doses of saxagliptin (10 mg) and omeprazole (40 mg), a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3, did not alter the pharmacokinetics of saxagliptin.

Aluminum hydroxide + magnesium hydroxide + simethicone: Coadministration of a single dose of saxagliptin (10 mg) and a liquid containing aluminum hydroxide (2400 mg), magnesium hydroxide (2400 mg), and simethicone (240 mg) decreased the C_{max} of saxagliptin by 26%; however, the AUC of saxagliptin was unchanged.

Famotidine: Administration of a single dose of saxagliptin (10 mg) 3 hours after a single dose of famotidine (40 mg), an inhibitor of hOCT-1, hOCT-2, and hOCT-3, increased the C_{max} of saxagliptin by 14%; however, the AUC of saxagliptin was unchanged.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Saxagliptin did not induce tumors in either mice (50, 250, and 600 mg/kg) or rats (25, 75, 150, and 300 mg/kg) at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 870 (males) and 1165 (females) times the human exposure at the MRHD of 5 mg/day. In rats, exposures were approximately 355 (males) and 2217 (females) times the MRHD.

Saxagliptin was not mutagenic or clastogenic with or without metabolic activation in an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes. The active metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

In a rat fertility study, males were treated with oral gavage doses for 2 weeks prior to mating, during mating, and up to scheduled termination (approximately 4 weeks total) and females were treated with oral gavage doses for 2 weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at exposures of approximately 603 (males) and 776 (females) times the MRHD. Higher doses that elicited maternal toxicity also increased fetal resorptions (approximately 2069 and 6138 times the MRHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at approximately 6138 times the MRHD.

13.2 Animal Toxicology

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible at ≥20 times the MRHD but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1 to 3 times) the MRHD of 5 mg. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

14 CLINICAL STUDIES

ONGLYZA has been studied as monotherapy and in combination with metformin, glyburide, and thiazolidinedione (pioglitazone and rosiglitazone) therapy. ONGLYZA has not been studied in combination with insulin.

A total of 4148 patients with type 2 diabetes mellitus were randomized in six, double-blind, controlled clinical trials conducted to evaluate the safety and glycemic efficacy of ONGLYZA. A total of 3021 patients in these trials were treated with ONGLYZA. In these trials, the mean age was 54 years, and 71% of patients were Caucasian, 16% were Asian, 4% were black, and 9% were of other racial groups. An additional 423 patients, including 315 who received ONGLYZA, participated in a placebo-controlled, dose-ranging study of 6 to 12 weeks in duration.

In these six, double-blind trials, ONGLYZA was evaluated at doses of 2.5 mg and 5 mg once daily. Three of these trials also evaluated a saxagliptin dose of 10 mg daily. The 10 mg daily dose of saxagliptin did not provide greater efficacy than the 5 mg daily dose. Treatment with ONGLYZA at all doses produced clinically relevant and statistically significant improvements in hemoglobin A1c (A1C), fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to control. Reductions in A1C were seen across subgroups including gender, age, race, and baseline BMI.

ONGLYZA was not associated with significant changes from baseline in body weight or fasting serum lipids compared to placebo.

14.1 Monotherapy

A total of 766 patients with type 2 diabetes inadequately controlled on diet and exercise (A1C $\geq$7% to $\leq$10%) participated in two 24-week, double-blind, placebo-controlled trials evaluating the efficacy and safety of ONGLYZA monotherapy.

In the first trial, following a 2-week single-blind diet, exercise, and placebo lead-in period, 401 patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy, added on to placebo or ONGLYZA. Efficacy was evaluated at the last measurement prior to rescue therapy for patients needing rescue. Dose titration of ONGLYZA was not permitted.

Treatment with ONGLYZA 2.5 mg and 5 mg daily provided significant improvements in A1C, FPG, and PPG compared to placebo (Table 3). The percentage of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 16% in the ONGLYZA 2.5 mg treatment group, 20% in the ONGLYZA 5 mg treatment group, and 26% in the placebo group.

Table 3: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA Monotherapy in Patients with Type 2 Diabetes*

Efficacy Parameter	ONGLYZA 2.5 mg N=102	ONGLYZA 5 mg N=106	Placebo N=95
Hemoglobin A1C (%)	**N=100**	**N=103**	**N=92**
Baseline (mean)	7.9	8.0	7.9
Change from baseline (adjusted mean†)	−0.4	−0.5	+0.2
Difference from placebo (adjusted mean†)	−0.6‡	−0.6‡	
95% Confidence Interval	(−0.9, −0.3)	(−0.9, −0.4)	
Percent of patients achieving A1C <7%	35% (35/100)	38%§ (39/103)	24% (22/92)
Fasting Plasma Glucose (mg/dL)	**N=101**	**N=105**	**N=92**
Baseline (mean)	178	171	172
Change from baseline (adjusted mean†)	−15	−9	+6
Difference from placebo (adjusted mean†)	−21§	−15§	
95% Confidence Interval	(−31, −10)	(−25, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=78**	**N=84**	**N=71**
Baseline (mean)	279	278	283
Change from baseline (adjusted mean†)	−45	−43	−6
Difference from placebo (adjusted mean†)	−39¶	−37§	
95% Confidence Interval	(−61, −16)	(−59, −15)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo

§ p-value <0.05 compared to placebo

¶ Significance was not tested for the 2-hour PPG for the 2.5 mg dose of ONGLYZA.

A second 24-week monotherapy trial was conducted to assess a range of dosing regimens for ONGLYZA. Treatment-naive patients with inadequately controlled diabetes (A1C ≥7% to ≤10%) underwent a 2-week, single-blind diet, exercise, and placebo lead-in period. A total of 365 patients were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of ONGLYZA, or placebo.

Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy added on to placebo or ONGLYZA; the number of patients randomized per treatment group ranged from 71 to 74.

Treatment with either ONGLYZA 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of –0.4% and –0.3%, respectively). Treatment with ONGLYZA 2.5 mg every morning also provided significant improvement in A1C versus placebo (mean placebo-corrected reduction of –0.4%).

14.2 Combination Therapy

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycemic control (A1C ≥7% and ≤10%) on metformin alone. To qualify for enrollment, patients were required to be on a stable dose of metformin (1500-2550 mg daily) for at least 8 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily, for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to existing study medications. Dose titrations of ONGLYZA and metformin were not permitted.

ONGLYZA 2.5 mg and 5 mg add-on to metformin provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to metformin (Table 4). Mean changes from baseline for A1C over time and at endpoint are shown in Figure 1. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the ONGLYZA 2.5 mg add-on to metformin group, 13% in the ONGLYZA 5 mg add-on to metformin group, and 27% in the placebo add-on to metformin group.

Table 4: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Metformin*

Efficacy Parameter	ONGLYZA 2.5 mg + Metformin N=192	ONGLYZA 5 mg + Metformin N=191	Placebo + Metformin N=179
Hemoglobin A1C (%)	**N=186**	**N=186**	**N=175**
Baseline (mean)	8.1	8.1	8.1
Change from baseline (adjusted mean†)	−0.6	−0.7	+0.1
Difference from placebo (adjusted mean†)	−0.7‡	−0.8‡	
95% Confidence Interval	(−0.9, −0.5)	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	37%§ (69/186)	44%§ (81/186)	17% (29/175)
Fasting Plasma Glucose (mg/dL)	**N=188**	**N=187**	**N=176**
Baseline (mean)	174	179	175
Change from baseline (adjusted mean†)	−14	−22	+1
Difference from placebo (adjusted mean†)	−16§	−23§	
95% Confidence Interval	(−23, −9)	(−30, −16)	
2-hour Postprandial Glucose (mg/dL)	**N=155**	**N=155**	**N=135**
Baseline (mean)	294	296	295
Change from baseline (adjusted mean†)	−62	−58	−18
Difference from placebo (adjusted mean†)	−44§	−40§	
95% Confidence Interval	(−60, −27)	(−56, −24)	

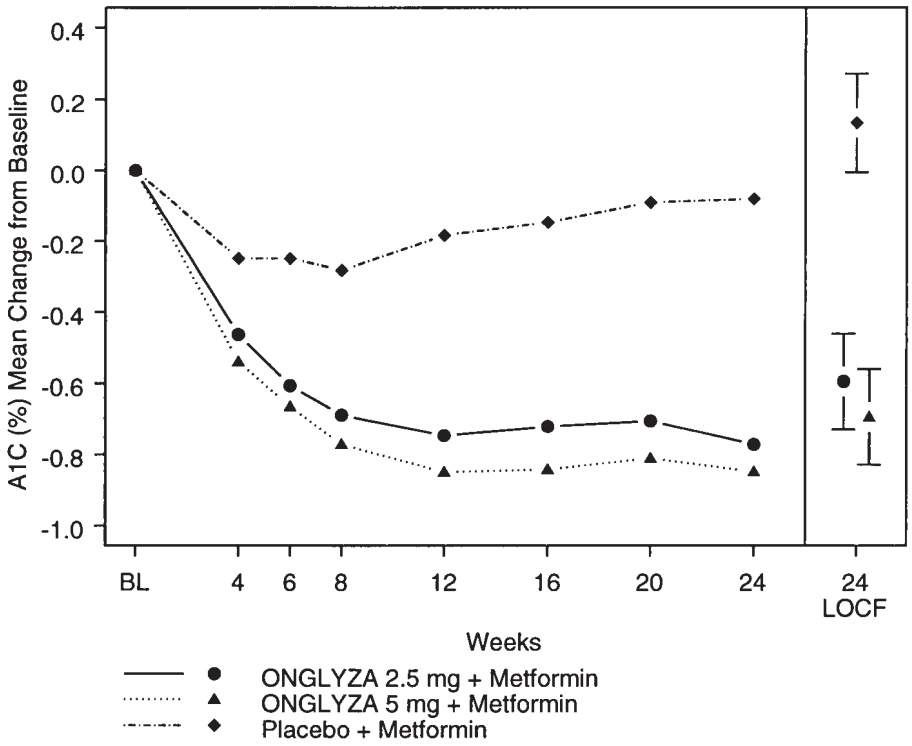
* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin

§ p-value <0.05 compared to placebo + metformin

Figure 1: **Mean Change from Baseline in A1C in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin***



* Includes patients with a baseline and week 24 value.
Week 24 (LOCF) includes intent-to-treat population using last observation on study prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.

Add-On Combination Therapy with a Thiazolidinedione

A total of 565 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a thiazolidinedione (TZD) in patients with inadequate glycemic control (A1C ≥7% to ≤10.5%) on TZD alone. To qualify for enrollment, patients were required to be on a stable dose of pioglitazone (30-45 mg once daily) or rosiglitazone (4 mg once daily or 8 mg either once daily or in two divided doses of 4 mg) for at least 12 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received TZD at their pre-study dose for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg or 5 mg of ONGLYZA or placebo in addition to their current dose of TZD. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to

existing study medications. Dose titration of ONGLYZA or TZD was not permitted during the study. A change in TZD regimen from rosiglitazone to pioglitazone at specified, equivalent therapeutic doses was permitted at the investigator's discretion if believed to be medically appropriate.

ONGLYZA 2.5 mg and 5 mg add-on to TZD provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to TZD (Table 5). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 10% in the ONGLYZA 2.5 mg add-on to TZD group, 6% for the ONGLYZA 5 mg add-on to TZD group, and 10% in the placebo add-on to TZD group.

Table 5: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with a Thiazolidinedione*

Efficacy Parameter	ONGLYZA 2.5 mg + TZD N=195	ONGLYZA 5 mg + TZD N=186	Placebo + TZD N=184
Hemoglobin A1C (%)	**N=192**	**N=183**	**N=180**
Baseline (mean)	8.3	8.4	8.2
Change from baseline (adjusted mean†)	−0.7	−0.9	−0.3
Difference from placebo (adjusted mean†)	−0.4§	−0.6‡	
95% Confidence Interval	(−0.6, −0.2)	(−0.8, −0.4)	
Percent of patients achieving A1C <7%	42%§ (81/192)	42%§ (77/184)	26% (46/180)
Fasting Plasma Glucose (mg/dL)	**N=193**	**N=185**	**N=181**
Baseline (mean)	163	160	162
Change from baseline (adjusted mean†)	−14	−17	−3
Difference from placebo (adjusted mean†)	−12§	−15§	
95% Confidence Interval	(−20, −3)	(−23, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=156**	**N=134**	**N=127**
Baseline (mean)	296	303	291
Change from baseline (adjusted mean†)	−55	−65	−15
Difference from placebo (adjusted mean†)	−40§	−50§	
95% Confidence Interval	(−56, −24)	(−66, −34)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + TZD

§ p-value <0.05 compared to placebo + TZD

Add-On Combination Therapy with Glyburide

A total of 768 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a sulfonylurea (SU) in patients with inadequate glycemic control at enrollment (A1C ≥7.5% to ≤10%) on a submaximal dose of SU alone. To qualify for enrollment, patients were required to be on a submaximal dose of SU for 2 months or greater. In this study, ONGLYZA in combination with a fixed, intermediate dose of SU was compared to titration to a higher dose of SU.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period, and placed on glyburide 7.5 mg once daily. Following the lead-in period, eligible patients with A1C ≥7% to ≤10% were randomized to either 2.5 mg or 5 mg of ONGLYZA add-on to 7.5 mg glyburide or to placebo plus a 10 mg total daily dose of glyburide. Patients who received placebo were eligible to have glyburide up-titrated to a total daily dose of 15 mg. Up-titration of glyburide was not permitted in patients who received ONGLYZA 2.5 mg or 5 mg. Glyburide could be down-titrated in any treatment group once during the 24-week study period due to hypoglycemia as deemed necessary by the investigator. Approximately 92% of patients in the placebo plus glyburide group were up-titrated to a final total daily dose of 15 mg during the first 4 weeks of the study period. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medication. Dose titration of ONGLYZA was not permitted during the study.

In combination with glyburide, ONGLYZA 2.5 mg and 5 mg provided significant improvements in A1C, FPG, and PPG compared with the placebo plus up-titrated glyburide group (Table 6). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 18% in the ONGLYZA 2.5 mg add-on to glyburide group, 17% in the ONGLYZA 5 mg add-on to glyburide group, and 30% in the placebo plus up-titrated glyburide group.

Table 6: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Glyburide*

Efficacy Parameter	ONGLYZA 2.5 mg + Glyburide 7.5 mg N=248	ONGLYZA 5 mg + Glyburide 7.5 mg N=253	Placebo + Up-Titrated Glyburide N=267
Hemoglobin A1C (%)	**N=246**	**N=250**	**N=264**
Baseline (mean)	8.4	8.5	8.4
Change from baseline (adjusted mean†)	−0.5	−0.6	+0.1
Difference from up-titrated glyburide (adjusted mean†)	−0.6‡	−0.7‡	
95% Confidence Interval	(−0.8, −0.5)	(−0.9, −0.6)	
Percent of patients achieving A1C <7%	22%§ (55/246)	23%§ (57/250)	9% (24/264)
Fasting Plasma Glucose (mg/dL)	**N=247**	**N=252**	**N=265**
Baseline (mean)	170	175	174
Change from baseline (adjusted mean†)	−7	−10	+1
Difference from up-titrated glyburide (adjusted mean†)	−8§	−10§	
95% Confidence Interval	(−14, −1)	(−17, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=195**	**N=202**	**N=206**
Baseline (mean)	309	315	323
Change from baseline (adjusted mean†)	−31	−34	+8
Difference from up-titrated glyburide (adjusted mean†)	−38§	−42§	
95% Confidence Interval	(−50, −27)	(−53, −31)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + up-titrated glyburide

§ p-value <0.05 compared to placebo + up-titrated glyburide

Coadministration with Metformin in Treatment-Naive Patients

A total of 1306 treatment-naive patients with type 2 diabetes mellitus participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA coadministered with metformin in patients with inadequate glycemic control (A1C ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naive to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 1-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: ONGLYZA

5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. ONGLYZA was dosed once daily. In the 3 treatment groups using metformin, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2000 mg per day based on FPG. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue as add-on therapy.

Coadministration of ONGLYZA 5 mg plus metformin provided significant improvements in A1C, FPG, and PPG compared with placebo plus metformin (Table 7).

Table 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=320	Placebo + Metformin N=328
Hemoglobin A1C (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	−2.5	−2.0
Difference from placebo + metformin (adjusted mean†)	−0.5‡	
95% Confidence Interval	(−0.7, −0.4)	
Percent of patients achieving A1C <7%	60%§ (185/307)	41% (129/314)
Fasting Plasma Glucose (mg/dL)	**N=315**	**N=320**
Baseline (mean)	199	199
Change from baseline (adjusted mean†)	−60	−47
Difference from placebo + metformin (adjusted mean†)	−13§	
95% Confidence Interval	(−19, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=146**	**N=141**
Baseline (mean)	340	355
Change from baseline (adjusted mean†)	−138	−97
Difference from placebo + metformin (adjusted mean†)	−41§	
95% Confidence Interval	(−57, −25)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue.

† Least squares mean adjusted for baseline value.

‡ p-value <0.0001 compared to placebo + metformin

§ p-value <0.05 compared to placebo + metformin

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONGLYZA™ (saxagliptin) tablets have markings on both sides and are available in the strengths and packages listed in Table 8.

Table 8: ONGLYZA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
5 mg	pink biconvex, round	"5" on one side and "4215" on the reverse, in blue ink	Bottles of 30	0003-4215-11
			Bottles of 90	0003-4215-21
			Bottles of 500	0003-4215-31
			Blister of 100	0003-4215-41
2.5 mg	pale yellow to light yellow biconvex, round	"2.5" on one side and "4214" on the reverse, in blue ink	Bottles of 30	0003-4214-11
			Bottles of 90	0003-4214-21

Storage and Handling

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

17.1 Instructions

Patients should be informed of the potential risks and benefits of ONGLYZA and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Physicians should instruct their patients to read the Patient Package Insert before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be

instructed to inform their doctor or pharmacist if they develop any unusual symptom or if any existing symptom persists or worsens.

17.2 Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C, with a goal of decreasing these levels toward the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust their dose based on changes in renal function tests over time.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

1256316
1256317

Iss July 2009

PATIENT INFORMATION
ONGLYZA (on-GLY-zah)
(saxagliptin)
tablets

Read the Patient Information that comes with ONGLYZA before you start taking it and each time you get a refill. There may be new information. This patient leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is ONGLYZA?

ONGLYZA is a prescription medicine used with diet and exercise to control high blood sugar (hyperglycemia) in adults with type 2 diabetes.

ONGLYZA lowers blood sugar by helping the body increase the level of insulin after meals.

ONGLYZA is unlikely to cause your blood sugar to be lowered to a dangerous level (hypoglycemia) because it does not work well when your blood sugar is low.

ONGLYZA has not been studied in children younger than 18 years old.

What should I tell my healthcare provider before taking ONGLYZA?

Before you take ONGLYZA, tell your healthcare provider about all of your medical conditions, including if you:

- have type 1 diabetes. ONGLYZA should not be used to treat people with type 1 diabetes.
- have a history or risk for diabetic ketoacidosis (high levels of certain acids, known as ketones, in the blood or urine). ONGLYZA should not be used for the treatment of diabetic ketoacidosis.
- have kidney problems
- are taking insulin. ONGLYZA has not been studied with insulin.
- are pregnant or plan to become pregnant. It is not known if ONGLYZA will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breast-feeding or plan to breast-feed. ONGLYZA may be passed in your milk to your baby. Talk with your healthcare provider about the best way to feed your baby while you take ONGLYZA.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

ONGLYZA may affect the way other medicines work, and other medicines may affect how ONGLYZA works. Contact your healthcare provider if you will be starting or stopping certain other types of medications, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of ONGLYZA might need to be changed.

How should I take ONGLYZA?

- Take ONGLYZA by mouth one time each day exactly as directed by your healthcare provider. Do not change your dose without talking to your healthcare provider.
- ONGLYZA can be taken with or without food.
- During periods of stress on the body, such as:
  - fever
  - trauma
  - infection
  - surgery

  Contact your healthcare provider right away as your medication needs may change.
- Your healthcare provider should test your blood to measure how well your kidneys work. You may need a lower dose of ONGLYZA if your kidneys are not working well.
- Your healthcare provider may prescribe ONGLYZA along with other medicines that lower blood sugar.
- Follow your healthcare provider's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.
- If you miss a dose of ONGLYZA, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time unless your healthcare provider tells you to do so. Talk to your healthcare provider if you have questions about a missed dose.
- If you take too much ONGLYZA, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of ONGLYZA?

Common side effects of ONGLYZA include:

- upper respiratory tract infection
- urinary tract infection
- headache

Low blood sugar (hypoglycemia) may become worse in people who already take another medication to treat diabetes, such as sulfonylureas. Tell your healthcare provider if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include:

- shaking
- sweating
- rapid heartbeat
- change in vision
- hunger
- headache
- change in mood

Swelling or fluid retention in your hands, feet, or ankles (peripheral edema) may become worse in people who also take a thiazolidinedione to treat diabetes. If you do not know whether you are already on this type of medication, ask your healthcare provider.

Allergic (hypersensitivity) reactions, such as rash, hives, and swelling of the face, lips, and throat. If you have these symptoms, stop taking ONGLYZA and call your healthcare provider right away.

These are not all of the possible side effects of ONGLYZA. Tell your healthcare provider if you have any side effects that bother you or that do not go away. For more information, ask your healthcare provider.

Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store ONGLYZA?

Store ONGLYZA between 68° to 77°F (20° to 25°C).

Keep ONGLYZA and all medicines out of the reach of children.

General information about the use of ONGLYZA

Medicines are sometimes prescribed for conditions that are not mentioned in patient leaflets. Do not use ONGLYZA for a condition for which it was not prescribed. Do not give ONGLYZA to other people, even if they have the same symptoms you have. It may harm them.

This patient leaflet summarizes the most important information about ONGLYZA. If you would like to know more information about ONGLYZA, talk with your healthcare provider. You can ask your healthcare provider for additional information about ONGLYZA that is written for healthcare professionals. For more information, go to www.ONGLYZA.com or call 1-800-ONGLYZA.

What are the ingredients of ONGLYZA?

Active ingredient: saxagliptin

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

The main goal of treating diabetes is to lower your blood sugar to a normal level.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

ONGLYZA (saxagliptin) tablets

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543
and
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

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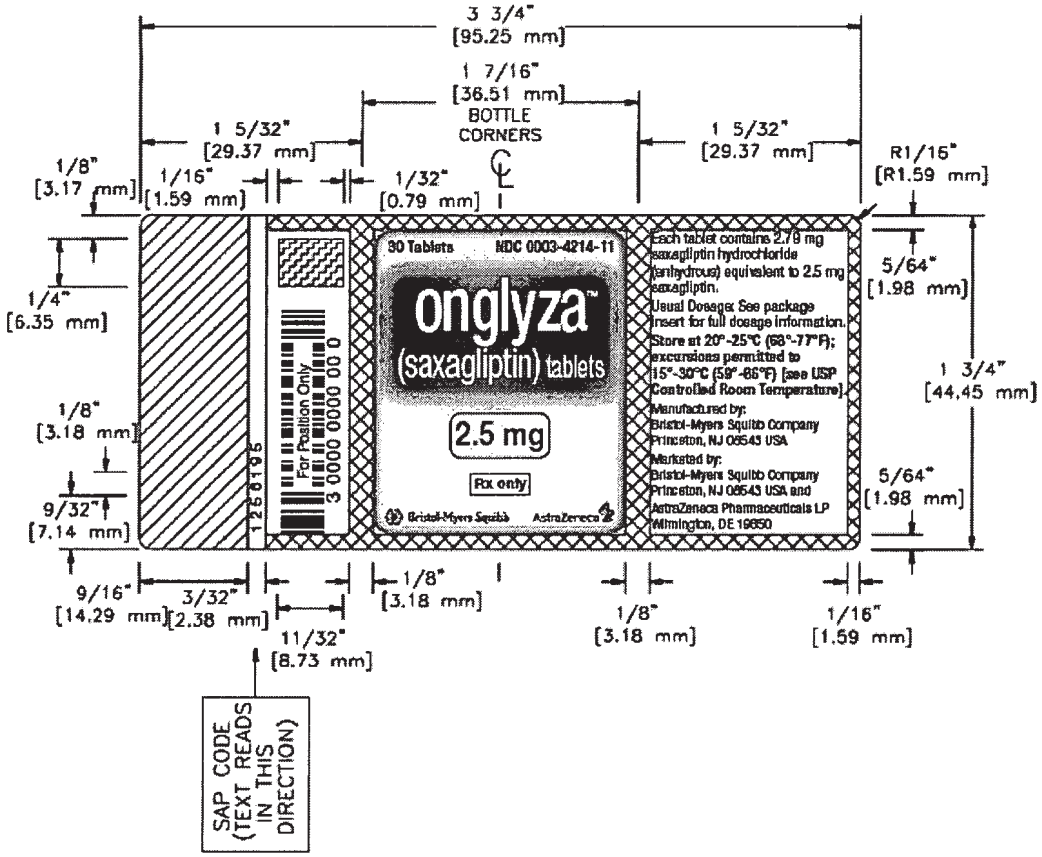
Iss July 2009



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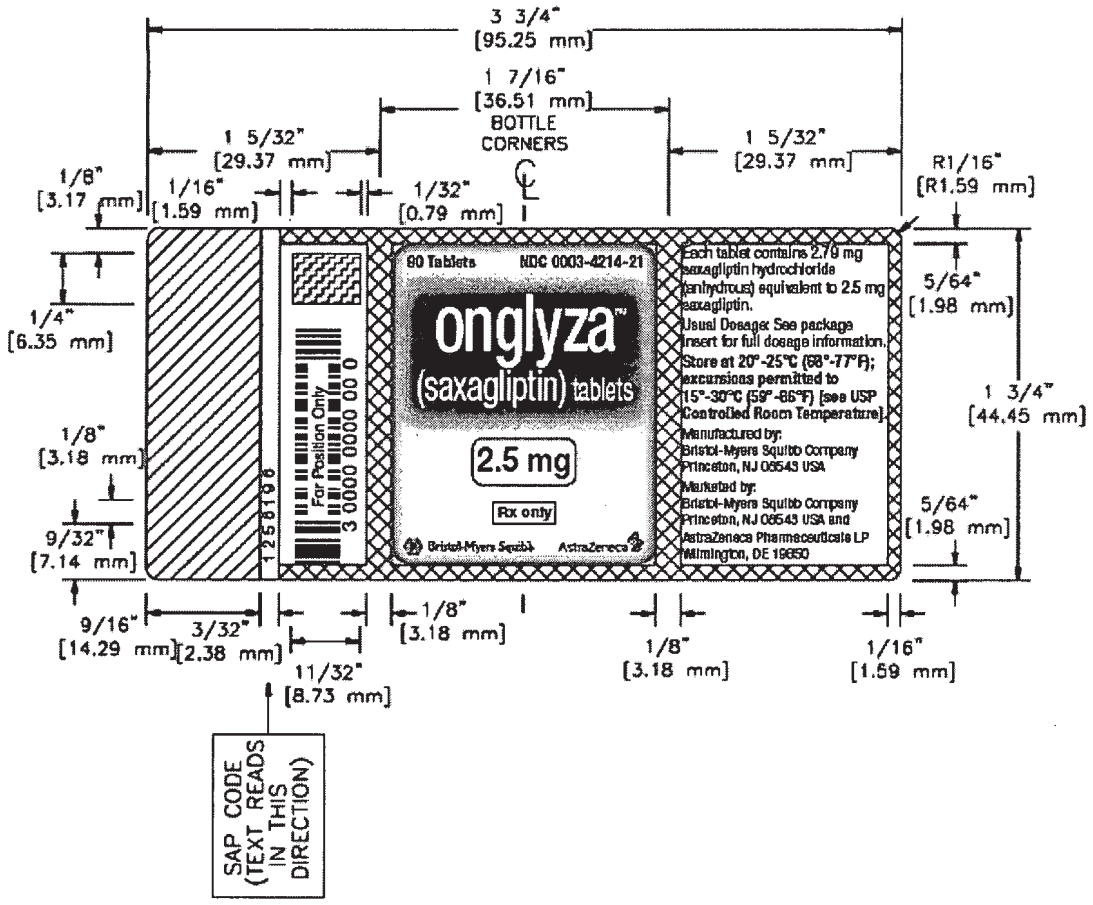

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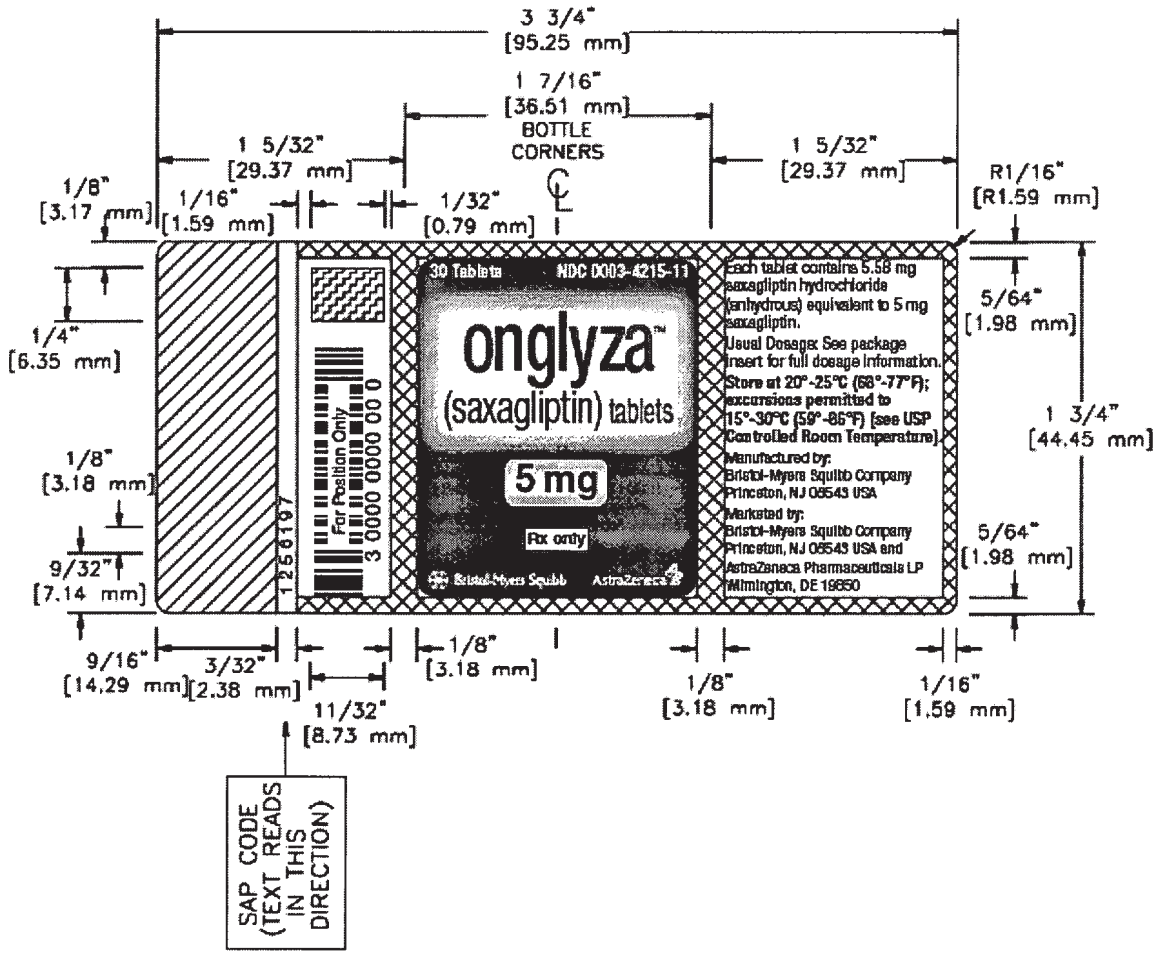
5 mg



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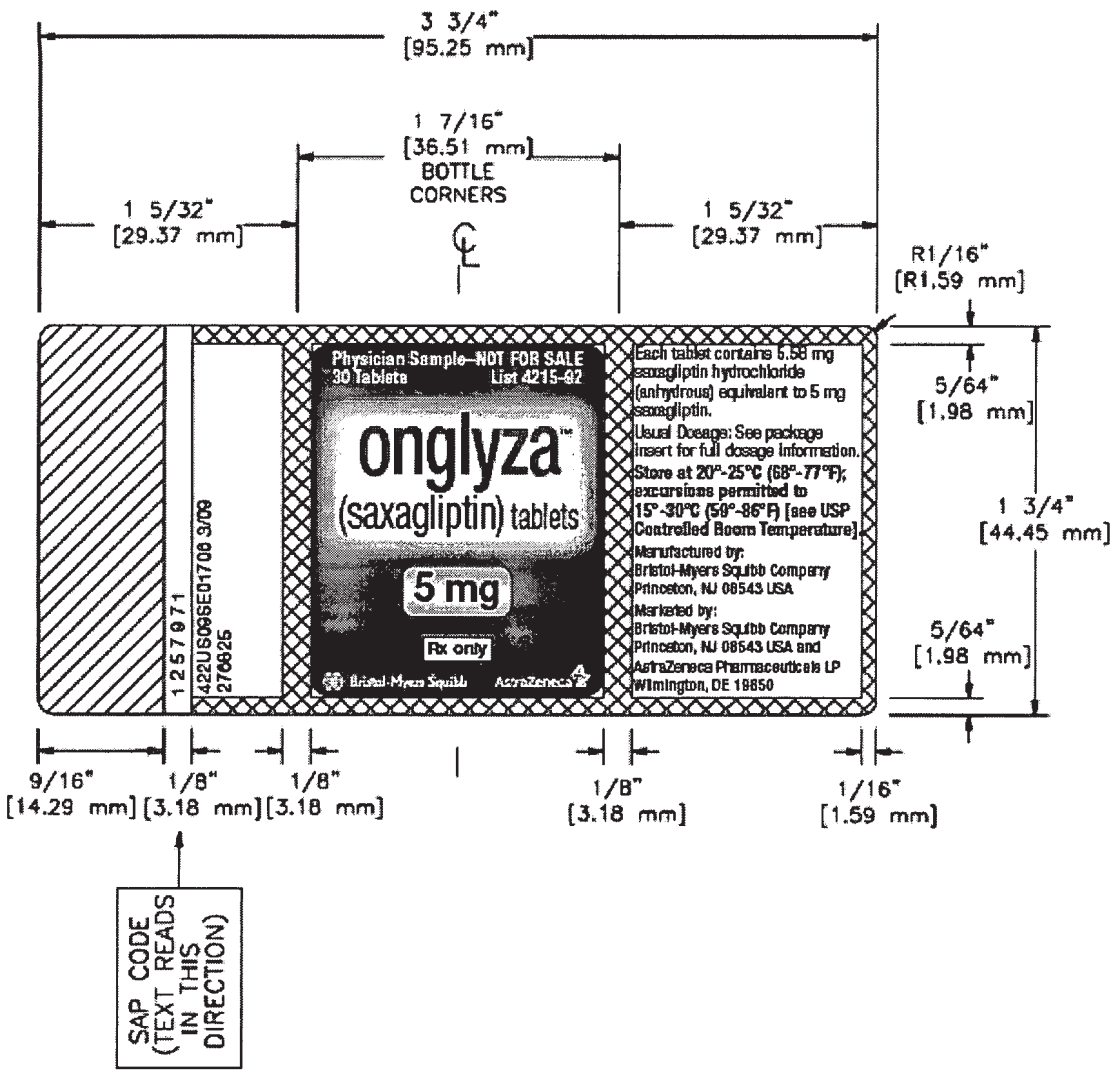

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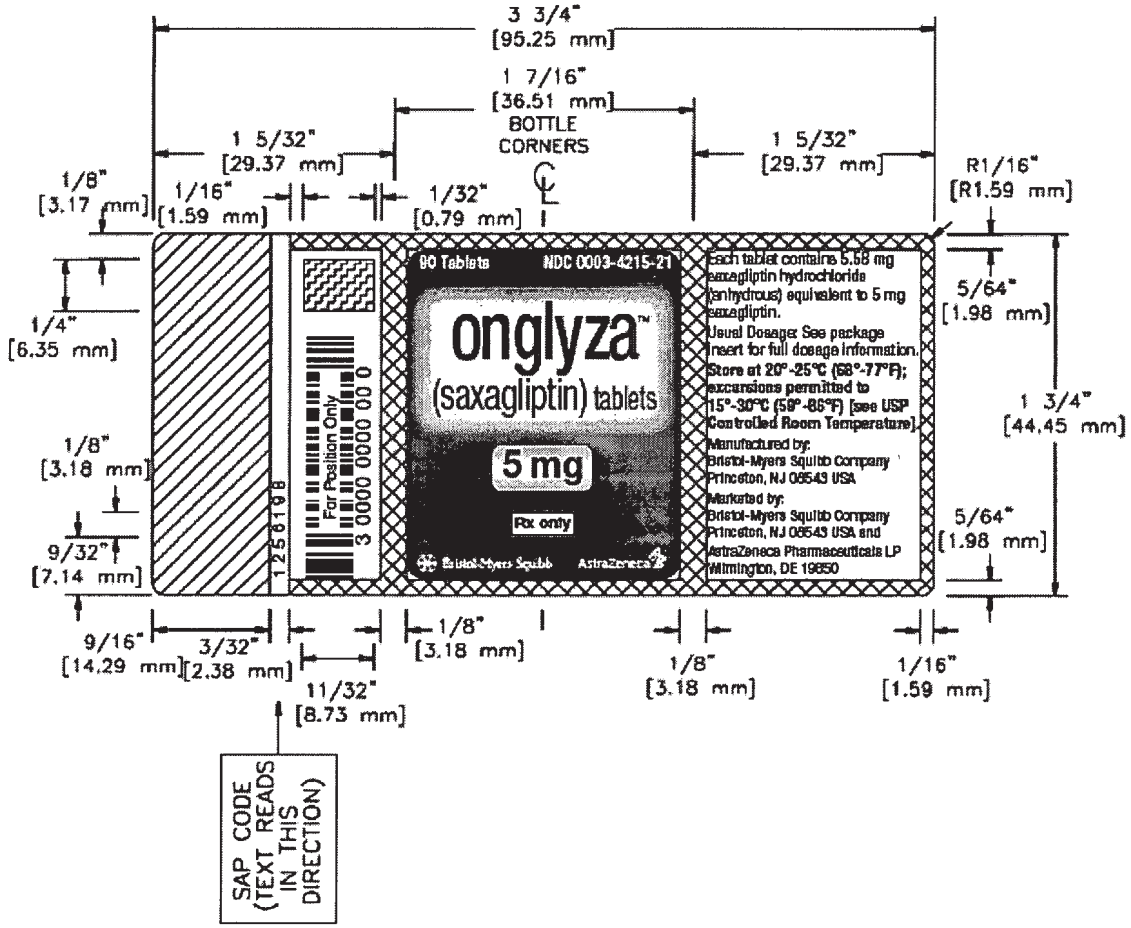

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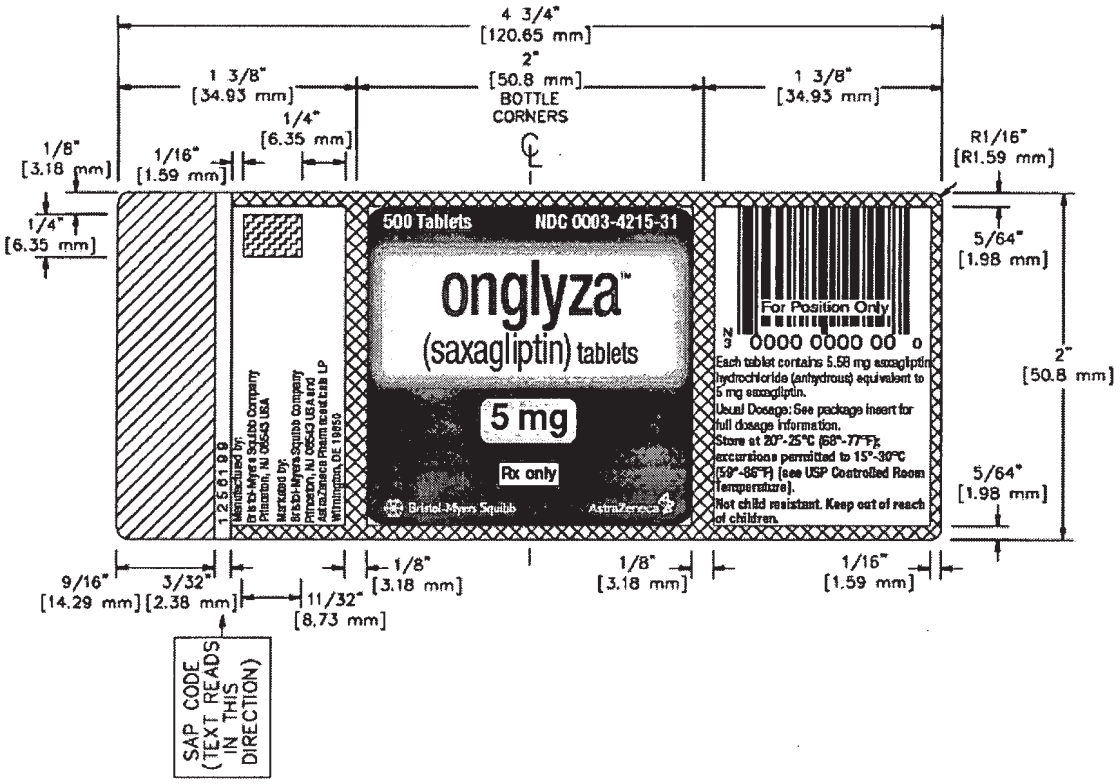

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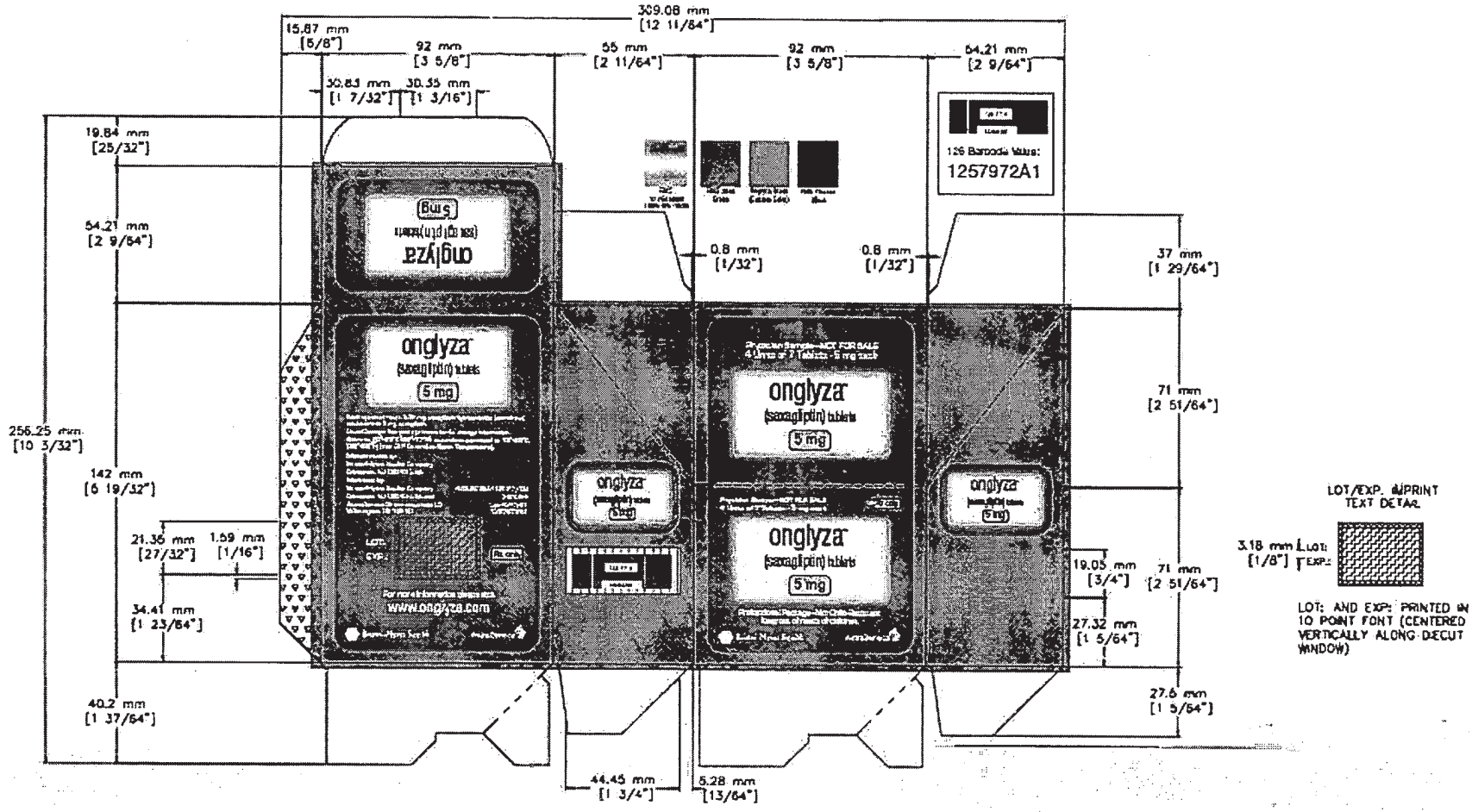

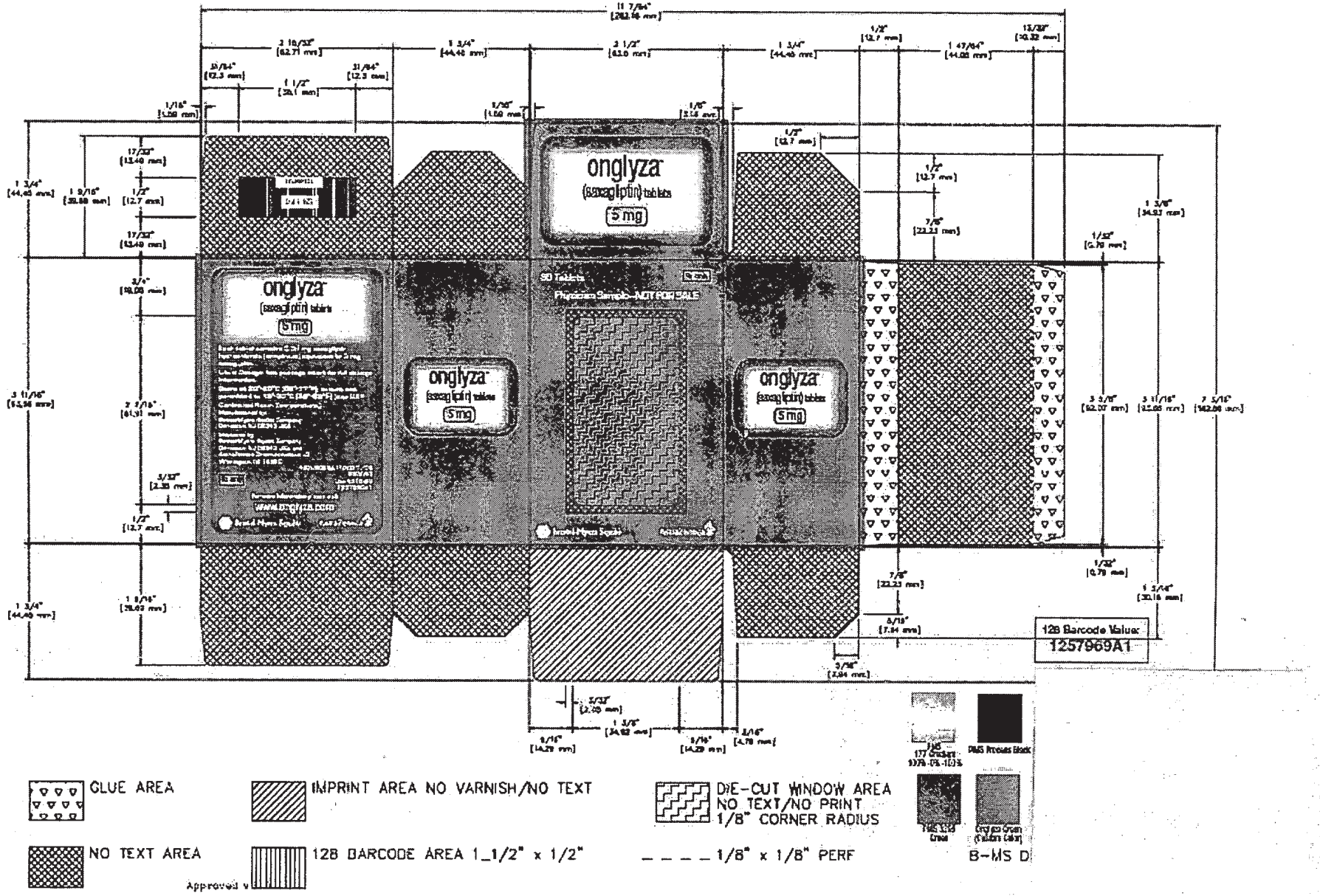

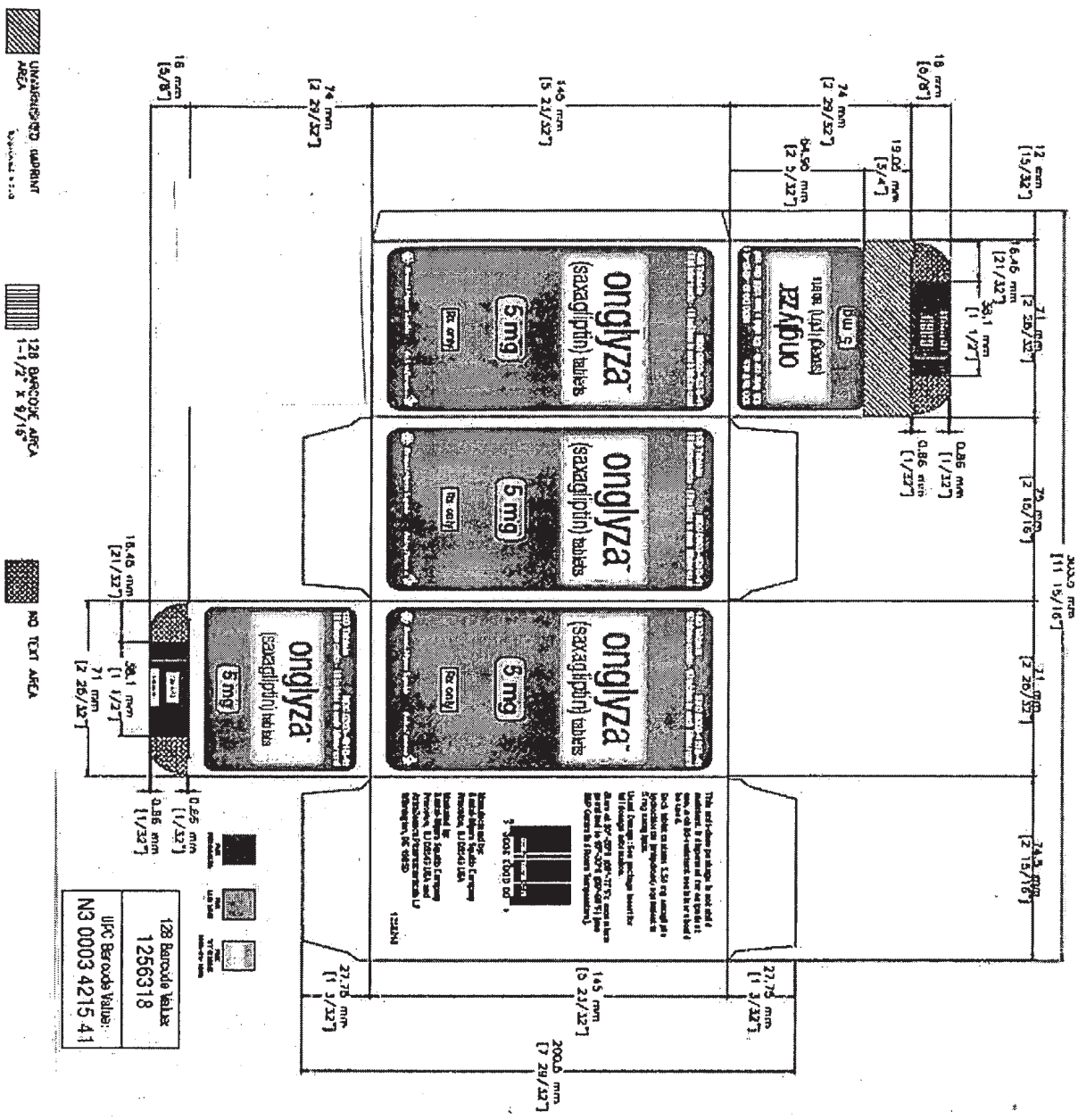

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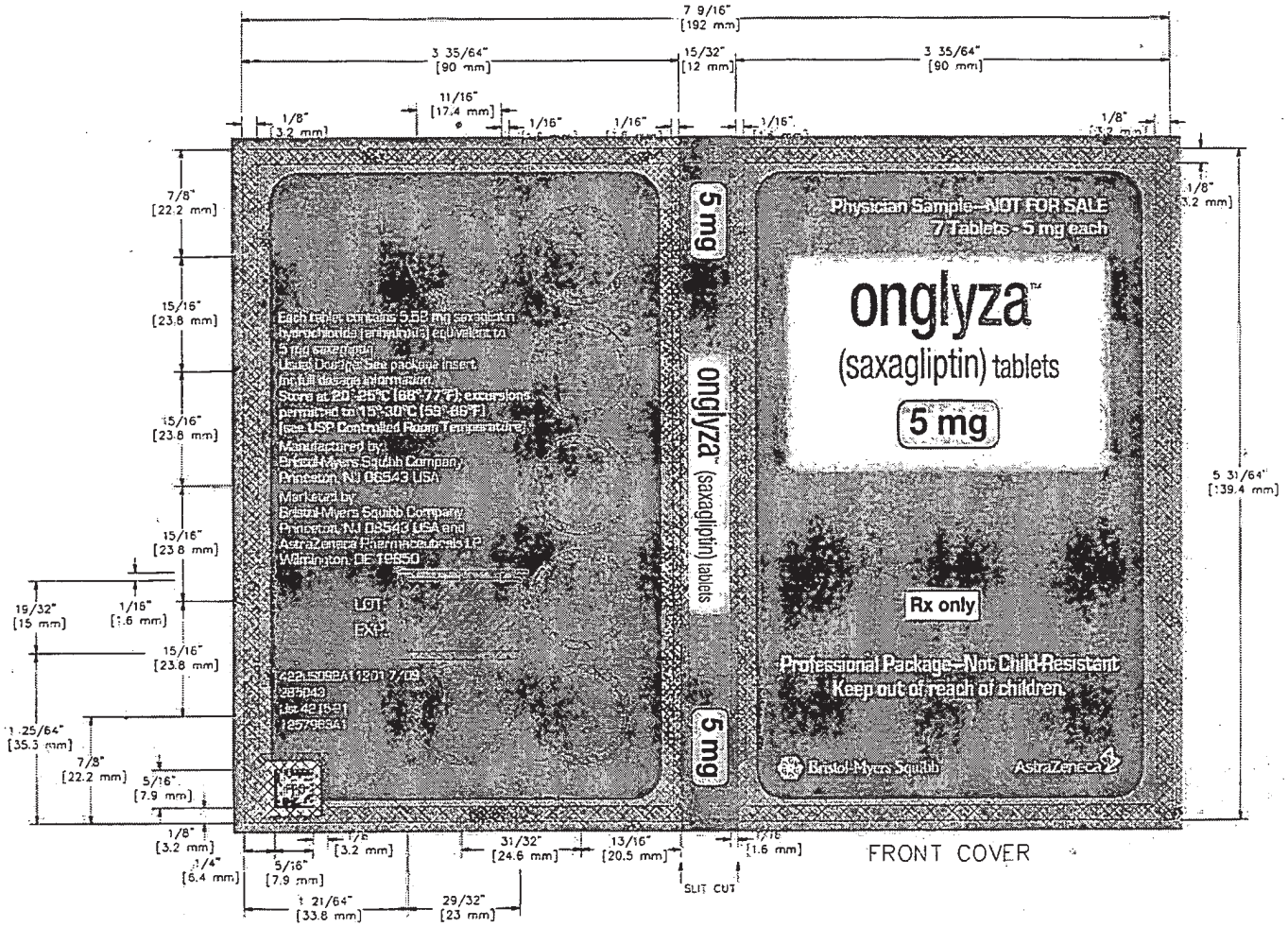

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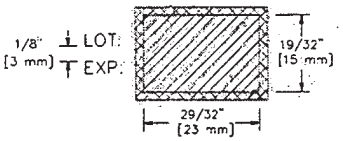

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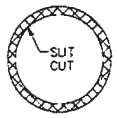
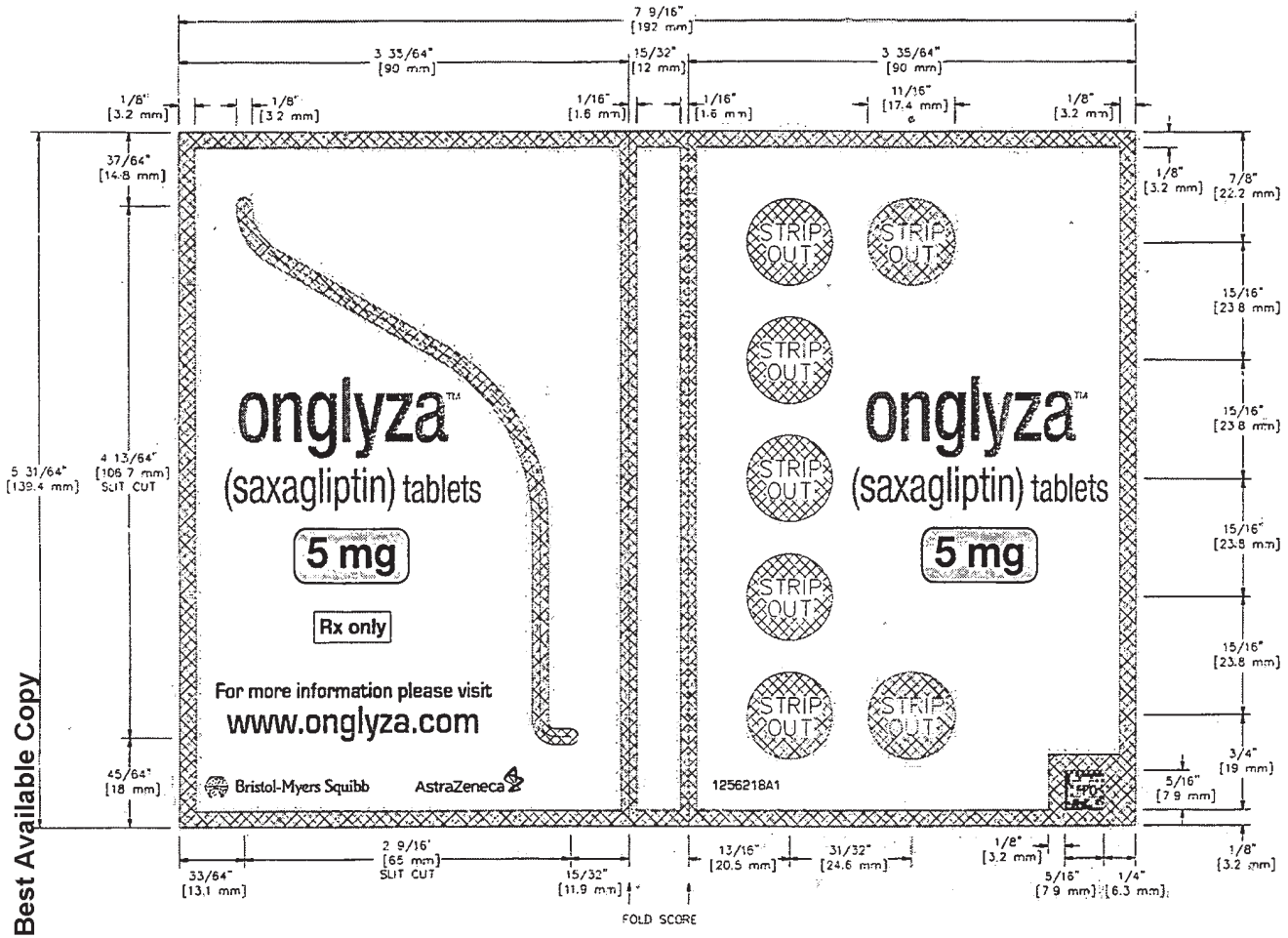
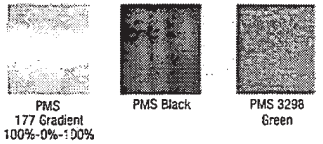


FRONT CARD
(INSIDE)





NO TEXT AREA

DATA MATRIX CODE AREA

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/s/

CURTIS J ROSEBRAUGH
07/31/2009

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9

Maintenance Fee Statement **09/16/2009 03:35 PM EDT**

Patent Number: 6395767

Customer Number: 23914

LOUIS J. WILLE
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,395,767	$900.00	$0.00	11/04/05	09/788,173	05/28/02	02/16/01	04	NO	LA0050 NP

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E

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

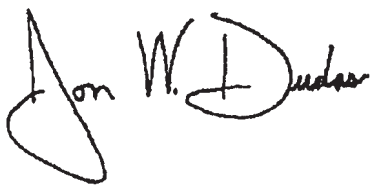
PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 91,
Lines 9-10, should read -- A compound having the structure: --
Line 54, should read -- A compound which is --.

Signed and Sealed this

Twenty-seventh Day of July, 2004



JON W. DUDAS
Acting Director of the United States Patent and Trademark Office

LA0050

UNITED STATES PATENT AND TRADEMARK OFFICE US-NP

CERTIFICATE OF CORRECTION

Rodney

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 7,
Line 6, change "PGI" to -- PG_1 --.

Column 14,
Line 50, insert --  --.

Line 56, between "refers" and "cycloheteroakyl", insert -- to --.
Line 57, between "a" and "atom", insert -- C --.

Column 15,
Line 54, change "γ" to -- β --.

Column 20,
Line 59, "2,1" should be -- 2,3 --.

Column 29,
Line 23, change "w" to -- % --.

Column 30,
Line 2, after "$(M+H)^+$" and before "197", insert -- = --.

Column 32,
Line 62, after "$(M+H)^+$" and before "222", insert -- = --.

Column 33,
Line 3, change "HO" to read -- H_2O --.
Line 7, change "$CH2cl_2$" to read -- CH_2Cl_2 --.
Line 11, after "METHOD", insert -- A --.

Column 34,
Line 62, delete "15".

Column 41,
Line 43, after "was", delete "a".
Line 44, after "over", delete "a".

LA0050

US-NP
Rodney

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 43,
Line 36, delete "E".
Line 55, change "48.61" to -- 8.61 --.

Column 44,
Line 39, change "200" to -- 300 --.

Column 46,
Line 58, change "ter" to -- water --.
Line 58, after "20" and before "Detection", insert -- mL/min. --.
Line 65, change "dimethylcylopentanone" to -- dimethylcyclopentanone --.

Column 52,
Line 64, change "25" to -- 28 --.

Column 53,
Line 31, change "OSO_4" to -- OsO4 --.
Line 65, after "100%" and before "Solvent A", insert -- B, --.
Line 66, after "vent B =" and before "MeOH", insert -- 90% --.

Column 62,
Line 67, change "549" to -- 540 --.

Column 66,
Line 24, change "$CH2Cl_2$" to read -- CH_2Cl_2 --.

Column 69,
Line 21, change "9" to -- 8 --.
Line 30, change "Hbl" to -- HCl --.

Column 70,
Line 56, move "Step 1" to line 65.

Column 72,
Line 36, change "50°" to -- 5° --.
Line 65, change "2.2(" to -- 2.28 --.
Line 65, change "30mL2" to -- 30 mL --.

Column 73,
Line 25, change "the n" to -- then --.
Line 26, change "et her" to -- ether --.

LA0050

US- NP
Rodney

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,395,767 B2
DATED : May 28, 2002
INVENTOR(S) : Jeffrey A. Robl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 74,
Line 32, change "50°" to -- 5° --.

Column 79,
Line 61, change "100" to -- 10% --.

Column 82,
Line 65, change "10EtOAc" to -- 10% EtOAc --.

Column 84,
Line 34, change "NS" to -- MS --.

Column 92,
Line 42, change "APR" to -- AR --.

Signed and Sealed this

Twenty-ninth Day of November, 2005

JON W. DUDAS
Director of the United States Patent and Trademark Office

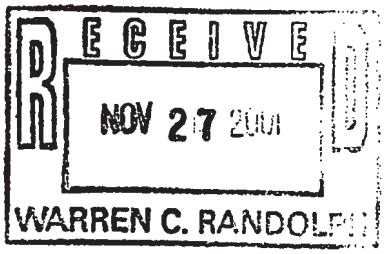
F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,634



Bristol-Myers Squibb
Attention: Warren Randolph
Director, Regulatory Science
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Randolph:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 63,634

Sponsor: Bristol-Myers Squibb

Name of Drug: BMS-477118 for Oral Administration

Date of Submission: November 8, 2001

Date of Receipt: November 8, 2001

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before December 8, 2001, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at 301-827-6381.

Sincerely,

{See appended electronic signature page}

James T. Cross
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Cross
11/16/01 04:21:56 PM

6

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-350

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
Attention: Pamela Smith, M.D.
Group Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, NJ 08543-400

Dear Dr. Smith:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ONGLYZA (saxagliptin) Tablet 2.5 mg, 5mg

Date of Application: June 30, 2008

Date of Receipt: June 30, 2008

Our Reference Number: NDA 22-350

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 29, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED
JUL 2 9 2008
PAMELA SMITH, M.D.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rachel E Hartford
7/21/2008 09:22:25 AM

IND 63,634 / NDA 22-350

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
08-NOV-2001	SN0000	INITIAL APPLICATION	SUBMISSION	INITIAL IND DPP4 FOR TYPE 2 DIABETES.
16-NOV-2001		CORRESPONDENCE		FDA LETTER RE: ACKNOWLDEGE RECEIPT OF IND FOR BMS-477118 FOR ORAL ADMINISTRATION. THE IND WAS ASSIGNED NUMBER 63,634.
20-NOV-2001	SN0001	OTHER	SUBMISSION	OTHER: RESPONSE TO FDA REQUEST. DR. COLERANGLE'S TWO QUESTIONS RE: DEGRADANT BMS-537679 AND CMAX VALUES.
21-NOV-2001		CORRESPONDENCE	TELEPHONE	TEL CONTACT RE: OPHTHALMOSCOPIC RESULTS. DR. COLERANGLE CALLED TO REQ. THE OPHTHALMOSCOPIC DATA. HE WAS INFORMED THAT THE DATA WAS SUBMITTED IN THE APPENDIX OF THE RPTS. FILED IN THE IND. HE WAS ALSO INFORMED THAT THE TISSUE SPECIMENS FOR HISTOPATHOLOGY IN THE DOG STUDY WERE TAKEN FROM ANIMALS AT ALL DOSES.
07-DEC-2001		CORRESPONDENCE	TELEPHONE	TEL. CONTACT TO CONFIRM THAT AGENCY DOES NOT INTEND TO PUT BMS-477118 ON CLINICAL HOLD FOLLOWING 30-DAY REVIEW OF IND.
10-DEC-2001	SN0002	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-001, TO INCREASE TOTAL BLOOD VOLUME COLLECTED IN STUDY TO 737 ML PER SUBJECT FOR USE IN ADD'L ANALYSES, AND REVISES SHIPPING INSTRUCTIONS FOR GLP-1 SAMPLES.
17-DEC-2001		CORRESPONDENCE	LETTER	FDA LTR. PROVIDING COMMENTS AND RECOMMENDATIONS FOLLOWING REVIEW OF SUBMISSION DATED 08-NOV-01, SERIAL #0000.
01-FEB-2002	SN0003	OTHER	SUBMISSION	OTHER:CHANGE IN CORRESPONDENT TO J. GENNARO. IND63,634
20-FEB-2002	SN0004	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC. CV181-002
04-MAR-2002	SN0005	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, BMS-477118.
13-MAR-2002	SN0006	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-002. AMEND. 2 (14-FEB-2002), ADMIN. LTR. 1 & 2(14-FEB-02 & 27-FEB-02). AMEND. TO MODIFY HBA1C.
27-MAR-2002	SN0007	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-002, AMEND. 3.
11-APR-2002		CORRESPONDENCE	LETTER	FDA LTR. RE: SN0004, DATED 20-FEB-02, AND INFORMATION RE: THE CLINICAL TRIALS DATA BANK.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
07-JUN-2002	SN0008	SAFETY REPORT: INITIAL/FOLLOW-UP	SUBMISSION	IND SAFETY RPT.: INITIAL WRITTEN RPT. PRELIMINARY FINDING RE: A DOSE OF 1SN000 UG/ML BMS-477118. A POSITIVE (MINIMAL) RESPONSE NOTED IN THE ABSENCE OF RAT-MICROSOMAL S9 MIX.
09-AUG-2002	SN0009	SAFETY REPORT: INITIAL/FOLLOW-UP	SUBMISSION	IND SAFETY RPT.: INITIAL RPT. OF DECREASED OSSIFICATION IN FETAL RAT PELVIS, AT MID AND HIGH DOSES, 930002160.
12-NOV-2002	SN0010	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, PROVIDING AMENDMENT AND A REVISED PROTOCOL FOR CV181-001, 930002843, 930000873.
18-NOV-2002	SN0011	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, FINAL TOX STUDY RPTS., 930002039, 930002987, 930002017, 930002469.
18-DEC-2002	SN0012	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, PROVIDING PRECLINICAL RPTS., 930003146, 930001339, 930003036, 930003089.
24-JAN-2003	SN0013	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, 930003282, 930003281.
31-JAN-2003	SN0014	INFO AMENDMENT - CMC	SUBMISSION	INFO. AMEND: CMC, 2.5 MG POTENCY CAPSULE, UPDATED HPLC METHODS AND UPDATED DRUG SUBSTANCE STABILITY DATA. Minor API process change, new 2.5 mg capsules, updated API stability, and new HPLC assay method.
21-FEB-2003	SN0015	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, 930003433.
26-MAR-2003	SN0016	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROT., CHANGE IN PROT., NEW INVESTIGATOR, INFO. AMEND: CMC, INFO. AMEND: CLINICAL, CV181008.
01-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: LAB VALUES AVAILABILITY FOR CV181-002.
03-APR-2003		CORRESPONDENCE	EMAIL	FDA EMAIL PROVIDING SAMPLE FORMAT FOR HISTOPATHOLOGY DATA.
03-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST FOR TOX. RPTS.
04-APR-2003	SN0017	OTHER	SUBMISSION	RESPONSE TO FDA REQUEST FOR INFORMATION PER 01-APR-03 CONTACT, LAB VALUES FOR CV181-002.
08-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST FOR PK DATA, SINGLE/MULTIPLE ASCENDING DOSE STUDIES.
09-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING DATA PER FDA REQUEST 08-APR-03, DATA FROM STUDIES CV181-001, 002.
14-APR-2003	SN0018	ANNUAL REPORT	SUBMISSION	IND ANNUAL RPT. FOR PERIOD 01-DEC-01 TO 30- NOV-02.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
16-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST FOR CLARIFICATION ON NATURE OF BMS-537679.
18-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING RESPONSE TO 16-APR-03, TEL. REQUEST PROVIDING CLARIFICATION OF BMS-537679.
18-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING RESPONSE TO 18-APR-03, TEL. REQUEST PROVIDING CLARIFICATION OF DOSING FOR STUDY DN02015.
18-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST ON CONTROL GROUPS IN EMBRYO-FETAL TOX. STUDIES.
18-APR-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: FDA REQUEST ON DOSING SCHEDULE IN EMBRYO-FETAL STUDY, DN02015
21-APR-2003	SN0019	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-008, Amendment 02 to Protocol CV181008 VD.
23-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING RESPONSE TO 18-APR-03, HISTORICAL CONTROL DATA FOR EMBRYO-FETAL STUDIES.
28-APR-2003		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING RESPONSE TO FDA, HISTORICAL CONTROL DATA ON RATS-PARIETALS AND SUPRAOCCIPITALS.
06-MAY-2003	SN0020	INFO AMENDMENT - CMC	SUBMISSION	INFO. AMEND: CMC, RESCUE MEDICATION IN UPCOMING CLINICAL STUDIES, BMS-477118-08. IND amendment adding modified Metformin.
21-MAY-2003	SN0021	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEN: PHARM/TOX, 930003282, Six-Month Oral Toxicity Study in Rats.
03-JUN-2003	SN0022	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATORS, CV181-008
25-JUN-2003	SN0023	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATORS, CV181-008.
07-JUL-2003		CORRESPONDENCE	LETTER	FDA LTR. W/ COMMENTS AND REQUEST RE: PRECLINICAL PHARMACOLOGY REVIEW OF IND.
17-JUL-2003	SN0024	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
29-JUL-2003	SN0025	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, PRECLINICAL REPORTS, 930000835, 930000844.
31-JUL-2003	SN0026	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, CV181-008.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
06-AUG-2003	SN0027	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC, CV181-010.
11-AUG-2003	SN0028	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, NOTIFICATION OF REQUEST FOR SPECIAL PROTOCOL ASSESSMENT, BMS NOTIFCATION OF SUBMISSION OF REQUEST FOR SPECIAL PROTOCOL ASSESSMENT.
13-AUG-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: RESPONSE TO AUG. 11 NOTIFICATION OF REQUEST FOR SPECIAL PROTOCOL ASSESSMENT.
18-AUG-2003	SN0029	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, 930004458
26-AUG-2003	SN0030	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
15-SEP-2003	SN0031	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
30-SEP-2003	SN0032	OTHER	SUBMISSION	OTHER: REQUEST FOR SPECIAL PROTOCOL ASSESSMENT, CARCINOGENICITY STUDIES, INFO. AMDN: PHARM/TOX.
30-SEP-2003	SN0033	OTHER	SUBMISSION	OTHER: REQUEST FOR SPECIAL PROTOCOL ASSESSMENT, CARCINOGENICITY STUDIES, INFO. AMEND: PHARM/TOX.
06-OCT-2003		CORRESPONDENCE	LETTER	FDA LTR. ACKNOWLEDGING RECEIP OF SUBMISSION DATED 30-SEP-03, SN032, SPECIAL CARC. PROTCOL ASSESSMENT.
07-OCT-2003	SN0034	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
09-OCT-2003	SN0035	OTHER	SUBMISSION	CHANGE IN BMS CORRESPONDENT TO PAMELA SMITH, M.D.
09-OCT-2003	SN0036	GENERAL CORRESPONDENCE	SUBMISSION	GENERAL CORRESPONDENCE PROVIDING CORRECT FDA FORM 1571 FOR SN# 0034.
14-OCT-2003		CORRESPONDENCE	LETTER	FDA LTR. RE: FDA IN REVIEW OF SPECIAL CARC. PROTOCOL ASSESSMENT DATED 30-SEP-03, SN# 033.
15-OCT-2003		CORRESPONDENCE	TELEPHONE	TEL. CONTACT RE: PHARM/TOX REVIEWER (J. COLERANGEL) DPP4 INHIBITOR, W/ QUESTION RE: MAX. HUMAN DAILY DOSE IN IND 63, 634.
15-OCT-2003		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONT. REP. (15 & 29-OCT) RE: PHARM/TOX REVIEWER ASKED IF MAX. HUMAN DOSE HAD BEEN CHANGED FROM 40 MG TO 200 MG. CONFIRMED AS CORRECT.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
29-OCT-2003		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONT. REP. (15 & 29-OCT) RE: PHARM/TOX REVIEWER ASKED IF MAX. HUMAN DOSE HAD BEEN CHANGED FROM 40 MG TO 200 MG. CONFIRMED AS CORRECT.
30-OCT-2003	SN0037	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181- 008, 930003574, Protocol CV181008 VD.
30-OCT-2003	SN0038	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, 930004940, Administrative Letter 01 to Protocol CV181010 VD.
31-OCT-2003	SN0039	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, OTHER: CHANGE IN INVESTIGATOR INFO., CV181-008.
10-NOV-2003		CORRESPONDENCE	FAX	FDA FAX RE: RESPONSE TO CARCINOGENICITY SPECIAL PROTOCOL ASSESSMENT REQUEST.
17-NOV-2003	SN0040	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND.: 4 NEW INVESTS; AND 4 CHANGE OF INVEST. INFO.
02-DEC-2003	SN0041	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND.: 3 NEW INVESTS; AND 4 CHANGE OF INVEST. INFO.
12-DEC-2003	SN0042	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND.: CHANGE IN PROT. RE: AMEND. 4 FOR CV181008 ADDING 100 MG DOSE ARM AND AN ADD'L PLACEBO ARM.
18-DEC-2003	SN0043	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: THREE-MONTH ORAL RANGE-FINDING TOXICITY STUDY IN RATS, FULLY AUDITED FINAL REPORT.
23-DEC-2003	SN0044	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND.: NEW INVEST.
08-JAN-2004	SN0045	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: TWO-WEEK ORAL TOXICOKINETICS STUDY IN RATS; AND QUALIFYING REVERSE-MUTATION STUDY IN SALMONELLA TYPHIMURIUM AND ESCHERICHIA COLI.
16-JAN-2004	SN0046	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: TWO WEEK ORAL TOXICOKINETICS STUDY IN MICE, FULLY AUDITED FINAL REPORT.
29-JAN-2004	SN0047	OTHER	SUBMISSION	RESPONSE TO FDA CAC REVIEW FOR MOUSE AND RAT CARCINOGENICITY STUDY DOSE SELECTION.
03-FEB-2004		CORRESPONDENCE	TELEPHONE	TEL. CONT. REP. RE: IN RESPONSE TO CAC REVIEW BMS WILL BE SUBMITTING A RESPONSE AGREEING TO USE ALL RECOMMENDED DOSES IN MOUSE AND RAT CARCINOGENICITY STUDIES. BMS WILL BE ADDING AN ADD'L DOSE FOR BOTH MALE AND FEMALES IN RAT STUDY TO ENSURE ACHIEVEMENT OF MAXIMAL TOLERATED DOSE (MTD).

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
11-FEB-2004	SN0048	SAFETY REPORT: INITIAL/FOLLOW-UP	SUBMISSION	INIT SAFETY REP. RE: GASTROENTERITIS, REP NO. 12491080
12-FEB-2004	SN0049	ANNUAL REPORT	SUBMISSION	ANNUAL REPORT FOR PERIOD 01-DEC-02 TO 30-NOV-03.
25-FEB-2004	SN0050	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: REVERSE-MUTATION STUDY IN SALMONELLA TYPHIMURIUM AND ESCHERICHIA COLI, 930004892 V.1.O
27-FEB-2004	SN0051	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND.: CHANGE IN PROT. RE: AMENDS. 1 & 2 OF CV181010; AND AMEN
18-MAR-2004	SN0052	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROTOCOL AMENDMENT, OTHER: CHANGE IN INVESTIGATOR INFORMATION, PROTOCOL CV181-008
19-MAY-2004	SN0053	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, CHANGE IN PROTOCOL, CV181-003.
15-JUN-2004	SN0054	INFO AMENDMENT - CMC	SUBMISSION	To provide information on drug substance in free base monohydrate form and on film-coated tablets (5 and 40 mg)
28-JUN-2004	SN0055	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND.: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND.: CMC
16-JUL-2004	SN0056	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND.: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND.: CMC
06-AUG-2004	SN0057	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND.: REVISED PROTOCOL FOR CV181005
25-AUG-2004	SN0058	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND.: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND. CMC, To provide information on C14-labeled drug substance and drug product to support the ADME study (CV181-004)
26-AUG-2004	SN0059	OTHER	SUBMISSION	OTHER: REQUEST END OF PHASE 2 MTG.
13-SEP-2004	SN0060	OTHER	SUBMISSION	OTHER: REQUEST END OF PHASE 2 MTG. RE: TYPE B MTG. TO REVIEW RESULTS OF CLINICAL TRIALS AND RELEVANT PRECLINICAL STUDIES SUPPORTING PROPOSED PHASE 3.
14-SEP-2004	SN0061	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND.: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND. CMC RE: CV181-022.
14-SEP-2004	SN0062	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND.: PHARM/TOX RE: ORAL STUDY OF FERTILITY AND EARLY EMBRYONIC DEVELOPMENT IN RATS, 930007579 V.1.O; AND TWELVE-MONTH ORAL TOXICITY STUDY IN DOGS, 930008126 V.1.O
22-SEP-2004		CORRESPONDENCE	LETTER	FDA LTR. RE: TYPE B END OF PHASE 2 MTG SET FOR 19-NOV-04.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
23-SEP-2004	SN0063	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND.: CHANGE IN PROTOCOL, RE: CV181-022. AMEND. 02
21-OCT-2004		CORRESPONDENCE	FAX	BMS FAX PROVIDING COPY OF IND SAFETY RPT.: NON-CLINICAL EXPEDITED. ADDENDUM TO INV. BROCHURE FOR BMS-477118.
21-OCT-2004		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONTACTS (OCT. 21 & 22)RE: CANCELLATION OF EOP2 MTG.
21-OCT-2004	SN0064	OTHER	SUBMISSION	IND SAFETY RPT.: NON-CLINICAL EXPEDITED. ADDENDUM TO INV. BROCHURE FOR BMS-477118.
22-OCT-2004		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONTACTS (OCT. 21 & 22)RE: CANCELLATION OF EOP2 MTG.
20-DEC-2004	SN0066	OTHER	SUBMISSION	OTHER: REQUEST FOR MEETING.
29-DEC-2004		CORRESPONDENCE	LETTER	FDA LTR. RE: NO NEED FOR REQUESTED MTG. PER BMS LTR. DATED 20-DEC-04.
14-JAN-2005	SN0067	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, CONVERSION OF BMS-477118, AND INITIATION OF 104-WK. ORAL GAVAGE CARC. STUDY IN RATS.
07-FEB-2005	SN0068	ANNUAL REPORT	SUBMISSION	Annual Report FOR 01-DEC-03 TO 30-NOV-04, INCLUDING Quality Section.
22-FEB-2005	SN0069	INFO AMENDMENT - CLINICAL	SUBMISSION	INFO. AMEND: CLINICAL, 930009626, Placeo-Controlled, Ascending Single-Dose Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of BMS-477118 in Healthy Subjects.
02-MAR-2005	SN0070	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, RESULTS FROM CNS TOXICITY/ HISTOPATHOLOGY STUDY IN RATS.
21-APR-2005	SN0071	INFO AMENDMENT - CMC	SUBMISSION	IND amendment - To provide drug products information to support Phase III clinical studies
28-APR-2005		CORRESPONDENCE	TELEPHONE	TEL. CONTACT INFORMING FDA THAT UPDATE ON RAT CNS FINDINGS TO BE SUBMITTED SOON.
11-MAY-2005	SN0072	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND: PHARM/TOX, PROVIDING 1-YEAR INTERIM ANALYSIS OF THE CHRONIC INVESTIGATIONAL CNS TOXICITY STUDY IN RATS.
11-MAY-2005	SN0073	OTHER	SUBMISSION	OTHER: REQUEST END OF PHASE 2 MEETING.
13-MAY-2005		CORRESPONDENCE	TELEPHONE	TEL. CONTACT TO CONFIRM AGENCY RECEIPT OF SUBMISSIONS; CNS TOX. SAFETY UPDATE AND REQUEST FOR EOP2 MEETING.
17-MAY-2005		CORRESPONDENCE	TELEPHONE	TEL. CONTACT STATING THAT CNS TOX. UPDATE REVIEWED BY FDA, AND EOP2 MTG. TO BE SCHEDULED FOR 27-JUL-05.

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19-MAY-2005		CORRESPONDENCE	LETTER	FDA LTR. PROVIDING DETAILS FOR EOP2 MTG. SCHEDULED FOR 27-JUL-05.
01-JUN-2005	SN0074	OTHER	SUBMISSION	OTHER: UPDATED INVESTIGATOR BROCHURE.
16-JUN-2005	SN0075	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND: CMC, CV181-011.
20-JUN-2005	SN0076	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND:PHARM/TOX.
23-JUN-2005	SN0077	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR; INFO. AMEND: CMC.
27-JUN-2005	SN0078	OTHER	SUBMISSION	EOP2 BRIEFING BOOK
27-JUN-2005		OTHER	SUBMISSION	OTHER: RESPONSE TO REQUEST FOR INFORMATION, PROVIDING DESK COPY OF PROTOCOL CV181-011.
08-JUL-2005	SN0079	INFO AMENDMENT - CLINICAL	SUBMISSION	INFO. AMEND: CLINICAL, FINAL STUDY RPT. 930011138.
15-JUL-2005	SN0080	INFO AMENDMENT - CMC	SUBMISSION	To request CMC end of Phase 2 meeting
19-JUL-2005		CORRESPONDENCE	EMAIL	BMS EMAIL PROVIDING ADD'L ANALYSIS OF NON-CLINICAL EXPOSURE FOR SAXAGLIPTIIN.
19-JUL-2005	SN0081	RESPONSE TO REQUEST	SUBMISSION	RESPONSE TO REQUEST FOR ADDITIONAL INFO RE:NONCLINICAL SAXAGLIPTIN EXPOSURE.
20-JUL-2005	SN0082	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROTOCOL AMEND:NEW INVESTIGATOR/CHANGE IN INVESTIGATOR
22-JUL-2005	SN0083	INFO AMENDMENT - CLINICAL	SUBMISSION	INFO.AMEND.:CLINICAL CV181-008
26-JUL-2005		CORRESPONDENCE	FAX	FAX CORRESPONDENCE RE:IND 63,634 DRAFT VERSION OF PRE-MEETING RESPONSES FOR END OF PHASE 2 MEETING
01-AUG-2005	SN0084	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO.AMEND.:PHARMACOLOGY/TOXICOLOGY
22-AUG-2005	SN0085	INFO AMENDMENT - CMC	SUBMISSION	INFO. AMEND: CMC, CM EOP2 MTG.-BACKGROUND INFO. To provide the briefing package for the CMC end of Phase 2 meeting
23-AUG-2005		CORRESPONDENCE	LETTER	FDA LTR. PROVIDING OFFICIAL MINUTES FROM EOP2 MTG. ON 27-JUL-05.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
24-AUG-2005	SN0086	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, CV181-011, 014.
24-AUG-2005		CORRESPONDENCE	LETTER	FDA LTR. PROVIDING COMMENTS AND RECOMMENDATIONS FOR SUBMISSION DATED 16-JUN-05, SN 075, CV181-011.
25-AUG-2005	SN0087	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC, CV181-018.
29-AUG-2005		CORRESPONDENCE	FAX	FDA FAX PROVIDING CMC WITH LTR. COPY PREVIOUSLY SENT RE: EOP2 MTG.
30-AUG-2005	SN0088	INFO AMENDMENT - CLINICAL	SUBMISSION	INFO. AMEND: CLINICAL, CV181-008.
08-SEP-2005	SN0089	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, CV181-011, 014.
09-SEP-2005	SN0091	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC, CV181-028
09-SEP-2005	SN0090	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT. AMEND: NEW PROTOCOL, NEW INVESTIGATOR, INFO. AMEND: CMC, CV181-026.
22-SEP-2005	SN0092	OTHER	SUBMISSION	OTHER: REQUEST FOR FDA REVIEW AND COMMENT, RE: CARCINOGENICITY STUDY IN MICE.
27-SEP-2005		CORRESPONDENCE	TELEPHONE	Telephone contact w/ FDA re: a F/U to the BMS-477118 mouse carcinogenicity study phone discussion on Sep 27, 2005 b/w Dr.El-Hage(US FDA) & Greg Cosma and Joseph Lamendola(both from BMS)
27-SEP-2005	SN0093	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	PROT. AMEND: CHANGE IN PROTOCOL, CV181-018, (AMEND. 3 & REVISED PROT. 2).
05-OCT-2005	SN0094	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROT. AMEND: NEW INVESTIGATOR, CV181-011, 014, 018, 026.
10-OCT-2005	SN0095	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND. Pharm/Tox. Providing, Tocicology info.Re: Mouse carcinogencity.
13-OCT-2005		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONTACT (OCT. 13, 18) RE: BMS SUBMISSION OF EXPEDITED NONCLINICAL SAFETY RPT. AND TELECONF. TO BE SCH.TO DISSCUSS FINDINGS IN 1 MTH. MONKEY STUDY.
13-OCT-2005	SN0096	SAFETY REPORT: INITIAL/FOLLOW-UP	SUBMISSION	RE: IND SAFETY REPORT: NON- CLINICAL EXPEDITED RE: INVESTIGATOR BROCHURE TO BMS

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
14-OCT-2005	SN0097	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFO. AMEND. PHARM/TOX. PROVIDING FINAL STUDY REPORTS.
18-OCT-2005		CORRESPONDENCE	TELEPHONE	MULTI. TEL. CONTACT (OCT. 13, 18) RE: BMS SUBMISSION OF EXPEDITED NONCLINICAL SAFETY RPT. AND TELECONF. TO BE SCH.TO DISSCUSS FINDINGS IN 1 MTH. MONKEY STUDY.
20-OCT-2005	SN0098	OTHER	SUBMISSION	Other: Response to FDA Review and Comment RE: ANCOVA Model
25-OCT-2005	SN0099	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Prot. Amend. New Investigator, CV181-011,014.
01-NOV-2005		CORRESPONDENCE	EMAIL	FDA E-MAIL RE:FDA LTR. RE: DIVISION RECOMMENDS CONDUCTING A 3 MTH. ORAL TOXICITY RELATING TO (DPP-4).
01-NOV-2005		CORRESPONDENCE	LETTER	FDA LTR. RE: DIVISION RECOMMENDS CONDUCTING A 3 MTH. ORAL TOXICITY RELATING TO (DPP-4).
04-NOV-2005	SN0100	OTHER	SUBMISSION	NOTICE OF SITE CLOSURE FOR CV181-014-101
07-NOV-2005	SN0101	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROT., AMEND. NEW PROT. NEW INVESTIGATOR, INFO. AMEND.:CMC, CV181-032
16-NOV-2005	SN0102	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Prot. Amend.: New Investigator For CV181-011,014
30-NOV-2005	SN0103	INFO AMENDMENT - CMC	SUBMISSION	Info. Amend: CMC, Information amendment to support BA studies for the 10 mg tablets. The 1 mg tablets formulation will be included in the amendment
01-DEC-2005	SN0104	OTHER	SUBMISSION	Other - Addendum #1 to IB version 3 dated 11-May-2005
01-DEC-2005	SN0105	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-033; Information Amendment - CMC for the clinical supplies to be used in the conduct of Protocol CV181-033
07-DEC-2005	SN0106	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	Protocol Amendment - Change in protocol for CV181-011
12-DEC-2005	SN0107	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Protocol Amendment - New Investigator for CV181-011, CV181-014; Other - Change in Investigator Information for CV181-011 & CV181-014
14-DEC-2005	SN0108	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-013; Info. Amendment - CMC
14-DEC-2005	SN0109	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	Protocol Amendment - Change in Protocol for CV181-014

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
14-DEC-2005		CORRESPONDENCE	LETTER	FDA ltr. providing comments & recommendations upon completion of review of submission dated 07-Nov-2005 (Serial# 101).
16-DEC-2005	SN0110	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-020; Info. Amendment CMC.
16-DEC-2005	SN0111	OTHER	SUBMISSION	Other - Transfer of Obligations to a CRO (ICON Clinical Research,Inc.) for CV181-013
19-DEC-2005	SN0112	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-036; Info. Amendment - CMC
22-DEC-2005	SN0113	OTHER	SUBMISSION	Other - Request for FDA review & comment, on the draft protocol synopsis of Protocol CV181-039 and its acceptability to support an indication for first line combination therapy w/ Saxagliptin & Metformin as well as ques. re: CV181-039
23-DEC-2005	SN0114	INFO AMENDMENT - PHARM/TOX	SUBMISSION	Info. Amendment - Pharm/Tox. as a follow-up to the phone discussion that took place b/w Jeri El Hage from US FDA and Greg Cosma & Joseph Lamendola, both from BMS re: BMS-477118 mouse carcinogenecity study.
28-DEC-2005		CORRESPONDENCE	LETTER	Telephone contact w/ FDA re: completing arrangements for the Nov 2 teleconference.
29-DEC-2005		CORRESPONDENCE	LETTER	Telephone contact w/ FDA re: our proposed statistical aproach for the pivotal Phase 3 studies to include subgroup analysis by region
12-JAN-2006	SN0115	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Protocol Amendment - New Investigator for CV181-011 & CV181-014, Other - Change in Investigator Information for CV181-011
13-JAN-2006	SN0116	INFO AMENDMENT - PHARM/TOX	SUBMISSION	Information Amendment: Pharmacology/Toxicology, One Month Subcutaneous Investigative Toxicity Study in Rats
17-JAN-2006	SN0117	INFO AMENDMENT - PHARM/TOX	SUBMISSION	Information Amendment: Pharmacology/ Toxicology Re: 104 Week Oral Rat Carcinogenicity Study.
19-JAN-2006		CORRESPONDENCE	LETTER	FDA ltr. re: completion of review of amendment dated 14-Dec-2005 (serial 108). FDA provided comments & recommendations.
25-JAN-2006		CORRESPONDENCE	EMAIL	Email sent to FDA re: Saxagliptin initial combination questions. Per FDA request, the ques re: review of study design for Protocol 039, was provided in MS Word format.
27-JAN-2006	SN0118	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment - New Protocol, New Investigator for CV181-019 & CV181-027 & Info amendment CMC re: CV181-019 & CV181-027
30-JAN-2006		CORRESPONDENCE	TELEPHONE	Telephone contact w/ FDA re: the control group in the rat carcinogenicity study.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
30-JAN-2006		CORRESPONDENCE	LETTER	FDA ltr. re: completion of review of the Amendment dated 22-Dec-2005. FDA provided comments to BMS' questions
31-JAN-2006		CORRESPONDENCE	EMAIL	FDA email w/comments re: the Protocol synopsis (CV181-039), submitted by BMS on 22-Dec-2005
01-FEB-2006		CORRESPONDENCE	TELEPHONE	Telephone contact w/ FDA to clarify BMS' interest on Dr.Misbin's (Clinical Reviewer) comments on Protocol 013 (TZD study), as well as BMS' decision to accept Dr. El-Hage's suggestion re: control group in the rat carcinogenicity study.
02-FEB-2006		RESPONSE TO REQUEST	SUBMISSION	Other - Response to Request for Info. re: a desk copy of Study DN03009, three-month Oral range finding toxicity study in rats
03-FEB-2006	SN0119	ANNUAL REPORT	SUBMISSION	IND annual report for the period 01-Dec-2004 to 30-Nov-2005
03-FEB-2006		CORRESPONDENCE	FAX	BMS Fax Re: Saxagliptin: 1 to 3-Month Monkey Toxicity Study.
13-FEB-2006		CORRESPONDENCE	EMAIL	FDA Email re: IND 63,634, Draft Statement for ESR (Saxagliptin).
14-FEB-2006	SN0120	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROTOCOL AMENDMENT: NEW INVESTIGATOR OTHER: CHANGE IN INVESTIGATOR INFORMATION
15-FEB-2006	SN0121	OTHER	SUBMISSION	RE IND SAFETY REPORT: NON-CLINICAL EXPEDITED
24-FEB-2006	SN0122	INFO AMENDMENT - PHARM/TOX	SUBMISSION	INFORMATION AMENDMENT: PHARMACOLOGY/TOXICOLOGY
03-MAR-2006		CORRESPONDENCE	EMAIL	FDA Email re: Draft Informed Consent. The Agency reviewed proposed revised language for the informed consent.
07-MAR-2006	SN0123	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	PROTOCOL AMENDMENT: NEW PROTOCOL, NWE INVESTIGATOR INFORMATION AMENDMENT: CHEMISTRY, MANUFACTURING, AND CONTROL. CV181037
13-MAR-2006	SN0124	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	PROTOCOL AMENDMENT: NEW INVESTIGATOR OTHER: CHANGE IN INVESTIGATOR INFORMATION. CV181-013
17-MAR-2006	SN0125	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	Protocol Amend: Change in Protocol. Amendment #03 and Revised Protocol 01 and 02 to Protocol CV181-019 and CV181-032.
23-MAR-2006	SN0126	INFO AMENDMENT - PHARM/TOX	SUBMISSION	Information Amendment: Pharm/Toxic: BMS-477118
23-MAR-2006	SN0127	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amend: New Protocol, New Investigator Info Amend: CMC: Primary Obj. of Protocol CV181-040 is to compare after 24 weeks of oral adm. of double-blind treatment.

Sent Date	Serial / Sequence No.	Submission Type	Correspondence Type	Submission Title
23-MAR-2006	SN0128	OTHER	SUBMISSION	Other: Revised Informed Consent Form: BMS-477118 and email communication approving text for ICFs.
30-MAR-2006	SN0129	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Protocol Amendment: New Investigator:Protocol CV181-013.
12-APR-2006		CORRESPONDENCE	LETTER	FDA Ltr. Re: Saxagliptin (BMS-477118) Capsules and Amendment dated 01/12-05 (serial #105) New Protocol CV181033: Pharmacokinetic Drug Interaction Study with Saxagliptin and Simvastatin in Healthy Subjects," completed review with comments and recommendations.
20-APR-2006	SN0130	OTHER	SUBMISSION	Other - Request for Meeting via teleconference to discuss our plans to monitor events of special interest in the saxagliptin program
24-APR-2006	SN0131	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment: New Protocol, New Invesitgator Info Amend: CMC and Control Other: Transfer of Obligations to Contract Research Organization. Re: CV181038
24-APR-2006	SN0132	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment: New Protocol, New Invesitgator Info Amend: CMC and Control Other: Transfer of Obligations to Contract Research Organization. Re: CV181039
26-APR-2006		CORRESPONDENCE	TELEPHONE	FDA Telephone Contact re: Off-target binding activities (other DPP enzymes) of Saxagliptin.
27-APR-2006	SN0133	PROT. AMEND.: CHANGE IN PROTOCOL	SUBMISSION	Protocol Amend: Change in Protocol re: Protocol CV181027 study has been discontinued due to protocol deviation.
28-APR-2006	SN0134	PROT. AMEND.: NEW INVESTIGATOR	SUBMISSION	Protocol Amend: New Investigator: Other: Change in Investigator Information re: Protocols CV181013 & CV181040.
28-APR-2006		CORRESPONDENCE	LETTER	FDA Ltr. re: The Request for a Teleconference mtg to discuss Saxagliptin prog have been denied, FDA provided written reponses to questions included in meeting request.
11-MAY-2006	SN0135	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment: New Protcol, New Investigator Information Amendment: CMC re: Protocol CV181035
17-MAY-2006	SN0136	PROT. AMEND.: NEW PROTOCOL	SUBMISSION	Protocol Amendment: New Protocol, New Investigator Information Amendment1: CMC re: Protocol CV181052
17-MAY-2006		CORRESPONDENCE	LETTER	FDA orginal Ltr re: FDA respond to BMS question regarding BMS Amendment dated 20-Apr-06, Serial #130 requesting a teleconference to discuss plans to implement additional monitor to collect info on saxagliptin prg. FDA denied mtg with written response to questions included in meeting request.