Formulary Drug Reviews

Alogliptin

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Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with *The Formulary Monograph Service*. Through the cooperation of *The Formulary, Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, call *The Formulary* at 800-322-4349. The July 2013 monograph topics are prothrombin complex concentrate (human), cysteamine bitartrate delayed-release capsules, doxylamine succinate/pyridoxine hydrochloride, tedizolid phosphate, and sofosbuvir. The DUE/MUE is on canagliflozin.

Generic Name:	Alogliptin
Proprietary Name:	Nesina (Takeda)
Approval Rating:	1S
Therapeutic Class:	Dipeptidyl Peptidase-4 Inhibitors
Similar Drugs:	Linagliptin, Saxagliptin, Sitagliptin
Sound- or Look-Alike Names:	Linagliptin, Saxagliptin, Sitagliptin

INDICATIONS

Alogliptin is indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It can be used as monotherapy or in combination with other antidiabetic medications, including metformin, sulfonylureas, thiazolidinediones, or insulin.¹ **Table 1** compares the US Food and Drug Administration (FDA)-approved indications for dipeptidyl

peptidase-4 (DPP-4) inhibitors. None of the agents in this class should be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.¹

CLINICAL PHARMACOLOGY

Alogliptin is a selective DPP-4 inhibitor. DPP-4 inhibitors lower blood glucose by preventing the breakdown of glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, thus prolonging the activity of these peptides.^{1,2} Alogliptin has demonstrated high selectivity to DPP-4 relative to other related serine proteases. It has exhibited more than 14,000-fold selectivity over the related serine proteases DPP-8 and DPP-9.^{3,4}

Following 14 days of once-daily dosing with doses from 25 to 400 mg, peak DPP-4 inhibition ranged from 94% to 99%, and mean inhibition at 24 hours after the last dose ranged from 82% to 97%.² Single doses of alogliptin from 25 to 800 mg produced peak DPP-4 inhibition ranging from 93.3% to 98.8%. The mean DPP-4 inhibition ranged from 74.3% to 97% at 24 hours and from 47.5% to 83% at 72 hours. Plasma GLP-1 concentrations were increased 2- to

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Table 1. FDA-approved indications for DPP-4 inhibitors^{1,9,32,33}

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Brand name	<i>Nesina</i>	<i>Tradjenta</i>	<i>Onglyza</i>	<i>Januvia</i>
Manufacturer	Takeda	Boehringer Ingelheim	Bristol-Myers Squibb	Merck
Approved uses				
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus				
As monotherapy	Yes	Yes	Yes	Yes
As combination therapy with insulin	Yes	Yes	Yes	Yes
As combination therapy with an insulin secretagogue (eg, sulfonylurea)	Yes	Yes	Yes	Yes
As combination therapy with metformin	Yes	Yes	Yes	Yes
As combination therapy with a thiazolidinedione	Yes	Yes	Yes	Yes

6-fold in alogliptin-treated subjects compared with placebo recipients.^{3,5}

In animal models, alogliptin has been associated with dose-dependent inhibition of DPP-4 activity and increased active GLP-1; reduced hemoglobin A_{1c} (HbA_{1c}), plasma glucose, plasma glucagon, and plasma triglycerides; increased plasma insulin; and improved beta cell function, with neutral effects on body weight and food consumption.⁶ Enhanced activity has been observed with the combination of alogliptin and pioglitazone.⁷ Reductions in triglycerides have also been observed in patients with diabetes treated with alogliptin and alogliptin plus pioglitazone.⁸

DPP-4 inhibitors lower blood glucose by preventing the breakdown of GLP-1 and glucose-dependent insulinotropic polypeptide, thus prolonging the activity of these peptides.⁹⁻¹¹ The duration of action of the various DPP-4 inhibitors is influenced both by their elimination half-life and their rate of release from the enzyme-inhibitor complex (see Table 2).^{10,11} The clinical importance of the selectivity (DPP-4 vs other enzymes) of the individual inhibitor for DPP-4 remains to be proven, but there are differences between the various DPP-4 inhibitors: Selectivity for DPP-4 is greater than 10,000-fold for alogliptin and linagliptin, greater than 2,600-fold for sitagliptin, and approximately 100-fold for saxagliptin.^{3,4}

PHARMACOKINETICS

Following oral administration, peak plasma concentrations (C_{max}) are reached within 1 to 2 hours.^{1,2} The area under the curve (AUC) increases in a dose-dependent manner over a range of doses from 25 to 800 mg.² Oral bioavailability is approximately 100%.¹

Administration with a meal does not affect total or peak exposure.¹ Protein binding is approximately 20%.^{1,12} Its volume of distribution (V_d) is 417 L.¹

The mean half-life is approximately 21 hours.^{1,2,5} Alogliptin is primarily excreted renally.^{1,2} Approximately 60% to 80% of the administered dose is excreted unchanged in the urine within 24 to 72 hours.^{1-3,5} Two metabolites have been identified, 1 active and 1 inactive. The active metabolite is present at concentrations of less than 1% of the parent drug, and the inactive metabolite is present at concentrations of less than 6% of the alogliptin concentration.^{1,5}

The pharmacokinetic parameters of DPP-4 inhibitors are compared in Table 3.

The pharmacokinetic parameters of alogliptin are altered in patients with renal impairment. The AUC was increased 1.7-, 2.1-, 3.2-, and 3.8-fold in subjects with mild renal impairment (creatinine clearance [CrCl] 51 to 80 mL/min), moderate renal impairment

Table 2. Comparison of DPP-4 inhibition for selected DPP-4 inhibitors^{1,4,10,34}

Drug	DPP-4 inhibition	
	Maximum inhibition	Postdose inhibition
Alogliptin	≈ 90%	> 75% 24 hours post dose
Linagliptin	≈ 80% to 90%	≥ 70% 24 hours post dose
Saxagliptin	≈ 80%	≥ 70% 24 hours post dose
Sitagliptin	≈ 97%	≥ 80% 24 hours post dose

Table 3. Pharmacokinetic parameters of DPP-4 inhibitors^{1,9,32,33,35}

Parameter	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Bioavailability, oral	100%	30%	67%	87%
Time to C _{max}	1 to 2 hours	1.5 hours	2 hours, 4 hours ^a	1 to 4 hours
V _d	417 L	1,110 L	151 L	198 L
Protein binding	20%	75% to 99%	Negligible	38%
Half-life	21 hours	12 hours	2.5 hours, 3.1 hours ^a	12.4 hours
Primary route of elimination	Renal as unchanged drug	Enterohepatic system as unchanged drug	Renal and hepatic	Renal as unchanged drug
Metabolism	Minor (10%): CYP2D6, ^b CYP3A4	Minor (10%): CYP3A4	CYP3A4/5	Minor (21%): CYP3A4, CYP2C8
Active metabolite	Yes	No	Yes	No
Percentage excreted unchanged in the urine	60% to 80%	6%	24%, 36% ^a	79%

^aActive metabolite.^bCYP2D6 = cytochrome P450 (CYP-450) 2D6.

(CrCl 30 to 50 mL/min), severe renal impairment (CrCl less than 30 mL/min), or end-stage renal disease on dialysis, respectively. Peak concentrations were increased 1.1- to 1.4-fold. Metabolite exposure remained low in all subjects. Approximately 7.2% (3.6 mg) of a 50-mg oral dose was removed after 3 hours of hemodialysis. Dosage adjustments are recommended for patients with moderate to severe renal function impairment or end-stage renal disease.¹² Alogliptin pharmacokinetics were not significantly altered in subjects with mild to moderate hepatic impairment.¹³

COMPARATIVE EFFICACY

Indication: Initial Type 2 Diabetes Mellitus Therapy in Patients with Inadequate Control with Diet and Exercise Alone

Guidelines

Guideline: 2012 management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association and the European Association for the Study of Diabetes

Reference: Inzucchi SE, et al, 2012¹⁴

Comments: Metformin is recommended for initial drug therapy unless contraindicated or not tolerated. It should be initiated at or soon after diagnosis, especially in patients for whom lifestyle intervention alone has not achieved or is unlikely to achieve HbA_{1c} goals. If metformin cannot be used,

an alternative oral therapy, such as a sulfonylurea/meglitinide, pioglitazone, or a DPP-4 inhibitor, should be considered; a GLP-1 receptor agonist could also be considered. This guideline advises consideration of patient factors (age, weight, racial/ethnic differences) and comorbidities (coronary artery disease, heart failure, chronic kidney disease, liver dysfunction, hypoglycemia) when selecting among the available therapies.

Studies

Drug: Alogliptin vs Placebo

Reference: Fleck P, et al, 2008¹⁵

Study Design: Randomized, double-blind, dose-ranging study

Study Funding: Not provided

Patients: 265 patients with type 2 diabetes who were newly diagnosed, previously diagnosed but managed only with diet and exercise, or receiving treatment with a sulfonylurea, metformin, or a combination of both. Patients receiving antidiabetic therapy underwent a 2-week washout before randomization. The study population was 48% men and 87% White; the mean age was 56 years, and the mean HbA_{1c} was 7.9% to 8.2%.

Intervention: Placebo (43 patients) or alogliptin 6.25 mg (44 patients), 12.5 mg (44 patients), 25 mg (45 patients), 50 mg (44 patients), or 100 mg (45 patients) once daily for 12 weeks.

Results:**Primary Endpoint(s):**

- Least squares mean change in HbA_{1c} from baseline to week 12 in the intent-to-treat (ITT) population ranged from −0.01% in the placebo group and −0.19% in the alogliptin 6.25 mg group to −0.54% with alogliptin 12.5 mg, −0.56% with alogliptin 25 mg, −0.44% with alogliptin 50 mg, and −0.51% with alogliptin 100 mg ($P < .05$ for doses between 12.5 and 100 mg vs placebo).

Secondary Endpoint(s):

- Least squares mean change in HbA_{1c} from baseline to week 12 in the 113 patients not previously treated with antidiabetic therapy ranged from −0.27% in the placebo group and −0.65% in the alogliptin 6.25 mg group to −0.92% with alogliptin 12.5 mg, −0.85% with alogliptin 25 mg, −0.72% with alogliptin 50 mg, and −0.89% with alogliptin 100 mg ($P < .05$ for 12.5, 25, and 100 mg doses vs placebo).
- The least squares mean change in fasting plasma glucose was +8.5 mg/dL in the placebo group, −7.8 mg/dL in the 6.25 mg group, −5.1 mg/dL in the 12.5 mg group, −27 mg/dL in the 25 mg group, −16.1 mg/dL in the 50 mg group, and −20.9 mg/dL in the 100 mg group ($P < .05$ for alogliptin 25 to 100 mg vs placebo).
- Weight changes were small in all groups (−0.5 to −1.17 kg in the alogliptin groups and −0.45 kg in the placebo group).
- The incidence of hypoglycemia also did not differ between groups.

Comments: Dose-ranging study established efficacy with alogliptin doses from 12.5 to 100 mg.

Reference: DeFronzo RA, et al, 2008^{1,16}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 329 patients with type 2 diabetes not adequately controlled with diet and exercise alone. The study population was 53% men and 67% White; the mean age was 53 years, and the mean baseline HbA_{1c} was 7.9%.

Intervention: Alogliptin 12.5 mg (133 patients), alogliptin 25 mg (131 patients), or placebo (65 patients) once daily for 26 weeks.

Results:**Primary Endpoint(s):**

- Least squares mean change in HbA_{1c} from baseline to week 26 in the ITT population: −0.56% with alogliptin 12.5 mg and −0.59% with alog-

liptin 25 mg compared with −0.02% in the placebo group ($P < .001$).

Secondary Endpoint(s):

- HbA_{1c} of 7% or less was achieved in 47.4% of patients in the alogliptin 12.5 mg group ($P = .001$) and 44.3% in the alogliptin 25 mg group ($P = .008$) compared with 23.4% of placebo recipients.
- Least squares mean change from baseline in fasting plasma glucose: −10.3 mg/dL in the alogliptin 12.5 mg group and −16.4 mg/dL in the alogliptin 25 mg group compared with an increase of 11.3 mg/dL in the placebo group ($P < .001$).
- Changes in weight were similar in the alogliptin (−0.09 and −0.22 kg) and placebo (+0.18 kg) groups.
- The incidence of hypoglycemia also did not differ between groups (3% and 1.5% in the alogliptin groups vs 1.6% in the placebo group).

Drug: Alogliptin vs Placebo or Metformin or Alogliptin plus Metformin

Reference: *Nesina* package insert¹

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 784 patients inadequately controlled with diet and exercise; the mean baseline HbA_{1c} was 8.4%.

Intervention: Placebo, metformin 500 mg or 1,000 mg twice daily, alogliptin 12.5 mg twice daily, alogliptin 25 mg once daily, or alogliptin 12.5 mg plus metformin 500 or 1,000 mg twice daily.

Results:**Primary Endpoint(s):**

- Least squares mean change in HbA_{1c} from baseline: 0.1% with placebo, −0.6% with alogliptin 12.5 mg twice daily, −0.7% with metformin 500 mg twice daily, −1.1% with metformin 1,000 mg twice daily, −1.2% with alogliptin 12.5 mg plus metformin 500 mg twice daily ($P < .05$ vs alogliptin and metformin alone), and −1.6% with alogliptin 12.5 mg plus metformin 1,000 mg twice daily ($P < .05$ vs alogliptin and metformin alone).

Secondary Endpoint(s):

- Patients achieving HbA_{1c} less than 7%: 4% with placebo, 20% with alogliptin 12.5 mg twice daily, 27% with metformin 500 mg twice daily, 34% with metformin 1,000 mg twice daily, 47% with alogliptin 12.5 mg plus metformin 500 mg twice daily ($P < .05$ vs alogliptin and metformin alone), and 59% with alogliptin 12.5 mg plus

metformin 1,000 mg twice daily ($P < .05$ vs alogliptin and metformin alone).

- Least squares mean change in fasting plasma glucose: 12 mg/dL with placebo, -10 mg/dL with alogliptin 12.5 mg twice daily, -12 mg/dL with metformin 500 mg twice daily, -32 mg/dL with metformin 1,000 mg twice daily, -32 mg/dL with alogliptin 12.5 mg plus metformin 500 mg twice daily ($P < .05$ vs alogliptin and metformin alone), -46 mg/dL with alogliptin 12.5 mg plus metformin 1,000 mg twice daily ($P < .05$ vs alogliptin and metformin alone).
- Least squares mean change in 2-hour postprandial glucose: -21 mg/dL with placebo, -43 mg/dL with alogliptin 12.5 mg twice daily, -49 mg/dL with metformin 500 mg twice daily, -54 mg/dL with metformin 1,000 mg twice daily, -68 mg/dL with alogliptin 12.5 mg plus metformin 500 mg twice daily ($P < .05$ vs alogliptin and metformin alone), and -86 mg/dL with alogliptin 12.5 mg plus metformin 1,000 mg twice daily ($P < .05$ vs alogliptin and metformin alone).

Limitations: Results have only been published in the *Nesina* package insert. No results were reported for the alogliptin 25 mg once daily group.

Drug: Alogliptin vs Pioglitazone vs Alogliptin plus Pioglitazone

Reference: Rosenstock J, et al, 2010^{1,17}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 655 patients inadequately controlled with diet and exercise. The patient population was 49% male and 80% White; the mean age was 53 years, and the mean baseline HbA_{1c} was 8.8%.

Intervention: Alogliptin 25 mg, pioglitazone 30 mg, alogliptin 12.5 mg plus pioglitazone 30 mg, or alogliptin 25 mg plus pioglitazone 30 mg once daily for 26 weeks.

Results:

Primary Endpoint(s):

- Least squares mean change from baseline in HbA_{1c} in the ITT population: -1% with alogliptin 25 mg, -1.2% with pioglitazone 30 mg, -1.6% with alogliptin 12.5 mg plus pioglitazone 30 mg, and -1.7% with alogliptin 25 mg plus pioglitazone 30 mg ($P < .01$ vs alogliptin or pioglitazone alone).

Secondary Endpoint(s):

- HbA_{1c} 7% or less: 24.4% with alogliptin 25 mg, 33.7% with pioglitazone 30 mg, 53.4% with alogliptin 12.5 mg plus pioglitazone 30 mg,

and 62.8% with alogliptin 25 mg plus pioglitazone 30 mg ($P < .05$ vs alogliptin or pioglitazone alone).

- Least squares mean change from baseline in fasting plasma glucose: -26 mg/dL with alogliptin 25 mg, -37 mg/dL with pioglitazone 30 mg, -48 mg/dL with alogliptin 12.5 mg plus pioglitazone 30 mg, and -50 mg/dL with alogliptin 25 mg plus pioglitazone 30 mg ($P < .01$ vs alogliptin or pioglitazone alone).
- Marked hyperglycemia, exceeding 200 mg/dL, occurred in 44.4% of patients treated with alogliptin 25 mg, 38.2% with pioglitazone 30 mg, 30.9% with alogliptin 12.5 mg plus pioglitazone 30 mg, and 25.3% with alogliptin 25 mg plus pioglitazone 30 mg ($P < .05$ vs alogliptin or pioglitazone alone).
- Hyperglycemic rescue was necessary in 11.3% of patients treated with alogliptin 25 mg, 6.4% with pioglitazone 30 mg, 3.8% with alogliptin 12.5 mg plus pioglitazone 30 mg, and 2.5% with alogliptin 25 mg plus pioglitazone 30 mg ($P < .05$ vs alogliptin alone).
- Body weight was increased significantly with alogliptin 25 mg plus pioglitazone 30 mg relative to alogliptin 25 mg alone (+3.14 vs -0.29 kg; $P < .05$) and relative to pioglitazone 30 mg alone (+3.14 vs +2.19 kg; $P < .05$).

Comments: Both alogliptin and pioglitazone produced significant reductions in HbA_{1c}; however, initial combination therapy was more effective.

Indication: Combination Therapy in Type 2 Diabetes Mellitus Patients with Inadequate Control with Metformin, Pioglitazone, a Sulfonylurea, or Insulin

Guidelines

Guideline: 2012 management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association and the European Association for the Study of Diabetes

Reference: Inzucchi SE, et al, 2012¹⁴

Comments: If monotherapy alone does not achieve target HbA_{1c}, a sulfonylurea/meglitinide, pioglitazone, DPP-4 inhibitor, GLP-1 receptor agonist, or basal insulin should be added. If adequate reductions in HbA_{1c} are not achieved with a 2-drug regimen, adherence should be verified and then an alternative second agent from another class should be tried. If needed, a 3-drug regimen may be tried. This guideline advises consideration of patient factors (age, weight, racial/ethnic differences) and

comorbidities (coronary artery disease, heart failure, chronic kidney disease, liver dysfunction, hypoglycemia) when selecting among the available therapies.

Studies

Drug: Alogliptin vs Placebo, as add-on therapy with Metformin

Reference: Nauck MA, et al, 2008^{1,18}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 527 patients with type 2 diabetes inadequately controlled on metformin monotherapy at a dosage of at least 1,500 mg per day. The study population was about 50% men and 77% White; the mean age was 55 years, and the mean baseline HbA_{1c} was 7.9%.

Intervention: Alogliptin 12.5 mg (213 patients), alogliptin 25 mg (210 patients), or placebo (104 patients) once daily in addition to their ongoing metformin regimen (mean dosage, 1,837 to 1,868 mg/day) for 26 weeks.

Results:

Primary Endpoint(s):

- Least squares mean change in HbA_{1c} from baseline to week 26 in the ITT population: -0.6% in the alogliptin 12.5 mg group and -0.6% in the alogliptin 25 mg group, compared with -0.1% in the placebo group ($P < .001$).

Secondary Endpoint(s):

- HbA_{1c} of 7% or less was achieved in 52% of patients in the alogliptin 12.5 mg group and 44% in the alogliptin 25 mg group compared with 18% of the placebo recipients ($P < .001$).
- The least squares mean change from baseline in fasting plasma glucose was -19 mg/dL in the alogliptin 12.5 mg group and -17 mg/dL in the alogliptin 25 mg group compared with no change in the placebo group ($P < .001$).
- Incidence of fasting plasma glucose of 200 mg/dL or greater: 29% with alogliptin 12.5 mg ($P < .001$) and 31% with alogliptin 25 mg ($P = .003$) compared with 51% with placebo.
- Incidence of hyperglycemic rescue: 9% with alogliptin 12.5 mg ($P = .004$) and 8% with alogliptin 25 mg ($P = .003$) compared with 24% with placebo.
- Changes in weight were similar in the alogliptin (-0.39 and -0.67 kg) and placebo (-0.39 kg) groups.

- The incidence of hypoglycemia also did not differ between groups (0% to 1% in the alogliptin groups vs 3% in the placebo group); there were no reports of severe hypoglycemia in any of the groups.

Comments: Alogliptin also demonstrated greater efficacy over 12 weeks than placebo in 288 Japanese patients with type 2 diabetes inadequately controlled with metformin plus diet and exercise when added to metformin.¹⁹

Drug: Alogliptin vs Pioglitazone vs Alogliptin plus Pioglitazone, as add-on therapy with Metformin

Reference: DeFronzo RA, et al, 2012^{1,20}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 1,554 patients inadequately controlled on metformin (mean dosage, 1,887 mg/day). The study population was 45% male and 71% White; the mean age was approximately 54 years, and the mean baseline HbA_{1c} was 8.5%.

Intervention: Placebo; alogliptin 12.5 or 25 mg once daily; pioglitazone 15, 30, or 45 mg once daily; or alogliptin 12.5 or 25 mg in combination with pioglitazone 15, 30, or 45 mg, in addition to the patients' ongoing metformin regimen.

Results:

Primary Endpoint(s):

- Least squares mean change in HbA_{1c} from baseline: -0.1% with placebo, -0.9% with alogliptin 25 mg, -0.8% with pioglitazone 15 mg, -0.9% with pioglitazone 30 mg, -1% with pioglitazone 45 mg, -1.3% with alogliptin 25 mg plus pioglitazone 15 mg ($P \leq 0.01$ vs alogliptin 25 mg and pioglitazone 15 mg alone), -1.4% with alogliptin 25 mg plus pioglitazone 30 mg ($P < .01$ vs alogliptin 25 mg and pioglitazone 30 mg alone), and -1.6% with alogliptin 25 mg plus pioglitazone 45 mg ($P \leq .01$ vs alogliptin 25 mg and pioglitazone 45 mg alone).

Secondary Endpoint(s):

- Patients achieving HbA_{1c} of 7% or less: 6% with placebo, 27% with alogliptin 25 mg, 26% with pioglitazone 15 mg, 30% with pioglitazone 30 mg, 36% with pioglitazone 45 mg, 55% with alogliptin 12.5 mg plus pioglitazone 15 mg ($P \leq .01$ vs alogliptin 25 mg and pioglitazone 15 mg alone), 53% with alogliptin 25 mg plus pioglitazone 30 mg ($P \leq .01$ vs alogliptin 25 mg and pioglitazone 30 mg alone), and 60% with alogliptin 25 mg plus pioglitazone 45 mg ($P \leq .01$ vs alogliptin 25 mg and pioglitazone 45 mg alone).

- Least squares mean change in fasting plasma glucose from baseline: 7 mg/dL with placebo, -19 mg/dL with alogliptin 25 mg, -24 mg/dL with pioglitazone 15 mg, -29 mg/dL with pioglitazone 30 mg, -32 mg/dL with pioglitazone 45 mg, -38 mg/dL with alogliptin 25 mg plus pioglitazone 15 mg ($P \leq .01$ vs alogliptin 25 mg and pioglitazone 15 mg alone), -42 mg/dL with alogliptin 25 mg plus pioglitazone 30 mg ($P \leq .01$ vs alogliptin 25 mg and pioglitazone 30 mg alone), and -53 mg/dL with alogliptin 25 mg plus pioglitazone 45 mg ($P \leq .01$ vs alogliptin 25 mg and pioglitazone 45 mg alone).
- Incidence of hyperglycemic rescue: 11.4% of patients receiving pioglitazone alone versus 3.9% of patients receiving alogliptin 12.5 mg plus pioglitazone ($P = .005$) and 3.4% of patients receiving alogliptin 25 mg plus pioglitazone ($P \leq .001$).
- Changes in body weight: -0.7 kg with placebo, -0.02 kg with alogliptin 12.5 mg, -0.7 kg with alogliptin 25 mg, +1.5 kg with pioglitazone alone, +1.8 kg with alogliptin 12.5 mg plus pioglitazone, and +1.9 kg with alogliptin 25 mg plus pioglitazone.

Drug: Alogliptin vs Pioglitazone, as add-on therapy with Metformin and Pioglitazone

Reference: Bosi E, et al, 2011^{1,21}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 803 patients inadequately controlled on a regimen of pioglitazone 30 mg and metformin (at least 1,500 mg/day or the maximum tolerated dosage). The study population was 51% to 52% male and 60% to 64% White; mean age was 54.3 to 55.9 years, and the mean baseline HbA_{1c} was 8.1% to 8.3%.

Intervention: Alogliptin 25 mg once daily or pioglitazone 15 mg once daily was added to the pre-existing pioglitazone and metformin therapy (pioglitazone 30 mg once daily and a stable metformin dosage [median dosage, 1,700 mg/day]).

Results:

Primary Endpoint(s):

- Least squares mean change in HbA_{1c} from baseline: -0.7% with alogliptin 25 mg plus pioglitazone 30 mg plus metformin and -0.29% with pioglitazone 45 mg plus metformin (alogliptin regimen met predefined criteria for noninferiority and superiority compared with the pioglitazone and metformin regimen).

Secondary Endpoint(s):

- Patients achieving HbA_{1c} less than 7%: 33.2% with add-on alogliptin versus 21.3% with pioglitazone 45 mg ($P < .001$).
- Least squares mean change in fasting plasma glucose from baseline: -15 mg/dL with add-on alogliptin versus -4 mg/dL with pioglitazone 45 mg ($P < .001$).
- The incidence of hyperglycemic rescue was 10.9% with add-on alogliptin compared with 21.8% with pioglitazone 45 mg ($P < .001$).
- Mean increase in body weight from baseline to week 52 was similar in both treatment arms (1.1 kg with add-on alogliptin and 1.6 kg with pioglitazone dose increase).
- Hypoglycemia occurred in 4.5% of patients with add-on alogliptin and 1.5% with uptitrated pioglitazone.

Comments: Suggests greater improvement with the addition of alogliptin 25 mg to a 2-drug regimen of pioglitazone and metformin rather than increasing the pioglitazone dose.

Drug: Alogliptin vs Placebo, as add-on therapy with Pioglitazone with or without Metformin or a Sulfonylurea

Reference: Pratley RE, et al, 2009^{1,22}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 493 patients with type 2 diabetes inadequately controlled on a thiazolidinedione alone or on a thiazolidinedione with metformin or a sulfonylurea. The study population was 58% men and 74% White; the mean age was 55 years, and the mean baseline HbA_{1c} was 8%.

Intervention: Alogliptin 12.5 mg (197 patients), alogliptin 25 mg (199 patients), or placebo (97 patients) once daily in addition to their ongoing pioglitazone regimen (mean dosage, 34 to 36.2 mg/day) for 26 weeks. Those receiving metformin (54.3% to 57.7% of patients; median dose, 2,000 mg) or a sulfonylurea (18.6% to 22.1% of patients; median dose, 10 mg) prior to randomization were maintained on the combination during the treatment period.

Results:

Primary Endpoint(s):

- Least squares mean change in HbA_{1c} from baseline to week 26 in the ITT population: -0.66% in the alogliptin 12.5 mg group and -0.8% in the alogliptin 25 mg group compared with -0.19% in the placebo group ($P < .001$).

Secondary Endpoint(s):

- Patients achieving HbA_{1c} of 7% or less: 44.2% with the addition of alogliptin 12.5 mg and 49.2% with the addition of alogliptin 25 mg compared with 34% with the addition of placebo ($P < .016$).
- The least squares mean change from baseline in fasting plasma glucose: A reduction of 19.7 mg/dL in the alogliptin 12.5 mg group and 19.9 mg/dL in the alogliptin 25 mg group compared with a reduction of 5.7 mg/dL in the placebo group ($P = .003$).
- Incidence of fasting plasma glucose of 200 mg/dL or greater (marked hyperglycemia): 25% with alogliptin 12.5 mg and 21.7% with alogliptin 25 mg compared with 44.3% with placebo ($P < .001$).
- Incidence of hyperglycemic rescue did not differ (9.7% with alogliptin 12.5 mg, 9% with alogliptin 25 mg, and 12.4% with placebo).
- No changes in weight or lipid profile were observed for either alogliptin dose compared with placebo.
- The incidence of hypoglycemia also did not differ between groups (5.1% and 7% in the alogliptin groups vs 5.2% in the placebo group).

Comments: Alogliptin also demonstrated greater efficacy over 12 weeks than placebo when added to pioglitazone in 339 Japanese patients with type 2 diabetes inadequately controlled with pioglitazone plus diet and exercise.²³

Drug: Alogliptin vs Placebo, as add-on therapy with Glyburide

Reference: Pratley RE, et al, 2009^{1,24}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 500 patients with type 2 diabetes inadequately controlled on sulfonylurea monotherapy. The study population was 48% men and 71% White; the mean age was 57 years, and the mean baseline HbA_{1c} was 8.1%.

Intervention: Alogliptin 12.5 mg (203 patients), alogliptin 25 mg (198 patients), or placebo (99 patients) once daily in addition to the ongoing glyburide regimen (mean dosage, 11.2 to 12.4 mg/day) for 26 weeks.

Results:**Primary Endpoint(s):**

- Least squares mean change from baseline in HbA_{1c} at week 26 in the ITT population: -0.38% in the alogliptin 12.5 mg group and -0.52% in

the alogliptin 25 mg group compared with $+0.01\%$ in the placebo group ($P < .001$).

Secondary End[oint(s):

- HbA_{1c} of 7% or less was achieved in 29.6% of patients in the alogliptin 12.5 mg group ($P = .057$) and 34.8% in the alogliptin 25 mg group ($P = .002$) compared with 18.2% of placebo recipients.
- Least squares mean change from baseline in fasting plasma glucose: -4.7 mg/dL in the alogliptin 12.5 mg group ($P = .241$) and -8.4 mg/dL in the alogliptin 25 mg group ($P = .072$) compared with an increase of 2.2 mg/dL in the placebo group.
- Changes in weight did not differ between groups ($+0.6$ and $+0.68$ kg in the alogliptin groups vs -0.2 kg in the placebo group).
- The incidence of hypoglycemia also did not differ between groups (15.8% and 9.6% in the alogliptin groups vs 11.1% in the placebo group); severe hypoglycemia was reported in 1 patient in the placebo group, 2 patients in the alogliptin 12.5 mg group, and none in the alogliptin 25 mg group.

Comments: Patients could have been on a different sulfonylurea prior to enrollment in the study. If so, they were switched to an equivalent dose of glyburide during the 4-week run-in/stabilization phase prior to the initial dose of their assigned study drug.

Drug: Alogliptin vs Placebo, as add-on therapy with Insulin with or without Metformin

Reference: Rosenstock J, et al, 2009^{1,25}

Study Design: Randomized, double-blind, multicenter study

Study Funding: Takeda

Patients: 390 patients with type 2 diabetes not adequately controlled on insulin alone (42%) or on insulin with metformin (58%). The study population was 34% to 48% men and 62% to 69% White; the mean patient age was 55 to 56 years, the mean HbA_{1c} was 9.3%, and the mean insulin dosage was 55 to 57 units per day.

Intervention: Alogliptin 12.5 mg (131 patients), alogliptin 25 mg (129 patients), or placebo (130 patients) once daily for 26 weeks plus their insulin therapy. Patients already receiving metformin (56% to 61%; mean dosage, 1,632 to 1,849 mg/day) continued metformin therapy.

Results:**Primary Endpoint(s):**

- Least squares mean change from baseline in HbA_{1c} at week 26 in the ITT population: -0.63% in the alogliptin 12.5 mg group and -0.71% in the

alogliptin 25 mg group compared with -0.13% in the placebo group ($P < .001$).

Secondary Endpoint(s):

- Greater proportions of patients receiving alogliptin 12.5 or 25 mg achieved reductions in HbA_{1c} of at least 0.5%, 1%, or 1.5% compared with placebo ($P < .05$).
- The least squares mean change from baseline in fasting plasma glucose was $+2.3$ mg/dL in the alogliptin 12.5 mg group ($P = .662$) and -11.7 mg/dL in the alogliptin 25 mg group ($P = .03$) compared with an increase of 5.8 mg/dL in the placebo group.
- The incidence of hyperglycemic rescue was 21% in the alogliptin 12.5 mg group and 20% in the alogliptin 25 mg group compared with 40% in the placebo group ($P < .001$).
- Changes in weight were similar in the alogliptin ($+0.7$ and $+0.6$ kg) and placebo ($+0.6$ kg) groups.
- The incidence of hypoglycemia also did not differ between groups (27% in both alogliptin groups vs 24% in the placebo group); 6 severe hypoglycemic events occurred in 2 patients in the placebo group and 1 event occurred in the alogliptin 25 mg group.

Other Endpoint(s):

- Patients achieving HbA_{1c} of 7% or less: 8% with addition of alogliptin and 1% with addition of placebo.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

The contraindications, warnings, and precautions for the DPP-4 inhibitors are compared in Table 4.

Contraindications

Alogliptin is contraindicated in patients with a history of serious hypersensitivity reactions, such as anaphylaxis, angioedema, or severe cutaneous adverse reactions, to alogliptin-containing products.¹

Warnings and Precautions

Acute pancreatitis has been reported in patients receiving alogliptin therapy. Patients should be monitored for signs and symptoms of pancreatitis, and therapy should be discontinued if pancreatitis is suspected. It is not known whether patients with a history of pancreatitis are at an increased risk of developing pancreatitis while receiving alogliptin.¹

Serious hypersensitivity reactions, including anaphylaxis, angioedema, and severe cutaneous reactions including Stevens-Johnson syndrome, have been ob-

served in patients receiving alogliptin therapy. It is not known whether patients with a history of angioedema with another DPP-4 inhibitor will be predisposed to angioedema with alogliptin.¹

There have been reports of fatal and nonfatal hepatic failure in patients receiving alogliptin, although a causal relationship has not been confirmed. A liver test panel should be obtained prior to initiating therapy with alogliptin and upon report of symptoms potentially indicative of liver injury.¹ Caution is advised when administering alogliptin to patients with liver disease. Dose adjustments are not necessary in patients with mild to moderate impairment. Alogliptin has not been studied in patients with severe hepatic impairment.¹

When used in conjunction with alogliptin, a reduced dose of insulin or insulin secretagogues, such as sulfonylureas, may be required to minimize the risk of hypoglycemia.¹

There have been no clinical studies establishing macrovascular risk reduction with alogliptin or any other antidiabetic drug.¹

The safety and effectiveness of alogliptin have not been established in pediatric patients.¹

Alogliptin is in Pregnancy Category B. Abnormalities were not observed in animal models; however, placental transfer to the fetus was observed. Alogliptin should be used in pregnancy only if clearly needed.¹

Alogliptin is secreted in the milk of lactating rats in a 2:1 ratio to plasma. It is not known whether it is excreted in human milk. Caution is advised if alogliptin is administered to a breast-feeding woman.¹

ADVERSE REACTIONS

Adverse reactions that occurred in at least 4% of patients treated with alogliptin and with more frequency with alogliptin than placebo were nasopharyngitis, headache, and upper respiratory tract infection.¹

DRUG INTERACTIONS

Alogliptin is primarily renally excreted, and CYP-450-related metabolism is negligible. Alogliptin is not an inducer or inhibitor of CYP-450 enzymes.¹ Clinically relevant interactions have not been observed with the CYP substrates or inhibitors tested or with renally excreted drugs.¹

Alogliptin pharmacokinetics were not altered by administration with a potent CYP2C9 inhibitor (fluconazole), CYP3A4 inhibitor (ketoconazole), or CYP2C8/9 inhibitor (gemfibrozil).²⁶ Pharmacokinetic interactions have also not been observed between alogliptin and glyburide, metformin, or pioglitazone.^{27,28}

Table 4. Contraindications, warnings, and precautions included in the product labeling of DPP-4 inhibitors^{1,9,32,33}

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Contraindications				
History of serious hypersensitivity to the agent	X	X	X	X
Warnings and precautions				
Use with medications known to cause hypoglycemia (eg, insulin, insulin secretagogues)	X	X	X	X
Serious allergic and hypersensitivity reactions	X		X	X
No data on macrovascular risk reduction	X	X	X	X
Acute pancreatitis	X		X	X
Dosage adjustment in renal insufficiency	X			X
Acute renal failure				X
Hepatic effects	X			
Special populations				
Geriatric	No unique precautions	No unique precautions	No unique precautions; careful dose selection with assessment of renal function	No unique precautions; careful dose selection with assessment of renal function
Pediatric	Not established	Not established	Not established	Not established
Pregnancy	Category B	Category B	Category B	Category B
Breast-feeding	Caution	Caution	Caution	Caution

Alogliptin did not have a significant effect on the pharmacokinetics or pharmacodynamics of warfarin with coadministration.²⁹

When used in conjunction with alogliptin, a reduced dose of insulin or insulin secretagogues, such as sulfonylureas, may be required to minimize the risk of hypoglycemia.¹

RECOMMENDED MONITORING

Renal function should be monitored before initiation of therapy and periodically during therapy because the dosage requires adjustment in patients with renal function impairment. A liver test panel is also recommended prior to initiating alogliptin therapy. Blood glucose and HbA_{1c} should be monitored periodically throughout therapy.¹

DOSING

The recommended dosage of alogliptin is 25 mg once daily with or without food. No dosage adjustment is necessary for patients with mild renal impairment (CrCl 60 mL/min or greater). In patients with moderate renal impairment (CrCl 30 to 59 mL/min), the recommended dosage is 12.5 mg once daily. In patients with severe renal impairment or end-stage renal disease (CrCl less than 30 mL/min or requiring hemodialysis), the recommended dosage is 6.25 mg once daily. Patients requiring hemodialysis can receive their dose of alogliptin without regard to the timing of the dialysis. No information is available for patients being treated with peritoneal dialysis.^{1,12} Dosing recommendations for the DPP-4 inhibitors are compared in Table 5.

Table 5. Dosing recommendations for DPP-4 inhibitors^{1,9,32,33}

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Usual dosage	25 mg once daily	5 mg once daily	2.5 to 5 mg once daily	100 mg once daily
Food	With or without food	With or without food	With or without food	With or without food
Dosage in special populations				
Renal impairment	CrCl 30 to < 60 mL/min: 12.5 mg once daily CrCl < 30 mL/min: 6.25 mg once daily	No dosage adjustment	CrCl ≤ 50 mL/min: 2.5 mg once daily	CrCl 30 to 50 mL/min: 50 mg once daily CrCl < 30 mL/min: 25 mg once daily
Hepatic impairment	No dosage adjustment	No dosage adjustment	No dosage adjustment	No dosage adjustment
Elderly	No dosage adjustment	No dosage adjustment	No dosage adjustment	No dosage adjustment
Drug interactions	No dosage adjustment	Avoid with rifampin	With a potent CYP3A4/5 inhibitor: 2.5 mg once daily	No dosage adjustment

PRODUCT AVAILABILITY

Alogliptin received FDA approval on January 25, 2013. It is available as 6.25, 12.5, and 25 mg tablets. Available dosage forms for the DPP-4 inhibitors are compared in Table 6. Alogliptin tablets should be stored at USP controlled room temperature.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for any of the currently available DPP-4 inhibitors. A REMS originally required that a medication guide be dispensed with every sitagliptin prescription, but this requirement was discontinued in April 2011.^{30,31}

CONCLUSION

Alogliptin is an addition to the DPP-4 inhibitor class of drugs for the treatment of patients with type 2 diabetes. It is intended to be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It can be used as monotherapy or in combination with other antidiabetic agents, including metformin, pioglitazone, sulfonylureas, and insulin; it was approved simultaneously for use as a single-agent product and in combination dosage forms with metformin and pioglitazone. All of the DPP-4 inhibitors are effective in lowering blood glucose levels and improving HbA_{1c}, and all can be given once daily without regard to meals. Like

Table 6. Available dosage forms and packaging for DPP-4 inhibitors^{1,9,32,33,36}

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Single agents	<i>Nesina</i> 6.25 mg tablets (30s and 90s), 12.5 mg tablets (30s, 90s, and 500s), 25 mg tablets (30s, 90s, and 500s)	<i>Tradjenta</i> 5 mg tablets (30s, 90s, and UD 100s)	<i>Onglyza</i> 2.5 mg tablets (30s and 90s), 5 mg tablets (30s, 90s, 500s, and UD 100s)	<i>Januvia</i> 25 mg tablets (30s, 90s, and UD 100s), 50 mg tablets (30s, 90s, and UD 100s), 100 mg tablets (30s, 90s, 1,000s, UD 30s, and UD 100s)
Combination agents	Alogliptin/metformin (<i>Kazano</i>), alogliptin/pioglitazone (<i>Oseni</i>)	Linagliptin/metformin (<i>Jentadueto</i>)	Saxagliptin/metformin (<i>Kombiglyze XR</i>)	Sitagliptin/metformin (<i>Janumet</i>), sitagliptin/metformin (<i>Janumet XR</i>), sitagliptin/simvastatin (<i>Juwisync</i>)

sitagliptin and saxagliptin, alogliptin requires dose reduction in patients with renal impairment. Like linagliptin and sitagliptin, it has not been associated with significant drug interactions. They all appear to be well tolerated. Postmarketing experience and direct comparative studies are necessary to determine which drug may be more efficacious and/or safer.

REFERENCES

1. *Nesina* [package insert]. Deerfield, IL: Takeda Pharmaceuticals America Inc; January 2013.
2. Covington P, Christopher R, Davenport M, et al. Pharmacokinetic, pharmacodynamic, and tolerability profiles of the dipeptidyl peptidase-4 inhibitor alogliptin: a randomized, double-blind, placebo-controlled, multiple-dose study in adult patients with type 2 diabetes. *Clin Ther*. 2008;30(3):499-512.
3. Christopher R, Covington P, Davenport M, et al. Pharmacokinetics, pharmacodynamics, and tolerability of single increasing doses of the dipeptidyl peptidase-4 inhibitor alogliptin in healthy male subjects. *Clin Ther*. 2008;30(3):513-527.
4. Golightly LK, Drayna CC, McDermott MT. Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. *Clin Pharmacokinet*. 2012;51(8):501-514.
5. Hirayama M, Matsuno K, Fujita T, et al. Pharmacokinetics, pharmacodynamics, and tolerability of single and multiple doses of the dipeptidyl peptidase-4 inhibitor alogliptin in Japanese healthy male subjects [abstract]. American Diabetes Association's 68th Scientific Sessions; June 6-10, 2008; San Francisco, CA. Abstract 521-P. http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=69829. Accessed May 30, 2008.
6. Moritoh Y, Takeuchi K, Asakawa T, Kataoka O, Odaka H. Chronic administration of alogliptin, a novel, potent, and highly selective dipeptidyl peptidase-4 inhibitor, improves glycemic control and beta-cell function in obese diabetic ob/ob mice. *Eur J Pharmacol*. 2008;588(2-3):325-332.
7. Moritoh Y, Takeuchi K, Asakawa T, Kataoka O, Odaka H. The dipeptidyl peptidase-4 inhibitor alogliptin in combination with pioglitazone improves glycemic control, lipid profiles, and increases pancreatic insulin content in ob/ob mice. *Eur J Pharmacol*. 2009;602(2-3):448-454.
8. Eliasson B, Möller-Goede D, Eeg-Olofsson K, et al. Lowering of postprandial lipids in individuals with type 2 diabetes treated with alogliptin and/or pioglitazone: a randomised double-blind placebo-controlled study. *Diabetologia*. 2012;55(4):915-925.
9. *Tradjenta* [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; September 2012.
10. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab*. 2011;13(1):7-18.
11. Gerich J. DPP-4 inhibitors: what may be the clinical differentiators? *Diabetes Res Clin Pract*. 2010;90(2):131-140.
12. Karim A, Fleck P, Hetman L, et al. Single-dose pharmacokinetics of the dipeptidyl peptidase-4 inhibitor alogliptin in subjects with renal impairment [abstract]. American Diabetes Association's 68th Scientific Sessions; June 6-10, 2008; San Francisco, CA. Abstract 538-P. http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=69845. Accessed May 30, 2008.
13. Karim A, Fleck P, Dorsey D, Zhang W, Mekki Q, Preston RA. Single-dose pharmacokinetics of alogliptin benzoate (SYR-322), a highly selective dipeptidyl peptidase-4 inhibitor, in subjects with moderate hepatic impairment [abstract]. *J Clin Pharmacol*. 2007;47(9):1207.
14. Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association; European Association for the Study of Diabetes. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364-1379.
15. Fleck P, Christopher R, Covington P, Wilson C, Mekki Q. Efficacy and safety of alogliptin monotherapy over 12 weeks in patients with type 2 diabetes [abstract]. American Diabetes Association's 68th Scientific Sessions; June 6-10, 2008; San Francisco, CA. Abstract 479-P. http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=69787. Accessed May 30, 2008.
16. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 010 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2008;31(12):2315-2317.
17. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naïve patients with type 2 diabetes. *Diabetes Care*. 2010;33(11):2406-2408.
18. Nauck MA, Ellis GC, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 008 Group. Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicentre, randomised, double-blind, placebo-controlled study. *Int J Clin Pract*. 2009;63(1):46-55.
19. Seino Y, Miyata Y, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study. *Diabetes Obes Metab*. 2012;14(10):927-936.
20. DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2012;97(5):1615-1622.
21. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active-controlled,

parallel-group study. *Diabetes Obes Metab.* 2011;13(12):1088-1096.

22. Pratley RE, Reusch JE, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 009 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Curr Med Res Opin.* 2009;25(10):2361-2371.

23. Kaku K, Itayasu T, Hiroi S, Hirayama M, Seino Y. Efficacy and safety of alogliptin added to pioglitazone in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label long-term extension study. *Diabetes Obes Metab.* 2011;13(11):1028-1035.

24. Pratley RE, Kipnes MS, Fleck PR, Wilson C, Mekki Q; Alogliptin Study 007 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. *Diabetes Obes Metab.* 2009;11(2):167-176.

25. Rosenstock J, Rendell MS, Gross JL, Fleck PR, Wilson CA, Mekki Q. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA(1C) without causing weight gain or increased hypoglycaemia. *Diabetes Obes Metab.* 2009;11(12):1145-1152.

26. Karim A, Fleck P, Harris S, Schuster J, Zhang W, Mekki Q. Effect of fluconazole, ketoconazole, and gemfibrozil on the pharmacokinetics of alogliptin benzoate (SYR-322) in healthy subjects [abstract]. *J Clin Pharmacol.* 2007;47(9):1207.

27. Karim A, Laurent A, Munsaka M, Wann E, Fleck P, Mekki Q. Coadministration of pioglitazone or glyburide and alogliptin: pharmacokinetic drug interaction assessment in healthy participants. *J Clin Pharmacol.* 2009;49(10):1210-1219.

28. Covington P, Christopher R, Davenport M, et al. Lack of pharmacokinetic interaction between alogliptin benzoate (SYR-322) and metformin in healthy subjects [abstract].

American Diabetes Association's 67th Scientific Sessions; June 22-26, 2007; Chicago, IL. Abstract 2136-PO. http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=55607. Accessed January 15, 2008.

29. Karim A, Harris S, Fleck P, Moore R, Zhang W, Mekki Q. Assessment of drug interaction between alogliptin benzoate (SYR-322), a highly selective dipeptidyl peptidase-4 inhibitor, and warfarin at steady state [abstract]. *J Clin Pharmacol.* 2007;47(9):1207.

30. Approved risk evaluation and mitigation strategies (REMS). US Food and Drug Administration Web site. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>. Updated December 31, 2012. Accessed January 28, 2013.

31. Merck Sharp & Dohme Corp. NDA 21-995: *Januvia* (sitagliptin) tablet risk evaluation and mitigation strategy (REMS). Food and Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021995s010s011s012s014REMSJanuvia.pdf. Published February 2010. Accessed May 5, 2011.

32. *Onglyza* [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; December 2011.

33. *Januvia* [package insert]. Whitehouse Station, NJ: Merck & Co Inc; April 2012.

34. Forst T, Uhlig-Laske B, Ring A, Ritzhaupt A, Graefe-Mody U, Dugi KA. The oral DPP-4 inhibitor linagliptin significantly lowers HbA1c after 4 weeks of treatment in patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2011;13(6):542-550.

35. Scheen AJ. Pharmacokinetics of dipeptidylpeptidase-4 inhibitors. *Diabetes Obes Metab.* 2010;12(8):648-658.

36. Dipeptidyl peptidase-4 inhibitors. Facts and Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2013. Accessed January 31, 2013. ■

Continuing Education Case Study Quiz

Goal—The goal of this program is to educate pharmacists about the use of alogliptin for the treatment of patients with diabetes mellitus.

Objectives—At the completion of this program, the reader will be able to:

1. Describe the pharmacology and pharmacokinetics of alogliptin.
2. Discuss the risks associated with the use of alogliptin.
3. Discuss the potential benefit of alogliptin for an individual patient.
4. Apply the information on the use of alogliptin to a case study.

Key Words—diabetes mellitus, dipeptidyl peptidase-4 inhibitors, new drugs

1. The US Food and Drug Administration (FDA)–approved indication for alogliptin is as an adjunct to diet and exercise to improve glycemic control:
 - a. in adolescents and adults with type 2 diabetes mellitus as monotherapy or in combination with other antidiabetic medications.
 - b. in adults with type 2 diabetes mellitus as monotherapy or in combination with other antidiabetic medications.
 - c. in adults with type 2 diabetes mellitus only in combination with other antidiabetic medications.
 - d. in children and adults with type 1 and type 2 diabetes mellitus as monotherapy or in combination with other antidiabetic medications.
2. Alogliptin is in which class of antidiabetic medications?
 - a. Alpha-glucosidase inhibitors
 - b. Dipeptidyl peptidase-4 (DPP-4) inhibitors
 - c. Sodium-glucose co-transporter-2 (SGLT2) inhibitors
 - d. Sulfonylureas
3. Alogliptin and which drug(s) have greater than 10,000 fold selectivity for the target enzyme?
 - a. Linagliptin
 - b. Saxagliptin
 - c. Sitagliptin
 - d. All of the above
4. What is the half-life of alogliptin?
 - a. 2 hours
 - b. 12 hours
 - c. 21 hours
 - d. 72 hours
5. Alogliptin is primarily eliminated hepatically.
 - a. True
 - b. False
6. In the Nauck et al study assessing alogliptin as add-on therapy with metformin, how much did the A1C change for patients receiving alogliptin 25 mg once daily?
 - a. -0.1%
 - b. -0.6%
 - c. -0.9%
 - d. -1.1%
7. In patients receiving alogliptin, there have been reports of fatal and nonfatal:
 - a. Central nervous system toxicity.
 - b. Hepatic failure.
 - c. Pulmonary toxicity.
 - d. Renal failure.
8. Which of the following serious hypersensitivity reactions have been observed in patients receiving alogliptin?
 - a. Anaphylaxis
 - b. Angioedema
 - c. Steven-Johnson syndrome
 - d. All of the above
9. Alogliptin is in Pregnancy Category:
 - a. A.
 - b. B.
 - c. C.
 - d. X.

Case History

FC is a 48-year-old male with a history of type 2 diabetes, hypertension, hypercholesterolemia, and hypertriglyceridemia. He is currently taking metformin 1,000 mg twice a day, lisinopril 30 mg once a day, hydrochlorothiazide 12.5 mg once a day, simvastatin 40 mg once a day, and glipizide 10 mg once a day. His last A1C level was 8.4%, and his most recent serum creatinine was 1.5 mg/dL. FC is 5 ft, 7 in. tall and weighs 240 pounds. His physician has decided to start him on alogliptin.

10. What is the recommended alogliptin dose for FC?
 - a. 6.25 mg once daily
 - b. 12.5 mg once daily
 - c. 25 mg once daily
 - d. 50 mg once daily
11. When should FC's pharmacist tell him is the best time for him to take his alogliptin?
 - a. On an empty stomach 30 minutes before breakfast
 - b. At least 30 minutes before dinner
 - c. 30 minutes before going to bed
 - d. With or without food at about the same time each day
12. Following initiation of alogliptin therapy, which of FC's medications may require a dosage reduction?
 - a. Glipizide
 - b. Hydrochlorothiazide
 - c. Lisinopril
 - d. Simvastatin
13. Alogliptin dose adjustment is required in patients with:
 - a. Mild hepatic impairment.
 - b. Moderate hepatic impairment.
 - c. Mild renal impairment.
 - d. Moderate renal impairment.
14. Which laboratory monitoring is NOT routinely recommended prior to initiating alogliptin therapy?
 - a. HbA1C
 - b. Liver function tests
 - c. Serum amylase
 - d. Serum creatinine
15. After being on alogliptin for 8 months, FC develops acute pancreatitis. What is the best course of action?
 - a. Determine the likely cause before making any decision regarding changes to the alogliptin therapy.
 - b. Increase his simvastatin dose and continue all other medications unchanged.
 - a. Reduce his alogliptin dose by 50%.
 - d. Discontinue alogliptin therapy.

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Release Date: July 1, 2013

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