NEW DRUG UPDATE

Drug Name:	**alogliptin; alogliptin/metformin; alogliptin/pioglitazone**
Trade Name (Manufacturer):	**Nesina®; Kazano; Oseni** (Takeda Pharmaceuticals)
Form:	Tablets
Strength:	**Nesina**: 6.25 mg, 12.5 mg, and 25 mg **Kazano**: 12.5 mg/500 mg and 12.5 mg/1,000 mg **Oseni**: 25 mg/15 mg, 25 mg/30 mg, 25 mg/45 mg, 12.5 mg/15 mg, 12.5 mg/30 mg, and 12.5 mg/45 mg
FDA Approval:	January 25, 2013
Market Availability:	Anticipated summer 2013
FDA Approval Classification:	Standard review
Classification:	Nesina: Antihyperglycemic, DPP-4 Inhibitors (C4J) Kazano: Antihyperglycemics, DPP-4 Inhibitor and Biguanide Combination (C4F) Oseni: Antihyperglycemics, DPP-4 Enzyme Inhibitor and Thiazolidinedione (C4C)

***Indication*:**[1,2,3] Alogliptin (Nesina), alogliptin/metformin (Kazano), and alogliptin/pioglitazone (Oseni) are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Nesina, Kazano, and Oseni are not indicated for type 1 diabetes or diabetic ketoacidosis.

***Contraindications/Warnings*:** Nesina, Kazano, and Oseni are contraindicated in patients with a history of sensitivity to products containing alogliptin. Kazano is contraindicated in patients who have a history of hypersensitivity reactions to metformin. Oseni is contraindicated in patients with a history of hypersensitivity to pioglitazone.

Kazano is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for men; greater than or equal to 1.4 mg/dL for women; or abnormal creatinine clearance [CrCl]).

Kazano is contraindicated in patients with acute or chronic metabolic acidosis including diabetic ketoacidosis. Insulin should be used to treat diabetic ketoacidosis.

Oseni should not be started in patients with heart failure, New York Heart Association (NYHA) Class III or IV.

Acute pancreatitis has been associated with the use of alogliptin. Patients should be monitored closely for signs and symptoms of acute pancreatitis. If pancreatitis is suspected therapy should be discontinued and appropriate management should be started.

Hypersensitivity reactions have occurred in patients taking alogliptin including anaphylaxis, angioedema, and severe cutaneous adverse reactions. If severe reactions occur the medication should be discontinued and the patient should start an alternative diabetes therapy. Caution should be used if the patient has experienced angioedema when previous DPP-4 inhibitors have been used.

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.

Fatal and non-fatal hepatic failure has been reported in patients taking alogliptin and pioglitazone. It is recommended that a liver test is performed prior to beginning therapy and, if abnormal, therapy should be started with caution. Kazano should be avoided in patients with clinical or laboratory evidence of hepatic impairment as it has been associated with incidences of lactic acidosis due to metformin. Patients who report symptoms of liver injury after beginning Nesina, Kazano, or Oseni should have a liver test performed and, if clinically significant elevations in liver enzymes are found and if abnormal liver tests persist or worsen, the medication should be interrupted to establish the cause. Nesina, Kazano, and Oseni should not be re-initiated in these patients without another explanation for the cause of the liver test abnormalities.

A lower dose of insulin or insulin secretagogues may be required when used with Nesina, Kazano, or Oseni to minimize the risk of hypoglycemia.

All contraindications and warnings are the same for the individual ingredients, pioglitazone and metformin. Please consult the prescribing information for full details.

***Drug Interactions*:** No significant drug-drug interactions were observed with alogliptin and CYP-substrates/inhibitors or with any renally excreted drugs tested.

All drug interactions are the same for the individual ingredients, pioglitazone and metformin. Please consult the prescribing information for full details.

***Common Adverse Effects*:** In clinical trials the overall incidence of adverse effects associated with Nesina, placebo, and active comparators was 66 percent, 62 percent, and 70 percent, respectively. The overall therapy discontinuation due to adverse effects in Nesina, placebo, and active comparators was 4.7 percent, 4.5 percent, and 6.2 percent, respectively. The most common adverse reactions of Nesina that occurred more frequently compared to patients treated with placebo includes nasopharyngitis (4.4 percent), headache (4.2 percent), and upper respiratory tract infection (4.2 percent). Pancreatitis (0.2 percent), hypersensitivity reactions (0.6 percent), and hypoglycemia (1.5 to 5.4 percent) have also been reported with the use of Nesina.

The overall incidence of adverse effects associated with Kazano and placebo was 74 and 76 percent, respectively. The overall discontinuation of therapy due to adverse effects with Kazano, placebo, metformin, and alogliptin were 6.2 percent, 1.9 percent, 6.4 percent, and five percent, respectively. The most common adverse effects associated with Kazano which occurred more frequently compared to patients treated with alogliptin, metformin, or placebo includes upper respiratory tract infection (eight percent), nasopharyngitis (6.8 percent), diarrhea (5.5 percent), hypertension (5.5 percent), headache (5.3 percent), back pain (4.3 percent), and urinary tract infection (4.2 percent).

The overall incidence of adverse effects associated with Oseni and placebo was 65 percent and 57 percent, respectively. The overall discontinuation of therapy due to adverse effects with Oseni, placebo, pioglitazone, and alogliptin was 2.5 percent, two percent, 3.7 percent, and 1.3 percent, respectively. The most common adverse effects associated with Oseni which occurred more frequently compared to patients treated with alogliptin, pioglitazone, or placebo includes nasopharyngitis (4.9 percent), back pain (4.2 percent), and upper respiratory tract infection (4.1 percent).

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.

All adverse effects are the same for the individual ingredients, pioglitazone and metformin. Please consult the prescribing information for full details.

***Special Populations*:**

Pediatrics: The safety and efficacy of Nesina, Kazano, and Oseni have not been established in pediatric patients.

Pregnancy: Nesina and Kazano are Pregnancy Category B. Oseni is Pregnancy Category C.

Renal Impairment: Assessment of renal function is recommended prior to starting Nesina and periodically thereafter. Dose adjustment for Nesina is not needed in patients with mild renal impairment (CrCl greater than or equal to 60 mL/minute). In patients with moderate renal impairment (CrCl greater than or equal to 30 mL/minute but less than 60 mL/minute) the dose of Nesina is 12.5 mg once daily. In patients with severe renal impairment (CrCl greater than or equal to 15 mL/minute but less than 30 mL/minute) or end-stage renal disease (ESRD) (CrCl less than 15 mL/minute or on hemodialysis) the dose of Nesina is 6.25 mg once daily.

Kazano is contraindicated in patients with renal impairment because of an increased risk of lactic acidosis due to metformin.

Assessment of renal function is recommended prior to starting Oseni and periodically thereafter. Dose adjustment is not needed in patients with mild renal impairment (CrCl greater than or equal to 60 mL/minute). Patients with moderate renal impairment (CrCl greater than or equal to 30 mL/minute but less than 60 mL/minute) should be administered 12.5 mg/15 mg, 12.5 mg/30 mg, or 12.5 mg/45 mg once daily. Treatment with Oseni is not recommended in patients who have severe renal impairment or ESRD. Coadministration of pioglitazone and alogliptin 6.25 mg once daily may be considered for these patients. Patients taking strong CYP2C8 inhibitors should not take more than 25 mg/15 mg of Oseni daily.

All special population considerations are the same for the individual ingredients, pioglitazone and metformin. Please consult the prescribing information for full details.

***Dosages*:** The recommended dose of Nesina is 25 mg taken once daily with or without food.

The starting dose of Kazano should be individualized for each patient based on their current diabetic therapy regimen. Kazano should be taken twice daily with food and cannot be split or crushed before swallowing. Gradual dose escalations may be needed to reduce gastrointestinal side effects caused by metformin. The dose of Kazano may be adjusted based on efficacy and tolerability but should not exceed the maximum daily dose of 25 mg alogliptin and 2,000 mg metformin.

Oseni should be taken once daily with or without food and swallowed whole. The recommended starting dose for patients insufficiently controlled on diet and exercise, insufficiently controlled on metformin monotherapy, or on alogliptin who require additional glycemic control is 25 mg/15 mg or 25 mg/30 mg. The recommended starting dose for patients on pioglitazone who require additional glycemic control is 25 mg/15 mg, 25 mg/30 mg, or 25 mg/45 mg based on current therapy. The recommended starting dose for patients with NYHA Class I or II congestive heart failure is 25 mg/15 mg. Patients who are switching from alogliptin coadministered with pioglitazone may start Oseni at the dose of their current alogliptin and pioglitazone therapy.

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.

Based on hemoglobin A1c (HbA1c) levels, Oseni can be titrated up to a maximum of 25 mg/45 mg once daily. After starting or adjusting Oseni doses the patient should be monitored closely for adverse effects such as heart failure. If heart failure develops it should be managed according to current standards of care and prescribers should consider pioglitazone dose reduction or discontinuation.

Clinical Trials**:** *A literature search was performed using "Nesina", "Kazano", "Oseni", and "alogliptin". Placebo-controlled trials were included in the absence of comparative trials.*

alogliptin (Nesina) versus placebo

A double-blind, placebo-controlled study was conducted over 26 weeks in patients (n=329) with type 2 diabetes.[4] Patients were randomized to receive Nesina 12.5 mg, 25 mg, or placebo once daily. The mean HbA1c baseline for patients taking Nesina 25 mg and placebo once daily was 7.9 percent and eight percent, respectively. The mean baseline fasting plasma glucose (FPG) was 172 mg/dL and 173 mg/dL for patients taking Nesina 25 mg and placebo once daily, respectively. Statistically significant improvements in baseline HbA1c and FPG occurred in patients taking Nesina 25 mg daily compared to patients taking placebo (95% CI, $p<0.01$). Patients achieving an HbA1c level of less than or equal to seven percent were 44 percent and 23 percent for Nesina 25 mg patients and placebo patients, respectively ($p<0.01$). The change in baseline FPG was -16 for Nesina treated patients and 11 for placebo treated patients.

alogliptin (Nesina) versus pioglitazone versus alogliptin/pioglitazone (Oseni)

A total of 655 patients with a mean baseline HbA1c of 8.8 percent were randomized to receive Nesina 25 mg alone, pioglitazone 30 mg alone, Nesina 12.5 mg with pioglitazone 30 mg, or Nesina 25 mg with pioglitazone 30 mg once daily in a double-blind, active-controlled study over 26 weeks.[5] The mean baseline FPG levels were 189 mg/dL, 189 mg/dL, and 185 mg/dL for patients taking Nesina 25 mg, pioglitazone 30 mg, and Nesina 25 mg with pioglitazone 30 mg once daily, respectively. Patients treated with Nesina 25 mg with pioglitazone 30 mg had statistically significant improvements from baseline HbA1c and FPG compared to Nesina 25 mg alone and pioglitazone 30 mg alone (95% CI, $p<0.01$). The percent of patients achieving an HbA1c of less than or equal to seven percent was 24 percent, 34 percent, and 63 percent for patients taking Nesina 25 mg alone, pioglitazone 30 mg alone, and Nesina 25 mg with pioglitazone 30 mg, respectively ($p<0.01$). The mean decrease in baseline FPG was 26 mg/dL, 37 mg/dL, and 50 mg/dL for Nesina 25 mg alone, pioglitazone 30 mg alone, and Nesina 25 mg with pioglitazone 30 mg, respectively.

alogliptin/pioglitazone (Oseni) versus pioglitazone

A 12 week randomized, double-blind, placebo-controlled study was performed in adult patients with type 2 diabetes throughout 33 centers across Japan to assess the efficacy and safety of alogliptin with pioglitazone compared to pioglitazone alone.[6] Patients had poor glycemic control (HbA1c greater than or equal to 6.9 percent and less than ten percent for at least 14 weeks and maximum HbA1c variation of ten percent between weeks six and two) despite diet, exercise, and taking 15 mg or 30 mg of pioglitazone daily for at least 16 weeks. Patients were randomized in a 1:1:1 ratio to receive alogliptin 12.5 mg or 25 mg or placebo once daily to their stable pioglitazone therapy for 12 weeks. Patients completing the 12 week double-blinded study were allowed to enter an open-label extension study for 40 weeks which compared alogliptin 12.5 mg and 25 mg combined with pioglitazone. Patients who were on alogliptin during the double-blind portion of the study were allowed to continue with the same therapy. Patients who were taking placebo plus pioglitazone during the double-blind phase were randomized to

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.

alogliptin 12.5 mg or 25 mg plus pioglitazone. After 12 weeks of treatment in the double-blind phase the change from baseline HbA1c was greater in the alogliptin plus pioglitazone treatment groups versus the placebo plus pioglitazone group (p<0.0001). Additionally, a greater proportion of patients treated with alogliptin achieved HbA1c levels of less than 6.9 percent and 6.2 percent compared to placebo (95% CI, p<0.05). Patients treated with alogliptin also had greater improvements in other laboratory levels such as fasting blood glucose, two hour postprandial blood glucose, total cholesterol, LDL-cholesterol, and triglycerides (95% CI, p<0.05). The open-label phase concluded that alogliptin significantly lowered patients' HbA1c, fasting blood glucose, and two hour postprandial glucose levels. During the 12 week double-blind study 37.8 percent, 45.1 percent, and 47.8 percent of patients treated with alogliptin 12.5 mg plus pioglitazone, alogliptin 25 mg plus pioglitazone, and placebo plus pioglitazone experienced an adverse event, respectively. Nasopharyngitis was the most common adverse event reported with an incidence of 4.5 percent, 12.4 percent, and 5.2 percent in patients taking alogliptin 12.5 mg plus pioglitazone, alogliptin 25 mg plus pioglitazone, and placebo plus pioglitazone, respectively. The study concluded that alogliptin added to pioglitazone therapy with diet and exercise improved glycemic control and is generally safe and well tolerated in Japanese patients with type 2 diabetes.

alogliptin (Nesina) versus metformin versus alogliptin/metformin (Kazano)

A total of 784 patients with a mean baseline HbA1c of 8.4 percent were randomized to one of seven treatment groups (placebo, metformin 500 mg or 1,000 mg twice daily, Nesina 12.5 mg twice daily, Nesina 25 mg daily, or Nesina 12.5 mg with metformin 500 mg or 1,000 mg twice daily) in a double-blind, placebo-controlled study for 26 weeks.[7] Patients treated with the Nesina with metformin regimens had statistically significant improvements in HbA1c and FPG compared to patients treated with Nesina and metformin alone (95% CI, p<0.05). The percent of patients achieving an HbA1c less than seven percent was four percent, 20 percent, 27 percent, 34 percent, 47 percent, and 59 percent for patients taking placebo, Nesina 12.5 mg twice daily, metformin 500 mg twice daily, metformin 1,000 mg twice daily, Nesina 12.5 mg with metformin 500 mg twice daily, and Nesina 12.5 mg with metformin 1,000 mg twice daily, respectively (p<0.05). The FPG change from baseline was 12 mg/dL, -10 mg/dL, -12 mg/dL, -32 mg/dL, -32 mg/dL, and -46 mg/dL for patients treated with placebo, Nesina 12.5 mg twice daily, metformin 500 mg twice daily, metformin 1,000 mg twice daily, Nesina 12.5 mg with metformin 500 mg twice daily, and Nesina 12.5 mg with metformin 1,000 mg twice daily, respectively.

metformin versus alogliptin/metformin (Kazano)

In a placebo-controlled study, 527 patients with type 2 diabetes already on metformin at doses of at least 1,500 mg per day or at maximum tolerated dose were randomized to receive Nesina 12.5 mg, Nesina 25 mg, or placebo and were maintained on a stable dose of metformin (mean dose equal to 1,700 mg) during a 26 week study.[8] Before randomization all patients entered a four-week, single-blind, placebo run-in period. Patients who were treated with Nesina 25 mg with metformin had statistically significant improvements in HbA1c and FPG compared to patients receiving placebo (95% CI, p<0.001). Patients had a mean baseline HbA1c of 7.9 percent and eight percent for the Nesina 25 mg with metformin group and placebo with metformin group, respectively. The percent of patients achieving an HbA1c of less than or equal to seven percent was 44 percent and 18 percent for the Nesina 25 mg with metformin group and placebo with metformin group, respectively (p<0.001). The FPG change from baseline was -17 mg/dL and zero mg/dL for patients treated with Nesina 25 mg with metformin and patients treated with placebo with metformin, respectively.

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.

metformin and placebo versus metformin and alogliptin (Nesina) versus metformin and pioglitazone versus alogliptin/metformin (Kazano) and pioglitazone

In a double-blind, placebo-controlled study, 1,554 patients with type 2 diabetes already on metformin at doses of at least 1,500 mg per day or at maximum tolerated dose were randomized to one of 12 treatment groups (placebo, 12.5 mg or 25 mg of Nesina alone, 15 mg, 30 mg, or 45 mg of pioglitazone alone, or 12.5 mg or 25 mg of Nesina with 15 mg, 30 mg, or 45 mg of pioglitazone) and maintained on a stable dose of metformin (mean dose equal to 1,700 mg) during a 26 week study.[9] Before randomization all patients entered a four-week, single-blind, placebo run-in period. Patients treated with Nesina with pioglitazone had statistically significant improvements in A_1c and FPG compared to patients treated with placebo, Nesina alone, or pioglitazone alone when added to background metformin treatment (95% CI, p≤0.01). The percent of patients achieving an HbA1c of less than or equal to seven percent was six percent, 27 percent, 26 percent, 30 percent, 36 percent, 55 percent, 53 percent, and 60 percent in patients treated with placebo, Nesina 25 mg, pioglitazone 15 mg, 30 mg, and 45 mg, Nesina 25 mg with pioglitazone 15 mg, Nesina 25 mg with pioglitazone 30 mg, and Nesina 25 mg with pioglitazone 45 mg, respectively (p≤0.01). The mean change from baseline in FPG was seven mg/dL, -19 mg/dL, -24 mg/dL, -29 mg/dL, -32 mg/dL, -38 mg/dL, -42 mg/dL, -53 mg/dL in patients treated with placebo, Nesina 25 mg, pioglitazone 15 mg, 30 mg, and 45 mg, Nesina 25 mg with pioglitazone 15 mg, Nesina 25 mg with pioglitazone 30 mg, and Nesina 25 mg with pioglitazone 45 mg, respectively.

pioglitazone/metformin plus alogliptin versus pioglitazone/metformin

In an active-comparator study over 52 weeks, 803 patients with type 2 diabetes who were insufficiently controlled on their current pioglitazone 30 mg and metformin (daily dose of at least 1,500 mg or at maximum tolerated dose) therapy were randomized to receive the addition of Nesina 25 mg or to titrate their pioglitazone dose from 30 mg to 45 mg.[10] Patients were maintained on a stable dose of metformin (median dose equal to 1,700 mg). Prior to randomization patients underwent a four-week single-blind, placebo run-in period. Patients treated with the addition of Nesina 25 mg with pioglitazone and metformin had statistically significant improvements in their HbA1c and FPG (p<0.001) compared to patients who had their pioglitazone dose increased from 30 mg to 45 mg (95% CI). The percent of patients achieving an HbA1c of less than seven percent was 33 percent (Nesina 25 mg with pioglitazone 30 mg and metformin) and 21 percent (pioglitazone 45 mg with metformin) (p<0.001). The mean change from baseline in FPG was -15 mg/dL (Nesina 25 mg with pioglitazone 30 mg and metformin) and negative four mg/dL (pioglitazone 45 mg with metformin).

pioglitazone/alogliptin (Oseni) or pioglitazone with or without sulfonylurea or metformin

A 26 week, placebo-controlled study was performed in 493 patients with type 2 diabetes who were insufficiently controlled on a thiazolidinedione alone or in combination with a sulfonylurea or metformin.[11] Prior to randomization patients underwent a four-week single-blind, placebo run-in period. Patients had a mean baseline HbA1c of eight percent and were randomized to receive Nesina 12.5 mg, 25 mg, or placebo. During the treatment period patients were maintained on a stable dose of pioglitazone (median dose equals 30 mg). Before randomization, patients who were previously treated with metformin (median dose equals 2,000 mg) or sulfonylurea (median dose equals ten mg) were maintained on therapy throughout the treatment period. Statistically significant improvements in baseline HbA1c and FPG occurred in patients who had Nesina 25

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.

mg daily added to their pioglitazone therapy compared to placebo (95% CI, p<0.01). The percent of patients achieving an HbA1c of less than or equal to seven percent was 49 percent (Nesina 25 mg with pioglitazone with or without metformin or a sulfonylurea) and 34 percent (placebo with pioglitazone with or without metformin or a sulfonylurea) (p<0.01). The mean change from baseline for FPG was -20 mg/dL (Nesina 25 mg with pioglitazone with or without metformin or a sulfonylurea) and negative six mg/dL (placebo with pioglitazone with or without metformin or a sulfonylurea).

alogliptin (Nesina) and glyburide versus glyburide

In a placebo-controlled study conducted over 26 weeks, 500 patients with type 2 diabetes who were insufficiently controlled on a sulfonylurea were randomized to receive Nesina 12.5 mg, 25 mg, or placebo.[12] Prior to randomization patients entered a four-week single-blind, placebo run-in period and had a mean baseline HbA1c of 8.1 percent. During the treatment period patients were maintained on a stable dose of glyburide (median dose equals 10 mg). Patients who had Nesina 25 mg added to their glyburide therapy had a statistically significant improvement in HbA1c compared to placebo (95% CI, p<0.01). The percent of patients achieving an HbA1c less than or equal to seven percent was 35 percent (Nesina 25 mg with glyburide) and 18 percent (placebo plus glyburide) (p<0.01). Statistically significant improvements in FPG did not occur when compared to placebo (95% CI). The mean change from baseline for FPG was two (placebo plus glyburide) and negative eight (Nesina 25 mg with glyburide).

alogliptin (Nesina) and insulin with or without metformin versus placebo and insulin with or without metformin

In a placebo-controlled study conducted over 26 weeks, 390 patients with type 2 diabetes who were insufficiently controlled on insulin alone or in combination with metformin were randomized to receive Nesina 12.5 mg, 25 mg, or placebo.[13] Upon entering the study patients were taking premixed, short-, intermediate-, or long-acting insulin and had a mean HbA1c baseline of 9.3 percent. Patients were maintained on their insulin therapy (median dose equals 55 IU) at randomization and patients who were previously taking insulin plus metformin (median dose equals 1,700 mg) before randomization continued with their combination therapy throughout the treatment period. The study concluded that adding Nesina 25 mg once daily to insulin therapy resulted in statistically significant improvements in HbA1c and FPG when compared to placebo (95% CI, p<0.05). The percent of patients who achieved an HbA1c less than or equal to seven percent was eight percent (Nesina 25 mg plus insulin with or without metformin) and one percent (placebo plus insulin with or without metformin). The mean change from baseline in FPG was six mg/dL (placebo plus insulin with or without metformin) and -12 mg/dL (Nesina 25 mg plus insulin with or without metformin).

***Other Drugs Used for Condition*:[14]** Other single-entity DPP-4 inhibitors currently available are sitagliptin (Januvia™), saxagliptin (Onglyza™), and linagliptin (Tradjenta™). Patients and prescribers have many options available when selecting an oral antihyperglycemic medication such as alpha-glucosidase inhibitors (Precose®, Glyset®, and acarbose), biguanides (Fortamet®, Glucophage/XR®, Glumetza™, metformin/XR, Riomet®), meglitinides (nateglinide, Prandin™, Starlix®), sulfonylureas (Amaryl®, chlorpropamide, Diabeta®, glimepiride, glipizide/XL, Glucotrol/XL®, glyburide, Glynase®, tolazamide, tolbutamide), and thiazolidinediones (Actos™ and Avandia®). Several convenient multi-strength combination products are also available such as biguanide/DPP-4 inhibitors (Janumet/XR™, Jentadueto™, and Kombiglyze XR™), biguanide/thiazolidinedione (Actoplus Met/XR® and Avandamet™), biguanide/meglitinide (PrandiMet®), and sulfonylurea/thiazolidinedione (Avandaryl®, Duetact®, glipizide/metformin,

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.

Glucovance®, glyburide/metformin, Metaglip™). Many of these single and combination products are available as low cost generics with similar efficacy.

***Place in Therapy*:** According to the 2013 American Diabetes Association (ADA) Standards of Medical Care in Diabetes selection of medications should be patient-centric and prescribers should consider potential issues such as efficacy, cost, side effects, comorbidities, hypoglycemic risk, and patient preferences.[15] If no contraindication exists and if well tolerated metformin is the preferred initial treatment for type 2 diabetes. If monotherapy at the maximum tolerated dose does not achieve or maintain the desired HbA1c level over three to six months prescribers should consider adding a second oral agent. The American Association of Clinical Endocrinologists (AACE) 2011 guidelines state that when achieving glycemic control all oral glucose-lowering medications that are currently available are more or less similar in their glucose-lowering potency.[16] For patients with inadequate response to monotherapy or when initial pharmacologic therapy is inadequate, DPP-4 inhibitors are recommended as an option for multidrug therapy. Similar to ADA's position, AACE also recommends a patient-centered approach when selecting antidiabetic medications. The AACE guidelines note that it is appropriate to combine antidiabetic medications since many patients do not achieve glycemic control with monotherapy. The AACE guidelines further note that DPP-4 inhibitors do not cause weight gain, can be administered to patients with renal insufficiency after dose adjustment considerations, do not cause significant gastrointestinal side effects, and are less likely to cause hypoglycemia compared to other agents which may need to be taken into consideration when selecting antidiabetic therapy.

In clinical trials, alogliptin (Nesina) resulted in HbA1c reductions of 0.4 to 0.6 percent versus placebo after 26 weeks. Alogliptin/metformin (Kazano) resulted in additional HbA1c reductions of 1.1 percent over alogliptin monotherapy and 0.5 percent over metformin monotherapy after 26 weeks. Alogliptin/pioglitazone (Oseni) resulted in additional HbA1c reductions of 0.4 to 0.6 percent over pioglitazone monotherapy and 0.4 to 0.9 percent over alogliptin monotherapy.

Alogliptin (Nesina) offers prescribers another option when a DPP-4 inhibitor is needed for glycemic control in adult patients with type 2 diabetes. Other single-entity DPP-4 inhibitors currently available are sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). Likewise, Kazano offers adult patients with type 2 diabetes another single tablet, fixed dose combination of a DPP-4 inhibitor and metformin. Other DPP-4 inhibitor/metformin single tablet, combination products include sitagliptin/metformin/XR (Janumet/XR), linagliptin/metformin (Jentadueto), and saxagliptin/metformin XR (Kombiglyze XR). Oseni is the first DPP-4 inhibitor/thiazolidinedione fixed dose combination product offered in the United States as a single tablet. These single tablet combination formulations may be of benefit when monotherapy is insufficient, the individual ingredients making up the combination product are more costly, or when noncompliance is of concern.

Suggested Utilization Management:

Anticipated Therapeutic Class Review (TCR) Placement	Hypoglycemics, Incretin Enhancers/Mimetics
Clinical Edit	Prior authorization if the product is determined to be non-preferred Trial and failure of a preferred combination product/single entity product(s)

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.

	Trial and failure of metformin Patient has diagnosis of type 2 diabetes Deny if patient has diagnosis of type 1 diabetes
Quantity Limit	Nesina:1 tablet/day (30 tablets/30 days); Kazano: 2 tablets/day (60 tablets/30 days); Oseni: 1 tablet/day (30 tablets/30 days)
Duration of Approval	1 year
Drug to Disease Hard Edit	Type 2 diabetes; renal impairment (Kazano); NYHA Class III or IV heart failure (Oseni)
Retro-DUR	Yes
Provider Profiling	No

References

1 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
2 Kazano [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
3 Oseni [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
4 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
5 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
6 Kaki K., Itayasu T., Hiroi S., et. al. 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, Obesity and Metabolism, 2011; 13(11):1028-1035.
7 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
8 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
9 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
10 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
11 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
12 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
13 Nesina [package insert]. Deerfield, IL; Takeda Pharmaceuticals America; January 2013.
14 Available at: www.clinicalpharmacology.com. Accessed February 12, 2013.
15 American Diabetes Association. Position Statement. Standards of Medical Care in Diabetes-2013. Diabetes Care. 2013; 36(1):S11-S66. Available at: http://care.diabetesjournals.org/content/36/Supplement_1/S11.full.pdf+html. Accessed February 19, 2013.
16 American Association of Clinical Endocrinologists. Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan. Endocrine Practice. 2011; 17(2):1-53. Available at: https://www.aace.com/files/dm-guidelines-ccp.pdf. Accessed February 19, 2013.

© 2013 Magellan Medicaid Administration, Inc., All Rights Reserved.

Restricted Access – Proprietary Information. Do not disseminate or copy without approval.