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PERAMPANEL: THE FIRST AMPA RECEPTOR ANTAGONIST

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Epilepsy is a neurologic disorder that affects the quality of life for an estimated 2.2 million Americans.[1,2] The term epilepsy is accepted after a person has had two or more seizures.[3] While there are many types of seizures, they can generally be classified into two broad groups consisting of either primary generalized seizures or partial seizures. In primary generalized seizures there is involvement of both sides of the brain, while partial seizures begin with a smaller, more localized area. In some instances, partial seizures can spread to involve widespread areas of the brain.[4]

For many patients with epilepsy, antiepileptic medications are the mainstay of therapy.[4] Most antiepileptic medications reduce excitation and neurotransmitter release or enhance the gamma-aminobutyric acid (GABA) system.[5] Unfortunately, approximately 30% of patients do not achieve seizure control with existing pharmacotherapy.[6] Other options include surgery and supplemental treatments such as vagal nerve stimulation and a ketogenic diet consisting of high fat and low carbohydrates with restricted calories.[4]

On October 22, 2012, Eisai Inc. gained FDA approval for Fycompa® (perampanel), an α-amino-3-hydroxy -5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist used for the treatment of partial onset seizures in patients with epilepsy ages 12 years and older.[4] Perampanel is the first medication to target the AMPA receptor.[7]

This article will review the pharmacology, pharmacokinetics, clinical trials, dosing and administration, adverse effects, and interactions associated with perampanel.

Pharmacology & Pharmacokinetics

Perampanel is a highly selective, non-competitive antagonist of the ionotropic AMPA glutamate receptor on post-synaptic neurons.[8] AMPA receptors, the most abundant ionotropic glutamate receptors in the brain, function to mediate excitatory neurotransmission.[8] While the precise mechanism by which perampanel exerts its antiepileptic effects has not been fully elucidated, studies suggest that reducing the overstimulation of AMPA may have an anticonvulsant effect and inhibit seizure generation and spread.[7,8] In addition to their anticonvulsant effects, AMPA receptor antagonists could play a vital neuroprotective role by preventing neuronal death.[7,9]

After oral administration, perampanel is rapidly and completely absorbed with negligible first-pass metabolism. Under fasted conditions, the median time to maximum concentration (Tmax) ranges from 0.5 to 2.5 hours. Food delays Tmax by 2 to 3 hours and decreases the maximum concentration (Cmax) by 28-40%, but does not affect the extent of absorption or area under the curve (AUC).[7,8] The half-life of perampanel is approximately 105 hours, therefore steady state is not reached for 2 to 3 weeks.[8]

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Plasma protein binding is approximately 95% to 96%, mainly bound to albumin and α1-acid glycoprotein. Perampanel undergoes extensive metabolization by primary oxidation and sequential glucuronidation.[8] Oxidative metabolism is mediated by cytochrome P450 (CYP) 3A4 and/or CYP3A5 as well as involvement of other CYP enzymes. Primarily as a mixture of oxidative and conjugated metabolites, 30% of orally administered perampanel is found in the urine and 70% in the feces.[7,8]

Clinical Trials

Perampanel has been studied in a total of 3 randomized, double-blind, placebo-controlled, multicenter trials in patients 12 years and older. (**Table 1**). Two trials assessed moderate and high once-daily doses of 8 mg and 12 mg,[10,11] while one trial assessed low to moderate once-daily doses of perampanel (2, 4, and 8 mg).[12] Each study consisted of four periods: baseline, titration, maintenance, and follow-up or optional placement into a long-term, extension trial. During a 6-week baseline period, patients were evaluated for seizure activity. In the titration phase, all patients began with perampanel 2 mg per day, and doses were increased by 2 mg per day once weekly until the randomized target doses were achieved. If patients could not tolerate dose increases due to adverse effects, patients could stay on the same dose or have a dose reduction, although dosage reductions were discouraged. By the end of the titration period, all patients who were not tolerating at least 2 mg of perampanel or placebo were discontinued from the study. During the maintenance period, patients continued the dose achieved during titration and were followed for 13 weeks. At the end of the maintenance period, patients were entered into either a 4 week follow-up period or an optional open-label extension trial.[10-12]

Patients were included in the three trials if they were 12 years of age or older, had a diagnosis of simple or complex partial seizures with or without secondary generalization, had at least five partial seizures in the 6 week baseline phase without a 25-day seizure-free period, experienced ongoing seizures despite prior therapy with at least two antiepileptic drugs (AEDs), and currently received stable doses of 1 to 3 antiepileptic medications. Efficacy assessments included patient diaries, Clinical and Patient Global Impression of Change (CGIC/PGIC), and the Quality of Life in Epilepsy questionnaire (QOLIE-31-P).[10-12]

The primary endpoints were responder rate, which is the proportion of patients who had at least a 50% reduction in seizure frequency during treatment relative to baseline, and the percent change in seizure frequency per 28 days. Secondary end points were the percent change in the frequency of complex partial plus secondarily generalized seizures, and a dose-response analysis of the percent change in seizure frequency. Safety assessments were also evaluated.[10-12]

Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304, 305, 306

Study 304 included a total of 387 patients randomly assigned to one of three groups: placebo (n = 121), 8 mg perampanel (n = 133), or 12 mg perampanel (n = 133).[10] After 13 weeks of treatment, perampanel 8 mg and 12 mg significantly reduced seizure frequency by 26.3% (p = 0.0261) and 34.5% (p = 0.0158) respectively, compared to placebo (21%). Fifty percent responder rates were achieved by 37.6% of patients receiving 8 mg perampanel (95% confidence interval [CI] 29.4 - 45.8, p = 0.0760) and 36.1% of patient receiving 12 mg perampanel (95% CI 27.9 - 44.3, p = 0.0914) versus 26.4% for patients receiving placebo (95% CI 18.6 - 34.3), although this was not statistically significant.[10]

Study 305 evaluated the efficacy 8 mg of perampanel and 12 mg perampanel versus placebo in a total

Table 1 | Primary Endpoints of Clinical Trials Involving Perampanel

Trial Number	Treatment Option	N	Change in Seizure Frequency (%)	p Value[+]	50% Responder Rates (%)	p Value[+]
304[10]	Placebo	121	-21.0		26.4	
	8 mg/day	133	-26.3	0.0261	37.6	0.0760
	12 mg/day	134	-34.5	0.0158	36.1	0.0914
305[11]	Placebo	136	-9.7		14.7	
	8 mg/day	129	-30.5	<0.001	33.3	0.002
	12 mg/day	121	-17.6	0.011	33.9	<0.001
306[12]	Placebo	185	-10.7		17.9	
	2 mg/day	180	-13.6	0.420	20.6	NS*
	4 mg/day	172	-23.3	0.003	28.5	0.013
	8 mg/day	169	-30.8	<0.001	34.9	<0.001

[+]p Value is comparing medication to placebo[10-12]
*Specific p value was not listed in article[12]
N – Number of Participants, NS – Non-significant.

of 386 patients.[11] Patients in the study were randomly assigned to receive 8 mg perampanel (n = 129), 12 mg perampanel (n = 121), or placebo (n = 136). The percent change in seizure frequency of once-daily perampanel 8 and 12 mg was -30.5% (p <0.001) and -17.6% (p = 0.011), respectively, compared to -9.7% for placebo. The 50% responder rates were 33.3% for 8 mg perampanel (p=0.002) and 33.9% for 12 mg perampanel (p<0.001) versus 14.7% for placebo.[11]

In Study 306, 706 patients received once daily treatment with perampanel 2 mg (n = 180), perampanel 4 mg (n = 172), perampanel 8 mg (n = 169) or placebo (n = 185).[12] The median percentage change in seizure frequency was −13.6% with perampanel 2 mg (p = 0.420), −23.3% with perampanel 4 mg (p = 0.003) and −30.8% with perampanel 8 mg (p < 0.001) versus −10.7% for placebo. The 50% responder rates of perampanel were 20.6% with 2 mg (p value not statistically significant), 28.5% with 4 mg (p = 0.013) and 34.9% with 8 mg (p < 0.001) versus 17.9% with placebo.[12]

As noted in the trials, perampanel was only assessed as adjunctive therapy to additional AEDs and has not been evaluated as monotherapy. Additionally, perampanel has not been compared head-to-head with other antiepileptic medications, therefore the exact place in therapy for perampanel is not known.[10-12]

Warnings and Precautions

Perampanel has a black box warning for serious psychiatric and behavioral reactions. In phase III trials, adverse reactions related to hostility and aggression were seen in 12% and 20% of patients taking 8 mg and 12 mg per day, respectively. This was compared to 6% of patients in the placebo group. In general, neuropsychiatric events including irritability, aggression, anger and anxiety occurred more frequently in those taking perampanel than those receiving placebo. Three patients out of a total of 4,368 (0.069%) perampanel-treated patients exhibited homicidal ideation or threat. Patients should be closely monitored for serious psychiatric and behavioral reactions while taking perampanel and for at least one month after taking the last dose of perampanel. If patient experiences such symptoms, the dose of perampanel should be reduced. Permanent discontinuation of perampanel is appropriate in patients with persistent severe or worsening symptoms or behaviors. Additional warnings and precautions include suicidal behavior and ideation occurring 0.43% in perampanel-treated patients compared to 0.24% in placebo-treated patients, neurologic effects such as dizziness, gait disturbance, somnolence and fatigue, and falls.[8]

Currently, perampanel is not commercially available as the FDA has recommended that perampanel be classified by the Drug Enforcement Administration (DEA) as a scheduled medication under the Controlled Substances Act. Immediately following the DEA's decision on the schedule classification, perampanel will be available.[13]

Adverse Reactions

In the three clinical trials with perampanel, a dose-related increase in adverse effects was noted. The most commonly reported adverse effects occurred at

Table 2 | Common adverse reactions with perampanel

Trial Number	Adverse Effect	Placebo (%)	2 mg (%)	4 mg (%)	8 mg (%)	12 mg (%)
304[10]	Dizziness	9.9	N/A	N/A	37.6	38.1
	Somnolence	13.2			18.0	17.2
	Headache	13.2			15	13.4
	Fall	6.6			9.8	12.7
	Irritability	5.0			7.5	14.2
	Ataxia	0			6	11.9
305[11]	Dizziness	7.4	N/A	N/A	32.6	47.9
	Somnolence	2.9			12.4	18.2
	Fatigue	8.1			13.2	16.5
	Headache	13.2			8.5	13.2
306[12]	Dizziness	9.7	10.0	16.3	26.6	N/A
	Somnolence	6.5	12.2	9.3	16.0	
	Headache	8.6	8.9	11.0	10.7	
	Fatigue	2.7	4.4	7.6	5.3	
	URTI	2.7	6.1	3.5	1.8	
	Nasopharngitis	1.6	3.9	5.2	1.8	
	Gait Disturbance	1.1	<1.0	1.2	5.3	

N/A—not applicable; URTI – Upper Respiratory Tract Infection

the 8 mg and 12 mg doses, with highest rates seen in those taking 12 mg per day. The adverse effects most commonly noted were dizziness, somnolence, headache, fatigue, irritability, falls, gait disturbance, and weight gain (**Table 2**).[8, 10-12]

The rate of discontinuation as a result of an adverse reaction was 3% in patients receiving 4 mg/day, 8% in those receiving 8 mg/day, and 19% in patients receiving doses of 12 mg/day. In comparison, 5% of patients randomized to receive placebo discontinued due to adverse effects. The adverse events most commonly leading to discontinuation were dizziness, somnolence, vertigo, aggression, anger, ataxia, blurred vision, irritability, and dysarthria.[8, 10-12]

Dosing and Administration

The recommended starting dose for perampanel depends on if the patient is taking enzyme-inducing antiepileptic medications such as phenytoin, carbamazepine, and oxcarbazepine. Recommended starting doses for patients in the absence of enzyme-inducing antiepileptic medications is 2 mg at bedtime. In the presence of enzyme-inducing antiepileptic drugs, a starting dose of 4 mg once daily is recommended. Based on patient's tolerability and efficacy, doses can be titrated at weekly intervals by 2 mg per day. For elderly patients, titration should occur once every two weeks. The recommended dose range is 8 mg to 12 mg daily but should be based on clinical response and patient tolerability.[8]

Special Populations

In patients with mild and moderate hepatic impairment (n=12), the pharmacokinetic profile of perampanel following a single 1 mg dose was compared with demographically matched healthy subjects (n=12). Compared to their controls, the total exposure of perampanel was 50% greater in subjects with mild hepatic impairment and was 2.55-fold greater in subjects with moderate hepatic impairment. The half-life of perampanel was also prolonged in subjects with mild impairment (306 versus 125 hours) and moderate impairment (295 versus 139 hours). Based on this information, dosage adjustments in patients with mild to moderate hepatic impairment are recommended. In patients with mild to moderate hepatic impairment, a starting dose of 2 mg daily is recommended with titration occurring once every two weeks. For those with mild hepatic impairment, the maximum recommended dose is 6 mg daily and for those with moderate hepatic impairment, the maximum dose is 4 mg daily. Patients with severe hepatic impairment have not been studied.[7]

Population pharmacokinetics of perampanel have been pooled from placebo-controlled trials to address those with renal impairment as a study in these patients has not been conducted. In those with mild renal impairment (creatinine clearance 50-80 mL/min), perampanel clearance was decreased by 27% and AUC increased 37% compared to patients with creatinine clearance > 80 mL/min. For those with mild to moderate renal impairment, use of perampanel should be done under close monitoring and slow titration should be considered based on clinical response and tolerability. Perampanel has not been studied in patients with severe renal impairment; therefore, use in these patients is not recommended (**Table 3**).[7,8]

Drug Interactions

Drug interactions with perampanel have been reported for levonorgestrol containing oral and implantable contraceptives, CYP 450 inducers, and CNS depressants. Levonorgestrel exposure was decreased by about 40% in those taking perampanel 12 mg daily, although this same effect was not seen with lower doses of perampanel. Studies comparing ethinyl estradiol and levonorgestrel to both 4 mg and 8 mg doses of perampanel noted that the maximum concentration of ethinyl estradiol or levonorgestrel was not altered. Currently, it appears that levonorgestrel is the only progestin that has been studied and it is still ad-

Table 3 | Dosing and titration of perampanel [7, 10-12]

Patient Type	Starting Dose	Titration	Recommended daily dose
Absence of Enzyme-Inducing AEDs	2 mg at bedtime	2 mg/day once weekly	8-12 mg/day
Presence of Enzyme-Inducing AEDs	4 mg once daily	2 mg/day once weekly	8-12 mg/day
Elderly	2 mg once daily	2 mg/day every 2 weeks	8-12 mg/day
Hepatic Impairment	Mild: 2 mg once daily Moderate: 2 mg once daily Severe: Not recommended	2 mg/day every 2 weeks	Mild: 6 mg/day Moderate: 4 mg/day

AEDs – Antiepileptic Drugs

vised to use additional non-hormonal forms of contraception when using perampanel with all levonorgestrel containing contraceptives.[8]

When used with known CYP enzyme inducers such as carbamazepine, phenytoin, or oxcarbazepine, the plasma levels of perampanel are decreased by about 50% to 67%. As described previously, if using perampanel with CYP enzyme inducers, the starting doses for perampanel should be increased. If introducing or withdrawing a CYP enzyme inducer while on perampanel, dosage adjustments of perampanel may be necessary and the patient should be monitored closely for clinical response as well as tolerability. Concomitant use of perampanel with strong CYP3A inducers (e.g., rifampin, St. John's wort) should be avoided.[7,8]

The concomitant use of perampanel and CNS depressants including alcohol may increase CNS depression. Therefore, care should be taken when administering perampanel with these agents. Patients should limit activity until they have experience with concomitant use of CNS depressants (e.g. benzodiazepines, narcotics, barbiturates, sedating antihistamines). Advise patients not to drive or operate machinery while taking perampanel until they have gained sufficient experience to gauge whether it adversely affects the activity.[7,8]

Summary

Perampanel is a first-in-class AMPA receptor antagonist used for the treatment of partial onset seizures in patients with epilepsy ages 12 years and older. As perampanel has not been compared head-to-head with other antiepileptic medications, the exact place in therapy is not known. At this time, perampanel should be considered as add-on treatment for patients who are not achieving adequate seizure control with other antiepileptic medications and when standard adjunctive treatment is not sufficient. The recommended starting dose for most patients is 2 mg once daily with careful titration based on patient tolerability and clinical response. For patients who are also taking enzyme-inducing antiepileptic medications, the recommended starting dose is 4 mg once daily. The dose range recommended for most patients is 8 mg to 12 mg once daily. Adverse effects such as dizziness, somnolence, fatigue, and headache are seen with perampanel and tend to occur more often in higher doses.

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ALOGLIPTIN: A NEW DIPEPTIDYL PEPTIDASE-4 INHIBITOR

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Type 2 diabetes mellitus (DM) is an epidemic disease state that is of growing concern in the United States. In 2010, the Centers of Disease Control and Prevention estimated that 25.8 million people in the United States suffer from DM. In patients greater than 20 years of age, 1.9 million new cases of diabetes were diagnosed in 2010.[1] The prevalence of DM is expected to increase from 2.8% of the population in 2000 to over 4.4% by 2030.[2]

Type 2 DM is a disorder of glycemic control characterized by impaired insulin secretion, insulin resistance, gradual decline in beta-cell activity, altered incretin hormone function, and abnormal glucagon

secretion.[2] The American Diabetes Association (ADA) recommends a glycated hemoglobin (HbA1c) goal of 7% in most non-pregnant adults.[3] Adequate control of diabetes can prevent long-term microvascular complications, but only 37% of patients achieve the target HbA1c.[2] Based on the 2013 ADA guidelines, initial management of type 2 DM usually includes metformin plus lifestyle modifications. Many patients may require the use of multiple anti-diabetic agents to achieve adequate glycemic control.[3] The class of dipeptidyl peptidase-4 (DDP-4) inhibitors represents another option in the treatment of type 2 DM.

Takeda Pharmaceuticals, Inc. received FDA approval in January 2013 for alogliptin (Nesina ®) for the treatment of type 2 DM in adults as adjuncts to diet and exercise. Alogliptin will also be marked as combination products with pioglitazone (Oseni ®) and metformin (Kazano ®). Alogliptin is a highly potent, highly selective DDP-4 inhibitor.[4] This article will review the pharmacologic and pharmacokinetic properties, relevant clinic trials, safety, dosing and administration of alogliptin and provide a cost comparison of alogliptin with other DDP-4 inhibitors.

Pharmacology & Pharmacokinetics

Incretin hormones, including glucagon-like polypeptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP), play an integral role in maintaining glucose homeostasis.[2] Following food consumption, GLP-1 and GIP are released from endocrine cells within the gut. These incretin hormones stimulate the pancreatic beta-cells to produce insulin in a glucose-dependent fashion. GLP-1 and GIP can also augment the proliferation of beta-cells and prevent apoptosis of these cells from occurring. GLP-1 specifically reduces glucagon release, decreases food intake, increases satiety, and lengthens time for gastric emptying. Unfortunately, the beneficial effects of incretin hormones on glycemic control are limited by the rapid metabolism of both GLP-1 and GIP by the DDP-4 enzyme.

Both incretin hormones have half-lives of only a several minutes because of this rapid degradation. The effects of GLP-1 and GIP can be augmented by administering a DDP-4 inhibitor.[2] By prolonging the actions of GLP-1 and GIP, the administration of a DDP-4 inhibitor leads to a decrease in fasting and postprandial glucose levels.[5] Alogliptin is a highly potent, highly selective, orally available quinazolinone-based non-covalent DDP-4 inhibitor.[2] It is >14,000 times more selective for DDP-4 than the other DDP isoenzymes such as DDP-2, DDP-8 and DDP-9. Following alogliptin administration, DDP-4 activity is decreased by more than 80% which causes approximately a 2- to 3- fold increase in GLP-1 levels.[6] Alogliptin has comparable pharmacodynamic and pharmacokinetic properties as other DDP-4 inhibitors (**Tables 1 and 2**).

Clinical Trials

Alogliptin was approved as monotherapy and in combination with metformin and pioglitazone for the management of type 2 DM based on three double-blind, placebo-controlled, randomized control trials (**Table 3**).

A 26-week, double-blind, placebo-controlled, multicenter trial assessed the use of alogliptin in drug-naïve patients with inadequately controlled type 2 DM.[11] Treatment-naïve was defined as patients with no current anti-diabetic therapy or less than 7 days of treatment within the past 30 days. Eligible patients underwent a 4-week run-in period with a fasting plasma glucose (FPG) of less than 275 mg/ml and ≥ 75% compliance determined by pill count. After successful completion of the run-in period, 329 patients were randomized in a 2:2:1 fashion to receive 12.5 mg of

Table 1 | Pharmacodynamic properties of DDP-4 inhibitors [6]

Characteristic	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin	Alogliptin
Brand Name	Januvia ®	Galvus ®	Onglyza ®	Tradjenta ®	Nesina ®
Therapeutic Dose	100mg daily	50mg BID	5mg daily	5mg daily	25mg daily
DDP-4 inhibition (nmol/L)	IC_{50}: 19	IC_{50}: 62	IC_{50}: 50	IC_{50}: 1	IC_{50}: 24
DDP4- selectivity					
Fold sensitivity vs. DDP-8 & DDP-9	>2600	<100	<100	>10000	>14000
Fold sensitivity vs. DDP-2	>5550	>100000	>50000	>100000	>14000
Effect on DDP-4 activity	≥80%	≥80%	≥70%	≥80%	≥80%
Effect on GLP-1 levels	~2-fold increase	~3-fold increase	1.5- to 3-fold increase	4-fold increase	2- to 3-fold increase

BID: twice daily; DDP: dipeptidyl peptidase; GLP-1: glucagon-like polypeptide; IC_{50}: half maximal inhibitory concentration; L: liter, mg: milligram, nmol: nanomole

Table 2 | Pharmacokinetic properties of the DDP-4 Inhibitor Class[10]

Characteristic	Sitagliptin	Vildagliptin	Saxagliptin	Linagliptin	Alogliptin
Brand Name	Januvia ®	Galvus ®	Onglyza ®	Tradjenta ®	Nesina ®
Therapeutic Dose (mg/day)	100	100 (50 x 2)	5	5	25
Administration	Once daily	Twice daily	Once daily	Once daily	Once daily
T_{max} (hour)	1-4	1.75	2	0.7-3	1-2
Terminal $T_{1/2}$ (hour)	12.4	2-3	2.5	128-124	12.4-21.4
Dose adjustment with renal impairment	Yes	No	Yes	No	Yes
Protein binding (%)	38	9.3	Minimal	>80%	28-38%[2]
Dose reductions with CYP- Inhibitors	No	No	Yes	No	No

CYP: cytochrome P450, mg: milligram, $T_{1/2}$: Half-life; T_{max}: time to maximum concentration

alogliptin, 25 mg of alogliptin or placebo for 26 weeks. Medication was taken before the first meal each day, and no other anti-diabetic medications were permitted during the study. The primary end point was mean change from baseline in HbA1C at week 26. Secondary endpoints included changes in FPG, clinical response rates, occurrence of marked hyperglycemia (FPG ≥ 200 mg/dl) and hyperglycemic rescue, and differences in body weight. Adverse events, clinical laboratory findings, 12-lead electrocardiograms, physical examination findings, vital signs, and hypoglycemic events were investigated as safety end points.[11]

Mean HbA1c was significantly decreased by 0.56% (p<0.001) and 0.59% (p<0.001) with 12.5 mg and 25 mg of alogliptin compared to placebo, respectively. FPG was also significantly reduced by 10.3 ± 3.6 mg/dL (p<0.001) with 12.5 mg of alogliptin and 16.4 ± 3.7 mg/dL (p<0.001) with 25 mg of alogliptin. HbA1c reductions were observed as early as 4 weeks and decreases in FBG were seen at week 1 of the study. The rate of adverse events and proportion of patients who discontinued treatment did not differ between treatment arms. Infection, gastrointestinal symptoms, and headaches were commonly observed adverse effects, but no deaths were reported during the study. Hypoglycemia was rare and alogliptin was determined to be weight neutral. Alogliptin monotherapy significantly improved glycemic control in patients with type 2 DM and was overall well tolerated.[11]

Metformin is considered a first-line treatment option in managing type 2 DM.[3] Over time, monotherapy with metformin may not provide adequate type 2 DM control. A 26-week, randomized, double-blind, placebo -controlled trial investigated both the safety and efficacy of once-daily doses of alogliptin 12.5 mg or 25 mg compared with placebo in combination with metformin in patients with HbA1c levels that were not adequately controlled with metformin monotherapy.[12] Eligible patients included men and women between the ages of 18 and 80 with a historical diagnosis of DM and inadequate glycemic control (HbA1c between 7.0% and 10.0%) despite metformin therapy of at least 1,500 mg for more than 8 weeks. During a 4-week run-in period, the metformin dose was stabilized and then remained unchanged for the rest of the study period. Following the run-in period, 527 patients were randomized in a 2:2:1 fashion to receive 12.5 mg of alogliptin plus metformin, 25 mg of alogliptin plus metformin or placebo plus metformin for 26 weeks. The primary endpoint of the study was change in HbA1c from baseline to week 26. Select secondary endpoints included change from baseline in FPG, incidence of marked hyperglycemia (FPG ≥ 200 mg/dl) and hyperglycemic rescue, changes from baseline in fasting C-peptide, proinsulin, insulin, and proinsulin:insulin ratio, and change from baseline in body weight.[12]

Mean HbA1c decreases were significantly greater (p<0.001) with alogliptin 12.5 mg (0.6%) and alogliptin 25 mg (-0.6%) compared to placebo. FPG reductions were 19.0 mg/dL with alogliptin 12.5 mg and 17.0 mg/dL with alogliptin 25 mg, which were both significantly greater (p<0.001) than placebo. These significant decreases were apparent in both alogliptin groups as early as week 4 and continued throughout the duration of the study. A larger proportion of patients in the alogliptin groups (p<0.001) reached an HbA1c of ≤ 7.0% and significantly fewer patients experienced marked hyperglycemia compared to the placebo group. The adverse event profile was similar between all three treatment arms, and the rate of hypoglycemia was low in all groups. Alogliptin was determined to be an effective and safe treatment for type 2 DM when added to metformin for patients

Table 3 | Summary of Alogliptin Clinical Trial Results

Trial	Change from Baseline A1c (vs. placebo)	Change in FPG (mg/dL) (vs. placebo)	Percent of Patients with A1c < 7.0% (vs. placebo)
DeFronzo RA, et al. 2008[11]			
Alogliptin 12.5 mg, N=133	-0.56% (p<0.001)	-10.3 ± 3.6 (p<0.001)	47.4% (p=0.001)
Alogliptin 25 mg, N=131	-0.59% (p<0.001)	-16.4 ± 3.7 (p<0.001)	44.3% (p=0.008)
Placebo, N=65	-0.02%	11.3 ± 5.24	23.4%
Nauck MA, et al. 2009[12]			
Alogliptin 12.5 mg + Metformin, N= 213	-0.6% (p<0.001)	-19.0 (p<0.001)	52% (p<0.001)
Alogliptin 25 mg + Metformin, N=207	-0.6% (p<0.001)	-17.0 (p<0.001)	44% (p<0.001)
Placebo + Metformin, N=104	-0.1%	0	18%
Pratley RE, et al. 2009[13]			
Alogliptin 12.5 mg + Pioglitazone, N=197	-0.66% (p<0.001)	-19.7 (p=0.003)	44.2% (p≤0.016)
Alogliptin 25 mg + Pioglitazone, N= 199	-0.80% (p<0.001)	-19.9 (p=0.003)	49.2% (p≤0.016)
Placebo + Pioglitazone, N= 97	-0.19%	-5.7	34.0%

A1c: glycated hemoglobin, dL: deciliter,FPG: fasting plasma glucose, mg: milligram, N: sample size

not sufficiently controlled on metformin monotherapy.[12]

Combining anti-diabetic agents with complementary mechanisms of action can be a beneficial technique in attempting to achieve adequate glycemic control. A 26- week multicenter, double-blind, placebo-controlled randomized study evaluated if the addition of alogliptin 12.5 mg or 25 mg once daily to pre-existing pioglitazone therapy significantly improved glycemic control in 493 patients with type 2 DM compared to the addition of placebo.[13] After completing a 2-week screening period, patients underwent a 4-week run-in period. Study participants previously treated with pioglitazone continued on their current doses, those receiving rosiglitazone converted to an equivalent dose of pioglitazone, and patients previously taking metformin or sulfonylureas continued on these medications throughout the course of the study. Patients with an HbA1c between 7.0% and 10.0%, FPG < 275 mg/dl and at least 75% compliance following the run-in period were randomized in a 2:2:1 fashion to once-daily alogliptin 12.5 mg, alogliptin 25 mg or placebo for 26 weeks. Of the 493 patients who underwent randomization, 197 received alogliptin 12.5 mg plus pioglitazone, 199 received alogliptin 25 mg plus pioglitazone, and 97 received placebo plus pioglitazone. Among all three treatment arms, 56.2% of the patients received metformin, 21.1% received a sulfonylurea, and 22.7% received no other anti-diabetic medication. The study's primary endpoint was to assess the change in HbA1c after 26 weeks compared to the baseline value. Secondary endpoints included FPG and body weight, and incidences of marked hyperglycemia (FPG ≥ 200 mg/dL) and rescue for hyperglycemia.[13]

Mean HbA1c was significantly decreased by 0.66% (p<0.001) and 0.80% (p<0.001) with 12.5 mg and 25 mg of alogliptin compared to placebo, respectively. FPG was also significantly reduced by 19.7 mg/dL (p=0.003) with 12.5 mg of alogliptin and 19.9 mg/dL (p=0.003) with 25 mg of alogliptin. The proportion of patients who reached the goal HbA1c of ≤ 7.0% was also significantly greater (p ≤0.016) with alogliptin 12.5mg or 25mg compared with placebo. Marked hyperglycemia occurred in a significantly smaller percentage of patients in the alogliptin groups compared to the placebo group. Additionally, the rate of adverse events was similar among all three treatment arms, but the alogliptin groups did have a higher occurrence of cardiac events. Cardiac disorders occurred in 6.5% of patients receiving alogliptin 25 mg, 3% of patients receiving alogliptin 12.5 mg and 1% of patients receiving placebo. Glycemic control was significantly improved in patients with type 2 DM following the addition of alogliptin to pioglitazone. The short duration of the trial limits the ability to interpret safety and efficacy data, and longer trials may be needed to investigate the cardiac risks associated with alogliptin plus pioglitazone. Additionally, patients included in the trial were permitted to continue metformin and sulfonylurea therapy, so no conclusion can be drawn about the use of alogliptin plus pioglitazone as first-line treatment for type 2 DM.[13]

Table 4 | Alogliptin Adverse Events Compared to Placebo[4]

Adverse Event	Alogliptin 25 mg (N=5902)	Placebo (N=2926)
Nasopharyngitis	4.4%	3.0%
Headache	4.2%	3.5%
Upper Respiratory Tract Infection	4.2%	2.1%
Hypoglycemia	1.5%	1.6%

Adverse Events & Drug Interactions

After combining data from a total of 14 placebo-controlled trials, 66% of the patients receiving alogliptin and 62% of the patients receiving placebo experienced adverse events. Therapy was discontinued due to adverse events in 4.7% of patients treated with alogliptin and 4.5% of patients treated with placebo. Nasopharyngitis, headache, and upper respiratory tract infections were commonly observed adverse events that occurred more frequently in patients receiving alogliptin compared to placebo (**Table 4**). More serious adverse events including pancreatitis and hypersensitivity reactions were rarely observed occurring in 0.2% and 0.8% of patients receiving alogliptin 25 mg, respectively. The development of hypoglycemia was uncommon in patients receiving alogliptin (1.5%) and significantly lower compared to hypoglycemia rates in patients receiving glipizide (26%). Alogliptin was not shown to significantly affect vital signs or laboratory parameters.[4]

Alogliptin has few drug-drug interactions due to its favorable pharmacokinetic profile. It is not an inhibitor or an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4 and alogliptin undergoes minimal CYP metabolism.[4] No drug interactions were observed when alogliptin was co-administered with CYP inhibitors such as ketoconazole, fluconazole, or gemfibrozil. P-glycoprotein inhibitors such as cyclosporine and other renally eliminated drugs such as cimetidine did not alter the pharmacokinetic properties of alogliptin. Dose-adjustments are not necessary when alogliptin is added to other anti-diabetic medications including metformin, pioglitazone or glibenclamide.[14]

Dosing and Administration

The recommended starting dose of alogliptin is 25 mg by mouth once daily. It can be administered without regards to meals. Dose adjustments are recommended in patients with moderate to severe renal impairment (creatinine clearance < 60 ml/min). Following the administration of a single 50 mg dose of alogliptin, patients with renal impairment had greater alogliptin exposure than corresponding healthy patients. Patients with mild impairment, moderate impairment, severe impairment, and those with end stage renal disease had 1.7-fold, 2.1-fold, 3.2- fold, and 3.8-fold increased concentrations of alogliptin, respectively.[10] Alogliptin should be initiated at 12.5 mg once daily in patients with moderate renal impairment (creatinine clearance ≥ 30 ml/min and < 60 ml/min). In patients with severe renal impairment (creatinine clearance < 30 ml/min) and those undergoing dialysis, alogliptin should be dosed at 6.25mg daily. It can be administered without regard to dialysis timing.[4] Alogliptin concentrations did not differ in patients with hepatic impairment compared to healthy volunteers following administration of 25 mg of alogliptin. Because alogliptin is mainly eliminated via the kidney, hepatic impairment is not expected to affect the pharmacokinetic properties.[10] No dose-adjustments are needed in moderate hepatic impairment defined as Child Pugh Grade A-B. The use of alogliptin has not been studied in patients with severe liver dysfunction (Child Pugh Grade C). Caution should be used when administering alogliptin to any patient with liver disease.[4]

Cost

Takeda Pharmaceuticals, Inc. will begin distributing alogliptin and its related combination products in the summer of 2013. Alogliptin will be available in 6.25 mg, 12.5 mg, and 25 mg tablets.[15] Kazano® (alogliptin/metformin) will be available as 12.5 mg/500 mg tablets and 12.5 mg/1000 mg tablets, which should be administered twice daily with food.[16] Oseni ® (alogliptin/pioglitazone) will be available as 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg tablets, which can be taken with or without food.[17] The cost comparison between available DDP-4 inhibitors for a 30-day supply is depicted in **Table 5.**[18]

Table 5 | Cost for 30-day Supply of Available DDP-4 Inhibitors

Alogliptin	Saxagliptin	Sitagliptin	Linagliptin
6.25mg: $264.83	2.5mg: $292.00	25mg: $296.40	5mg: $291.30
12.5mg: $264.83	5mg: $304.98	50mg: $302.33	
25mg: $272.78		100mg: $304.66	

*Prices averaged from 3 Gainesville, FL pharmacies; obtained February 17th, 2013

SUMMARY

Alogliptin is the newest addition to the DDP-4 inhibitor class. It is approved as monotherapy and in combination with both metformin and pioglitazone to treat type 2 DM in adults as an adjunct to diet and exercise. Head-to-head trials comparing alogliptin to other DDP-4 inhibitors have not been completed at this time. Alogliptin has the potential to reduce HbA1c by approximately 0.6% and fasting plasma glucose by approximately 16 mg/dl when used as monotherapy. The most commonly observed side effects include nasopharnygitis, headache, and upper respiratory tract infection. Alogliptin should be initiated at 25 mg by mouth once daily and must be dose-reduced in patients with moderate to severe renal impairment.

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