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LINAGLIPTIN: A NEW OPTION IN THE TREATMENT OF TYPE-II DIABETES

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In 2009, approximately 19.7 million people age 20 years and older were diagnosed with diabetes in the United States, and in 2010 that number escalated to 25.6 million.[1] This includes type I, type II and gestational diabetes. Of the three main types of diabetes, type II is the most common accounting for 90 -95% of newly diagnosed cases and ranking as the 7th leading cause of death in the United States.[2] Type II diabetes is primarily the result of either the body not producing enough insulin or cells in the body becoming immune to insulin. Consequences of uncontrolled diabetes include kidney failure, atraumatic lower-limb amputations and new cases of blindness.[2]

There are several currently accepted therapies for the management of type II diabetes. Some of these include biguanides (e.g., metformin), sulfonylureas (e.g., glipizide, glyburide, etc.), meglitinides (e.g., repaglinide, netaglinide), thiazolidinediones (e.g., pioglitazone), dipeptidyl peptidase-4 inhibitors (e.g., saxagliptin, sitagliptin) and insulin. These agents can be given as monotherapy or in combination in order to achieve adequate blood sugar control.

Linagliptin (Tradjenta®) is a new dipeptidyl peptidase-4 enzyme inhibitor (DPP-4 inhibitor) that was approved for the management of type II diabetes by the FDA on May 2, 2011, and is co-manufactured by Boehringer Ingelheim Pharmaceuticals and Eli Lilly and Co.[3] Linagliptin is the third DPP-4 inhibitor to be approved by the FDA and is indicated to lower blood glucose levels in patients with type II diabetes, in combination with diet and exercise. The objective of this article is to review the pharmacology, pharmacokinetics, past and present clinical trials, adverse effects, safety, dosage and administration, and cost of linagliptin.

Pharmacology

Dipeptidyl peptidase-4, an antigenic enzyme located on the majority of cells, plays a significant role in the metabolism of glucose by breaking down incretin mimetics (e.g., glucagon-like peptide 1, GLP-1), which is responsible for increasing the amount of insulin that is secreted by the beta cells of the pancreas.[3] Linagliptin, like all approved DPP-4 inhibitors, reversibly binds to and inhibits the DPP-4 enzyme. When food is consumed, there is a glucose-dependent increase in incretin concentrations which stimulate the release of insulin and inhibits the release of glucagon, resulting in decreased levels of circulating glucose. By inhibiting DPP-4, incretins remain in tact and thus naturally increase the body's own production of insulin (**Figure 1**).

Pharmacokinetics

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Linagliptin achieves peak plasma concentrations (C_{max}) in 0.5 to 3 hours after oral administration (**Table 1**).[3] The extent of linagliptin absorption is not affected by food; however, high fat meals can reduce the C_{max} up to 15%. This reduction in C_{max} is not clinically significant, allowing patients to take linagliptin without regard to meals. Linagliptin displays a non-linear dose response, suggesting that an increase in dose will not provide a similar increase in effect.[5]

Linagliptin has a large volume of distribution in healthy subjects, binding to plasma proteins in a concentration dependent manner. Plasma protein binding is not altered in patients with renal or hepatic impairment. According to the manufacturer, the terminal half-life of >100 hours is due to the saturable binding of DPP-4 enzyme receptors. However, this extended half-life does not result in accumulation of linagliptin when administered once daily, as the terminal half-life does not reflect the accumulation half-life which was measured to be between 10 and 15 hours. The drug is predominantly excreted unchanged in both the feces (90%) and urine (5%), indicating that metabolism plays a minor role in linagliptin elimination. A very small portion of the absorbed linagliptin is converted into an inactive metabolite.[3,5]

Clinical Trials

Linagliptin has been combined with and compared to several other anti-hyperglycemics in an effort to prove its safety and efficacy (**Table 2**). There are 12 currently recruiting or active studies being performed with linagliptin, including one that is studying the combination of linagliptin with insulin and one that is investigating the use in children younger than 18 years of age.[7]

Linagliptin is available as a 5 mg tablet to be administered once daily. There is only one dose due to the plateau of beneficial effect on HbA1c seen in the "The Oral DPP-4 Inhibitor linagliptin Significantly Lowers HbA1c after 4 Weeks of Treatment in Patients with Type II Diabetes Mellitus" trial.[8] Patients with type II diabetes were given a 14 day washout period from other anti-hyperglycemic medications and then randomized to receive 2.5, 5 or 10 mg of linagliptin or placebo for 28 days. Of the 77 patients that were initially enrolled, 61 were assigned to receive linagliptin and the other 16 were assigned to receive placebo. In order to measure the inhibition of the DPP-4 enzyme, blood samples were drawn at baseline and then 30 minutes following a standardized meal on days 1 and 29 of the study. At the end of the 24-hour dosing interval, inhibition of the DPP-4 enzyme was still significant (82%-90%), indicating that once daily dosing was adequate. With an average baseline HbA1c of 7.0%, the 5 mg dose of linagliptin provided the most statistically significant decrease (-0.37%, $p<0.025$) when compared to the other two doses (-0.31% and -0.28% for 2.5 and 10 mg, respectively, $p<0.025$) and placebo. The mean decrease from baseline of HbA1c with all studied doses of linagliptin compared to placebo was 0.69% ($p<0.0001$). Linagliptin also demonstrated a safety profile similar to that of placebo, with 31% of linagliptin patients and 34% of placebo patients re-

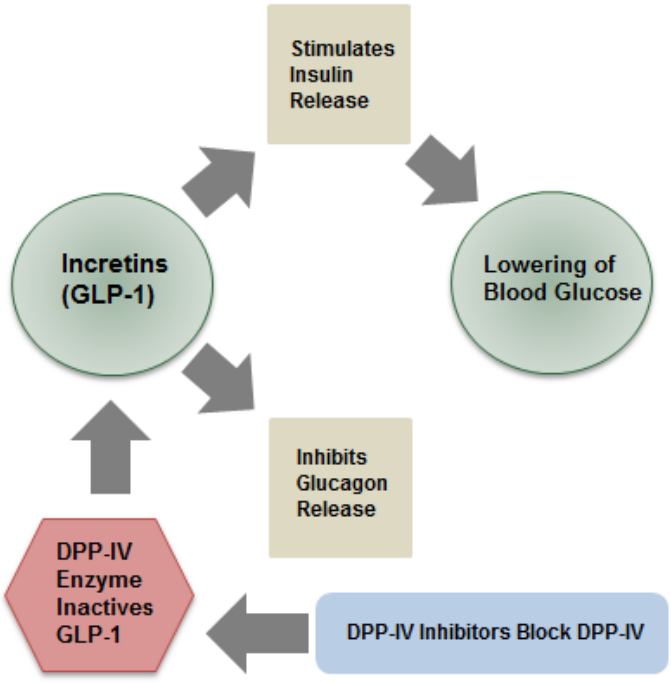

Figure 1 | Mechanism of Action of DPP-IV Inhibitors

Table 1 | Pharmacokinetic Information for Linagliptin[3]

Property	Linagliptin
Tmax	1.5 hours
AUC	139 nmol*h/L
Cmax	8.9 nmol/L
Terminal ½ life	>100 hours
Bioavailability	30%
Volume of distribution	1110 L
Elimination	90% feces, 5% urine

Table 2 | Summary of Clinical Trials[8,9,10,11,12]

Author/Year/ # of Subjects	Study Design	Dose	Primary Results	Author's Conclusions
• Forst, et.al.[8] • 2011 • 77 pts: 61 lin, 16 placebo	• DB, parallel, PCT • 14 day washout • 28 day trial	• Active: Lin 2.5, 5 or 10mg • Comparator: Placebo	• p-value <0.025 considered stat. sig. • Total mean dec. in HbA1c of 0.69% (p<0.0001) • Mean dec. in HbA1c of 0.31% (2.5mg) 0.37% (5mg) 0.28% (10mg) • 31% AE w/ lin vs 34% AE w/ placebo	• Lin caused sig reductions in HbA1c after only 4 wks of tx
• Del Prato, et.al.[9] • 2011 • 503 pts: 336 lin, 167 placebo	• Multicenter, R, parallel, phase III study • Compared lin 5mg to placebo for 24 wks	• Active: lin 5mg • Comparator: Placebo	• FPG dec of 1.3mmol/L (23.4mg/dL) and 2 hour PPG dec of 3.2mmol/L (57.6mg/dL) w/ lin; both p<0.0001 • Comparable AE profile to placebo	• Pt treated w/ lin more likely to achieve reduction in HbA1c • Improved β-cell function
• Gomis, et.al.[10] • 2011 • 389 pts: 259 lin, 130 placebo	• DB, R, PCT • 24 wks admin	• Pt received either 30mg pio and 5mg lin or 30mg pio and placebo, daily	• A dec. of 1.06% in HbA1c w/ pio and lin • A dec. of 0.56% in HbA1c w/ pio and placebo • Both had p-values <0.0001	• Combination valuable tx option, especially when metformin not possible tx
• Taskinen, et.al.[11] • 2011 • 688 pts: 516 lin, 175 placebo	• 24 wks, R, PCT, DB, parallel study • 82 centers in 10 countries	• Pt received ≥1500mg/d metformin for 6 wks before randomization • Active: lin 5mg • Comparator: Placebo	• HbA1c dec 0.49% w/ lin and metformin. Dec of 0.15% w/ placebo • FPG dec 0.59mmol/L (10.6mg/dL) w/ lin and 0.58mmol/L (10.4mg/dL) w/ placebo • All p<0.0001	• Body wt did not sig change in either group • Lin provided a sig dec in HbA1c; however was almost equal to placebo in change in FPG
• Boehinger Pharmaceutical[12] • Currently in Phase III • 1055 pts: 792 lin, 263 placebo	• 24 wk, DB, R, PCT • Pt already on metformin randomized 1:3 (placebo:lin) to either group	• Active: lin 5mg • Comparator: Placebo	• Dec from baseline of 0.6% HgA1c and 12.7mg/dL FPG • P<0.0001	• Lin provided statistically sig improvement in both A1c and FPG when combined with glim and metformin. • Risk of hypoglycemia increased when lin was added to a SU

Pt(s) = Patient(s); Lin = Linagliptin; DB = Double Blind; PCT = Placebo-Controlled Trial; stat = statistically sig = significant; HbA1c = Hemoglobin A1c; Dec. = Decrease; mg = milligrams; w/ = with; AE = Adverse Effect; Wk(s) = Week(s); Tx = Treatment; FPG = Fasting Plasma Glucose; mmol/L = millimoles per liter; PPG = Postprandial Glucose; R = Randomized; Pio = Pioglitazone; mg/d = milligrams per day; SU = sulfonylurea.

porting at least one adverse effect.[8]

The "Effect of linagliptin Monotherapy on Glycemic Control and Markers of β -cell Function in Patients with Inadequately Controlled Type II Diabetes" trial selected patients who were either treatment naïve or had a history of taking only one anti-diabetic drug and randomized them into either placebo (n=167) or linagliptin 5 mg (n=336).[9] After 24 weeks of treatment, patients who received linagliptin 5 mg achieved a statistically and clinically significant decrease in their fasting plasma glucose (-1.3 mmol/L, equivalent to 23.4 mg/dL; p<0.0001) and 2-hour postprandial glucose (-3.2 mmol/L, equivalent to 57.6 mg/dL; p<0.0001). These patients were also more likely to achieve a reduction of greater than 0.5% in HbA1c than patients who received placebo. Linagliptin patients also experienced improvement in β -cell function compared to placebo patients. β –cell improvements were measured by analyzing the change in ratio of relative change in adjusted mean HOMA-IR (homeostasis model assessment for insulin resistance) and disposition index. [9]

Adverse Effects

Overall, linagliptin is well-tolerated, both as monotherapy and when combined with other oral antiglycemic agents (**Table 3**). The risk of hypoglycemia when administering linagliptin as monotherapy is significantly reduced because incretin-based therapy controls hyperglycemia through glucose-dependent mechanisms. However, when combined with a sulfonylurea, the incidence increases from ≥2% with monotherapy to ≥5% with combination therapy.[5] Unlike the other two FDA approved DPP-4 inhibitors, linagliptin showed no difference in reported frequency of skin and subcutaneous tissue disorders when compared to placebo.[3]

Safety

Pregnancy and Lactation

Linagliptin is pregnancy category B, indicating that it should be used with caution in patients who are considering pregnancy or are already pregnant.[3] Although there have not been any adequate and well-controlled studies of linagliptin used in pregnant humans, linagliptin has been shown to cross the placental barrier when studied in rats and rabbits. Similarly, specific lactation studies have not been performed involving humans and it is unknown if linagliptin is excreted in human breast milk. Animal studies have shown that linagliptin is excreted in the breast milk at a milk-to-plasma ratio of 4:1.[5]

Drug Interactions

Linagliptin is both a p-glycoprotein (P-gp) and CYP 3A4 substrate. The effect of P-gp and CYP 3A4 inhibition was evaluated in a drug-drug interaction study where the AUC and Cmax were increased 2- and 3-fold, respectively, when linagliptin was co-administered with ritonavir. Alternatively, when 5 mg of linagliptin was co-administered with a CYP 3A4 and P-gp inducer, the bioavailability fell to the equivalent of a 1 mg dose. As a substrate of CYP 3A4, linagliptin is subject to a significant amount of drug-drug and drug-food interactions, unlike the other two DPP-4 inhibitors which are both unaffected by either CYP 3A4 or P-gp.[5,12]

Currently there is an active trial investigating the combination of linagliptin and insulin.[7] As this combination has not been approved by the FDA, co-

Table 3 | Adverse Reactions Reported in ≥ 2% of Patients Treated[3]

	Monotherapy*	Comb. w/ Metformin#	Comb. w/ SU	Comb. w/ Metformin + SU	Comb. w/ Pio
	T(765)/P(458)	T(590)/P(248)	T(161)/P(84)	T(791)/P(263)	T(259)/P(130)
Nasopharyn.	Not reported	Not reported	7/1	Not reported	Not reported
Hypergly.	Not reported	Not reported	Not reported	Not reported	7/1
Cough	Not reported	Not reported	Not reported	19/3	Not reported
Hypertrig.	Not reported	Not reported	4/0	Not reported	Not reported
Wt. Increase	Not reported	Not reported	Not reported	Not reported	6/1

Nasopharyn. = Nasopharyngitis; Hypergly = Hyperglycemia; Hypertrig = Hypertriglyceridemia; Wt = Weight; w/ = with; Comb. = Combination; SU = sulfonylurea; Pio = Pioglitazone; T = Tradjenta; P = Placebo
* = Pooled data from 7 studies
# = Pooled data from 2 studies

administration of linagliptin with insulin is discouraged until more information is available. If there is a need to institute a DPP-4 inhibitor in an insulin-dependent patient, both saxagliptin and sitagliptin are approved for use with insulin.

When linagliptin is added to a current regimen that includes a sulfonylurea the dose of the sulfonylurea should be decreased since this combination is more likely to cause hypoglycemia versus combining linagliptin with another anti-hyperglycemic.[13]

Special Populations

Linagliptin has not been studied in patients younger than 18 years of age and should be used with caution in this population.[3] Patients who have hepatic or renal insufficiencies do not require dose adjustments because renal elimination is not a primary excretion pathway and plasma protein binding is not affected in these patients. Currently, there are ongoing studies investigating the safe and effective use of linagliptin in patients with moderate to end-stage renal disease.[7]

Dosage and Administration

Linagliptin is dispensed under the brand name Tradjenta® as a 5 mg red, round, film-coated tablet that can be taken orally without regard to meals. It is dispensed in bottles of 30, 90 and 1000.[12] The maximum daily dose is 5 mg, allowing patients to take one tablet once a day. As linagliptin is unaffected by either renal or hepatic impairment, no dose adjustments are required.

Cost

Table 4 provides a mean retail cost and range for linagliptin 5 mg tablets from a chain, discount, and independent pharmacy. As of June 22, 2011, linagliptin was not on the Florida Medicaid formulary; however, both Januvia® and Onglyza® are available with no prior authorization required.[14] All three DPP-4 inhibitors are available as brand only.

Summary

Linagliptin is the third FDA approved DPP-4 enzyme inhibitor in the management of type II diabetes in combination with diet and exercise. Linagliptin is dispensed under the brand name Tradjenta® as a once-daily 5mg tablet to be taken without regard to meals. Without insurance, linagliptin ranges in price from $241.99 to $291.76, with an average price of $258.92 for a one month supply.

Table 4 | Retail Cost of Linagliptin: 1 Month Supply

Drug	Mean	Range
Linagliptin 5mg	$258.92	$241.99-$291.76

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EZOGABINE: A NEW OPTION IN THE TREATMENT OF PARTIAL SEIZURES

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Approximately 4 million people in the United States have some form of epilepsy and ~3% of the population will have a seizure at some point in their lives.[1] A partial seizure can be caused by abnormal firing of neurons in a localized area of the brain with motor, somatosensory, or autonomic impairment with or without loss of consciousness.[2] Loss of consciousness during the seizure describes it as complex while maintaining consciousness is termed simple. Both complex and simple seizures can lead to generalized seizures which occur when the seizure spreads throughout the brain.[2] Although seizures have multiple etiologies, known common risk factors include: tumors, substance abuse, fever, exposure to alcohol and lack of sleep. The main goal of therapy is to reduce the frequency of seizures. Approximately 30% of patients on antiepileptic drugs (AED) are uncontrolled on therapy, with the majority of those patients having partial seizures.[3] Multiple combinations of drugs are oftentimes used to control the seizure frequency due to the difficultly in identifying the exact cause of the seizure. Drug-resistant epilepsy is defined by the International League Against Epilepsy as a continued occurrence of partial seizures despite treatment with at least 2 approved AEDs alone or in combination, administered in adequate doses for a sufficient period of time.[4]

Ezogabine (Potiga®) is a new antiepileptic drug manufactured by Valeant Pharmaceuticals and distributed by GlaxoSmithKline that was approved in the United States on June 10, 2011 for adjunctive treatment of partial onset seizures in patients 18 years and older with or without secondary generalization. Ezogabine was developed in 1997 but had difficulty getting FDA approval. It will be a scheduled drug and is currently undergoing scheduling by the DEA. In past studies, the name of the drug was retigabine and some data and studies were completed under that name. The intent of this article is to provide information on the pharmacology, pharmacokinetics, efficacy, dosing, and safety of ezogabine.

PHARMACOLOGY

The mechanism of action for many AEDs are unknown, however it is thought that ezogabine works differently than existing AEDs by selectively acting on neuronal M-voltage-gated potassium channels instead of sodium channels.[5] By hyperpolarizing transmembrane potassium currents mediated by the potassium channel voltage gated KQT-like subfamily (KCNQ) of ions, the degree of depolarization needed to open the channel is reduced.[6] This causes the potassium channel to open faster and stay open longer, which reduces repetitive nerve firing and lowers brain excitability. Ezogabine can potentiate GABA-mediated currents, increasing their activity, and cause reduction in the release of glutamate, an excitatory neurotransmitter. The combined effects of these mechanisms all contribute to the anti-seizure activity of ezogabine.

PHARMACOKINETICS

Ezogabine has rapid, linear absorption from the gut, reaching peak concentrations (T_{max}) in 0.5-2 hours (**Table 1**). A high fat meal slows absorption by 0.75 hours and increases peak concentrations by 38%, however, the AUC remains the same. Ezogabine can be given with or without food.[7] Ezogabine is well distributed in the body and extensively metabolized by glucoronidation (UGT1A4) and acetylation (NAT2). There is no cytochrome P450 involvement which

makes an interaction by inducers or inhibitors of CYP450 unlikely. Ezogabine is metabolized to the N-acetylated metabolite of ezogabine (NAMR), which exerts anti-seizure activity. NAMR has similar elimination half-life data. Ezogabine is primarily eliminated renally with an elimination half life of 7-11 hours requiring TID dosing.

Clinical Trials

Dose Ranging Study

Porter et al evaluated the efficacy and safety of different doses of ezogabine.[8] The study was designed to add ezogabine, in escalating doses, to patients 16 to 70 years of age who were uncontrolled on an established AED regimen. Patients were required to have a minimum of 4 seizures per month and no 30 day seizure-free period. Patients kept a seizure diary and were seen every two weeks during the titration period and every four weeks during the maintenance period. Patients received three doses of ezogabine or placebo per day (600, 900, or 1,200 mg/day) for a total of 16 weeks (8-week forced titration period followed by an 8-week maintenance period). Ezogabine significantly decreased partial seizure frequency from baseline with median percent change in monthly total partial seizure frequency from baseline being 23% for 600 mg/day (p=0.199), 29% for 900 mg/day (p=0.043), and 35% for 1,200 mg/day (p<0.001). The responder rate, defined as a greater than 50% reduction in seizure frequency, was statistically significant for the 900 mg (32%, p=0.008) and 1200 mg/day doses (33%, p=0.001) but not for 600 mg/day (23%, p=0.189). Side effects were dose and titration dependent.

Table1 | Pharmacokinetics of Ezogabine[6,7]

Property	
Tmax	0.5 to 2h
Bioavalibility	60%
Protein Binding	80%
Vd	2-3 L/kg
Metabolism	Glucoronidation and acetylation (UGT1A4 and NAT2)
Elimination half life	7-11h
Excretion	85% Urine 14% Feces
Clearance	0.4-0.6ml/kg/hr
AUC	7823 ng*h/ml

Tmax: time to peak concentration, H: hour, Vd: volume of distribution, L/kg: liters/kilogram, ml/kg/hr: milliliters per kilogram per hour, AUC: area under the curve, ng*h/ml: nanogram hours per milliliter

High Dose Efficacy v Low Dose Efficacy

French et al completed a high dose study called the Retigabine Efficacy and Safety Trial for Partial Onset Refractory Seizures in Epilepsy (RESTORE 1).[3] It included 305 patients 18 to 75 years old with drug resistant epilepsy characterized by simple or complex partial onset seizures, with or without generalization, with ≥ 4 seizures in a 28 day period over 8 weeks while taking a stable regimen of 1-3 AEDs. RESTORE 1 was 18 weeks in duration and included a 6 weeks forced titration period, during which the dose was titrated up to 1200 mg/day, followed by a 12 week maintenance phase. Patients were given ezogabine 100 mg TID with a 150 mg/day per week titration until 1200 mg daily was achieved. The median percent reduction in monthly seizure frequency over the double-blind period was 44.3% for ezogabine vs placebo 17.5% (p<0.001). The responder rate, defined as ≥ 50% reduction in seizures frequency, was significant for 1200 mg of ezogabine compared to placebo (44.4% vs 17.8%, p<0.001).

The RESTORE 2 trial included 538 patients and compared 600 mg/day and 900 mg/day of ezogabine to placebo as add on seizure therapy.[9] Patients were started on ezogabine100 mg TID then titrated by 150 mg/day (50 mg/dose) at 1-week intervals to either 600mg or 900 mg per day. Patients then entered a 12 week maintenance phase. Ezogabine reduced seizure frequency in the 600 mg/d group by 27.9% (p=0.007) and by 39.9% for 900 mg/d group (p<0.001) versus placebo (15.9%) and significantly increased the maintenance phase responder rate by 38.6% and 47.0% (p<0.001 for both), respectively, vs placebo (18.9%).

Adverse Reactions

Due to urinary retention risks, the FDA has mandated that a postmarking cohort study be conducted to assess the risk in comparison to other AED therapies. This study is to be completed by November 2014 and involve 2000 to 4000 patients. In trials, clinical urinary retention occurred in ~2% of patients.[6] Urinary retention included symptoms such as unable to start urinating, having trouble emptying bladder, weak stream, and pain upon urination. Overall, dizziness occurred in 15%, 23%, and 32% of patients receiving ezogabine at 600, 900, and 1,200 mg/day, respectively versus 9% for placebo (Table 3). Somnolence occurred in 15%, 25%, and 27% versus 12% for placebo. Lastly, fatigue occurred in 16%, 15%, and 13% versus 6% for placebo.[7] Ezogabine was associated with CNS effects including confusion, tremor, vertigo, and speech disorder. The FDA label also lists disorientation, hallucina-

tions, psychosis, blurred vision, increased suicidal thoughts and behavior as possible side effects. These side effects were seen in the first 8 weeks of treatment and were dose related. The QTc interval was increased in healthy subjects on 1200 mg/day and increased monitoring is recommended in patients at risk for this condition.

Safety

Pregnancy and Lactation

Ezogabine is pregnancy category C since there are no adequate or controlled studies in pregnant women. However, in studies with rats and rabbits, an equivalent weight based dose of 1200 mg showed developmental toxicity in the offspring. At even larger doses in animals, the toxicities were limited by maternal toxicity rather than toxicity affecting the offspring. Ezogabine is found in breast milk in rats. The current recommendation is to evaluate the risks and benefits before prescribing to lactating mothers.[6]

Drug Interactions

Although ezogabine has no direct CYP450 involvement, there are clinically relevant drug interactions that could mandate a dose adjustment (Table 4). Carbamazepine and phenytoin can decrease the effect of ezogabine. Alcohol can increase the AUC of ezogabine as well as cause additional side effects such as drowsiness. Ezogabine has no absolute contraindications.

Dosing and Administration

Ezogabine is available as 50 mg, 200 mg, 300 mg, and 400 mg film-coated immediate release tablets. Dosing has three stages including initial, titration, and maintenance. The initial dose is 100 mg TID. The drug should be titrated at weekly intervals by no more than 50 mg three times daily (150 mg per day) until a dose of 200 mg to 400 mg three times daily is achieved. The maximum dose in otherwise healthy populations is 1200 mg per day. If ezogabine is discontinued, it should be tapered over 3 weeks to reduce the possibility of a refractory seizure.

Special Populations

Dose adjustments are necessary for patients with renal insufficiency including stage 3 and 4 chronic kidney disease and end stage renal disease. Dosing should start at 5 0mg TID and be titrated by no more than 50 mg three times daily (150 mg/day) at weekly

Table 2 | Summary of Clinical Trials with Ezogabine

Author/Year/# of subjects	Study Design	Study Drug and Comparator	Primary Results	Author's Conclusion
French et al[3] 2011 306 patients RESTORE 1	R, DB, PC	1200mg EZO /placebo	Total PSF reduction EZO 1200mg/d 44.3% (p<0.001) v PCB 17.5%; RR EZO 1200mg 44.4% (p<0.001) v. PCB 17.8%	EZO 1200mg is effective as add-on therapy for reducing seizure frequency in patients with drug-resistant partial-onset seizures
Brodie et al[9] 2010 538 patients RESTORE 2	DB, R, PC, MC	600mg, 900mg, 1200mg of EZO and placebo	PSF sig decreased in EZO 600 mg, 27.9% (p=0.007), 900 mg 39.9% (p<0.001), v PCB 15.9%. RR EZO 600 mg, 38.6% (p<0.001), EZO 900 mg, 47.0% (p<0.001), v. PCB 18.9%	EZO 600mg and 900mg were effective in reducing PSF
Ferron et al[7] 2002 45 healthy men	DB, PC	100mg, 200mg, 250mg, 300mg (every 12h) versus placebo	Pharmacokinetic information	Linearly dose proportional and time independent kinetics with multiple doses safe and well tolerated
Porter et al[8] 2007 396 patients	MC, DB, R, PC		PSF EZO 600mg 23% , EZO 900mg 29%, EZO 1200mg 35%	EZO 600mg, 900mg, 1200mg/d reduced PSF SIG

DB:double-blind PC: placebo controlled AE: adverse effects, SIG: significantly, Pt:patient, EZO: ezogabine, MC: multicenter R:randomized, PSF: partial seizure frequency RR: responder rates

intervals to a maximum dose of 200 mg TID (600 mg/day). In hepatic impairment, with a CHILD PUGH score of greater than 7-9, dosing is the same as for renal disease except a maximum dose of 250mg TID can be used. In severe hepatic impairment, with a CHILD PUGH score of greater than 7-9, the dosing regimen is the same as for renal disease except a maximum dose of 250 mg TID can be used. Geriatric dosing (age greater than 65 years old) is started at 50 mg TID then titrated by no more than 50 mg TID to a maximum dose of 250 mg three times daily (750mg/day).

Pricing

The price of Potiga® is not available at the moment because the drug is undergoing scheduling by the FDA.

Summary

Ezogabine is an adjunctive treatment for partial onset seizures with or without generalization approved for adults 18 years and older. It's unique mechanism of action, acting on potassium channels, reduces seizure frequency in clinical trials. The main side effects are urinary retention, dizziness, somnolence, and fatigue; however, more serious side effects such as suicide risk, psychosis, and QT prolongation were also seen. Ezogabine is well absorbed and has minimal drug interactions due to a lack of CYP450 metabolism. The typical dosing regimen is 100 mg TID to start, followed by a titration of 50 mg TID per week, until a maintenance dose of 600-1200 mg/day is achieved. Higher doses of ezogabine are more effective for seizure reduction but carry a higher frequency of side effects. Ezogabine has potential to be effective for treatment resistant partial onset seizure patients.

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Table 4 | Drug Interactions with Ezogabine

Drug	Influence of ezogabine on drug	Influence of drug on ezogabine	Dose Adjustment
Carbamazepine (Tegretol ®)	None	31% decrease in AUC, 23% decrease in Cmax	Consider increase in dose of ezogabine
Phenytoin (Dilantin®)	None	34% decrease in AUC, 18% decrease in Cmax	Consider increase in dose of ezogabine
Digoxin (Lanoxin ®)	Decreased renal excretion	None	Monitor digoxin levels
Urine Bilirubin	Falsely elevated numbers	None	None
Alcohol	None	Increases AUC by 37%	Consider decrease in dose of ezogabine

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CLINICAL TRIAL UPDATE

Azithromycin for Prevention of Exacerbations of COPD[1] | Patients who were at least 40 years old with a clinical diagnosis of COPD, had received systemic glucocorticoids within the previous year or were using continuous supplemental oxygen, had gone to an emergency room or had been hospitalized for an acute exacerbation of COPD, and had not had an acute exacerbation of COPD in the previous 4 weeks were randomized to received azithromycin (AZR) 250 mg daily (n=558) or placebo (n=559) for 1 year. The primary outcome was the time to the first acute exacerbation of COPD. Notable secondary outcomes included nasopharyngeal colonization with selected respiratory pathogens (i.e., *Staphylococcus aureus, Streptococcus pneumonia,* haemophilus species, and Moraxella species); respiratory pathogens were assessed for resistance to macrolides.

At study completion, AZR increased the time to the first acute exacerbation compared to placebo (266 days with AZR compared to 174 days with placebo; 95% CI 143 to 215 days; $p < 0.001$). AZR also reduced the risk of having an acute exacerbation compared to placebo (per-patient year, HR 0.73; 95% CI 0.63-0.84; $p < 0.001$); the rate of acute exacerbations of COPD per-patient year was 1.48 for azithromycin and 1.83 for placebo. Subgroup analyses showed that the response to AZR varied according to age (≤ 65 or > 65), smoking status (current vs. former), use or nonuse of oxygen, GOLD stage, and use or nonuse of inhalers.

Audiogram-confirmed hearing decrements occurred in 25% of patients receiving AZR compared to 20% receiving placebo ($p = 0.04$). Twenty-one of the 62 participants who discontinued AZR and in 6 of the 19 who did not discontinue had their hearing return to baseline.

Nasopharyngeal swabs were obtained at nearly 85% of clinic visits. At baseline, 14% of patients randomized to AZR were colonized with respiratory pathogens compared to 15% of patients assigned placebo. At study completion, 12% of patients receiving AZR and 31% of placebo who did not have colonization at enrollment had become colonized. Baseline cultures were obtained from 56% of patients randomized AZR and in 59% of patients randomized to placebo; prevalence of macrolide resistance was 52% and 57%, respectively ($p = 0.64$). At study completion, incidence of macrolide resistance increased to 81% in the AZR group and decreased to 41% in the placebo group ($p < 0.001$). The authors noted that patients randomized to AZR were less likely to become colonized with respiratory pathogens but were more likely to become colonized with macrolide-resistant organisms.

1. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011 Aug 25;365(8):689-98.

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