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DARIFENACIN (ENABLEX®): A NEW OPTION FOR TREATMENT OF OVERACTIVE BLADDER

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Overactive bladder (OAB) is a chronic and potentially debilitating condition that affects approximately 16% of the adult population in the U.S. and Europe. According to the National Overactive Bladder Evaluation (NOBLE) program, an estimated 34 million Americans have symptoms of OAB.¹ Overactive bladder is a common condition in both men and women of all ages, but is more prevalent in the elderly population.² In 2000, the combined direct and indirect costs associated with OAB were \$12.6 billion, which is similar to the economic impact of asthma and osteoporosis.³ However, due to low physician consultation rates, estimated costs are likely to be grossly underestimated, and the economic burden of OAB may be much larger. As the world's population continues to grow and age, the economic impact of this condition will continue to expand. By the year 2020, population growth estimations predict that there will be 44% more people over the age of 65, and that costs will escalate in line with this aging population.²

The International Continence Society has defined OAB as urinary urgency with or without urge incontinence, usually with frequency and nocturia without proven infection or other pathology.² These symptoms are believed to be caused by inappropriate contractions of the detrusor muscle during the filling phase of the micturition cycle.⁴ Muscarinic receptors

play important roles in cholinergic mediated functions throughout the body, including stimulating contractions of urinary bladder smooth muscle.⁵ Blockade of muscarinic receptors on the detrusor muscle with anticholinergic medications has become the most common and effective pharmacologic treatment for patients suffering from OAB.⁶ Anticholinergic therapy results in fewer and less forceful inappropriate bladder contractions, which allows for enhanced bladder capacity.⁴ Blockade of other muscarinic receptors located in the GI, CNS, myocardium, salivary glands, and eye, however, are associated with many adverse effects that may affect adherence. For thirty years, immediate release oxybutynin, a non-selective muscarinic antagonist, has been the "gold standard" for treatment of OAB, but its use has been limited by side effects.⁷ More selective agents, such as darifenacin, are being marketed for OAB. Newer agents offer a cleaner side effect profile compared to oxybutynin without sacrificing therapeutic efficacy.

Darifenacin (dâr ĭ fĕn' ă sĭn)(Enablex®[ĕ nā' blĕks]) is a new M₃ selective receptor antagonist approved by the FDA for OAB and its symptoms in December 2004 and is marketed by Novartis. In contrast to oxybutynin, darifenacin demonstrates a higher degree of selectivity for M₃ receptors than M₁,

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M₂, M₄, and M₅ receptors (9 and 12-fold greater for M₃ compared to M₁ and M₅, respectively and 59-fold greater affinity for M₃ to M₂ and M₄).⁸ This article will examine the safety, efficacy, and tolerability of darifenacin.

Pharmacology and Pharmacokinetics

Muscarinic receptors are responsible for mediating the effects of the parasympathetic nervous system.⁹ Five subtypes have been identified and are designated M₁ through M₅, each having a specific physiological role in the tissue in which it is found.¹⁰ M₃ receptor subtype is primarily responsible for parasympathetic mediated detrusor contractions and the symptoms of overactive bladder, though M₂ receptors are the predominant receptor type in the bladder.¹¹ Other receptors and their functions include: M₁ and M₃ receptors, which drive secretion from salivary glands; M₁ receptors in the brain are involved in learning and memory cognitive impairment; M₂ receptors modulate pacemaker activity, AV conduction, and force of contraction; and M₃ and M₅ receptors on the ciliary muscle of the eye are involved in contraction of the pupil. When these receptors are blocked by a non-selective blocker, unwanted side effects may occur.

Darifenacin's peak plasma concentration (C_{max}) is reached approximately seven hours after multiple dose oral administration and steady state plasma concentrations are achieved by day six. There is no affect of food on absorption. Darifenacin is approximately 98% bound to plasma proteins, mainly alpha-1-acid glycoprotein, and is extensively metabolized in the liver. Metabolism is mediated by CYP2D6 and CYP3A4 and no metabolites contribute to its clinical effect. A small subset of individuals (7% Caucasians and 2% African Americans) are poor metabolizers (PMs) of CYP2D6, while people with normal CYP2D6 activity are extensive metabolizers (EMs). In PMs, metabolism will be mediated by CYP3A4 only and thus the C_{max} and AUC will be increased by 90% and 70%, respectively compared to EMs. Furthermore, potent inhibitors of CYP3A4 (ketoconazole, itraconazole, ritonavir, nelfinavir, clarithromycin, and nefazodone) will extensively increase serum levels of darifenacin and the daily dose of 7.5 mg should not be exceeded in patients taking these medications. Other medications that induce CYP3A4 (ex. rifampin, carbamazepine, phenytoin) may also affect darifenacin serum levels. Caution should be used when darifenacin is combined with

medications that are substrates of CYP2D6 and have narrow therapeutic windows (ex. flecainide, thioridazine, and TCA's) as drug interaction studies have shown several fold increases in the serum levels of these drugs.⁸ Oral bioavailability of darifenacin 7.5 mg and 15 mg is 15% and 19%.¹² Estimated clearance is 40 L/h for EMs and 32 L/h for PMs. The elimination half-life (t_{1/2}) following chronic dosing is 12-19 hours. No dosing adjustments are required based on age, gender, or renal insufficiency. However, patients with moderate hepatic impairment should not exceed 7.5 mg daily and those with severe impairment should avoid this medication altogether. Since darifenacin is 98% protein bound, a decrease in serum proteins due to moderate hepatic dysfunction will increase unbound darifenacin exposure by 4.7 fold over patients with normal liver function.⁸

Clinical Trials

OAB

Several studies have investigated the safety and efficacy of darifenacin for the treatment of OAB. These studies include: dosing-ranging studies^{4,13}, comparison studies¹⁴, and safety trials.^{5,15} Several other important trials have been conducted using darifenacin (**Table 1**).

Dosing-ranging studies

Several double-blinded, placebo-controlled trials evaluated darifenacin's effect on OAB and its symptoms. Steers et al.⁴ evaluated the efficacy, safety, and tolerability of a flexible dosing strategy in a multicenter, double-blind, 12 week study (n=395). The primary endpoint was change from baseline in the number of incontinence episodes per week at the ends of weeks 2 and 12. Patients were randomized and received darifenacin 7.5 mg once daily or placebo. After two weeks, efficacy, tolerability, and safety were assessed and the dose was increased to 15 mg, if clinically necessary. Results showed a significant improvement in the primary endpoint at the end of weeks 2 and 12. Median % changes from baseline for darifenacin vs. placebo were -43% vs. -28.6% (p=0.042) and -62.9% vs. 48.1% (p=0.035). Patients that required a dose escalation to 15 mg had lower response rates at 2 weeks than those that continued with 7.5 mg. However, at week 12, patients taking 15 mg showed the most marked improvement in the study's primary endpoint. Darifenacin was well-tolerated as only 6% of patients in the darifenacin group discontinued the study as a result

Table 1. Summary of important clinical trials involving darifenacin

Study group	Demographics	Design	Dose	N	Primary endpoint
Haab, et al. ¹⁷	19-88 yo (85% F) with OAB symptoms > 6 months	-Randomized			% reduction of incontinence episodes/week:
		-DB, PC, PG	3.75mg	53	58.8*
		-Fixed dose	7.5mg	229	67.7 (p=0.010)**
		-12 weeks	15mg	115	72.8 (p=0.017)**
			placebo	164	55.9
Foote, et al. ¹⁸	M/F ≥65 yo with OAB symptoms	-Pooled subgroup analysis			% reduction of incontinence episodes/week:
		-Randomized	7.5mg vs.	97	66.7 (p<0.001)**
		-DB, PC	placebo	72	34.8
		-12 weeks			
			15mg vs.	109	75.9 (p<0.001)**
			placebo	108	44.8
Zinner, et al. ¹⁹	M/F ≥ 18 yo with OAB symptoms > 6months	-Randomized			Increase in mean warning time:
		-DB, PC, PG			
		-Fixed dose	15mg	212	0.68 minutes [#]
		-Community setting	placebo	220	0.36 minutes

M = male; F = female; DB = double-blind; PC = placebo-controlled; PG = parallel group
 *statistical analysis not performed; **significance vs. placebo; # not significant

of treatment related AE's compared with 2% in the placebo group. The most common AE's were constipation, dry mouth, and headache.

Another dose-ranging study by Hill et al.¹³ randomized 439 patients to darifenacin 7.5 mg (n=108), 15 mg (n=107), 30 mg (n=115), or placebo (n=109). After 12 weeks of treatment, patients receiving darifenacin showed a dose-related decrease from baseline in the number of incontinence episodes per week, with median percentage reductions of 68.7% (p=0.007), 76.5% (p<0.001), and 77.3% (p<0.001). A significant reduction in incontinence episodes was seen as early as week 2 of treatment for all doses of darifenacin. Improvements in secondary endpoints paralleled the improvement in the primary endpoint. Darifenacin treatment resulted in dose-related improvement when compared with placebo in a broad range of OAB symptoms including: fewer micturitions and urgency episodes per day, decreased severity of urgency, and increased bladder capacity. These improvements were statistically superior to placebo for darifenacin 15 and 30 mg and numerically superior for the 7.5 mg dose. The overall incidence of all-cause adverse events was 57.4%, 68.2%, and 80% in the 7.5mg, 15mg, and 30mg darifenacin groups. The most commonly reported adverse events, dry mouth and constipation, showed a dose-related trend among patients randomized to darifenacin. Adverse CNS and cardiovascular events were similar for all darifenacin treatment groups and placebo.

Darifenacin vs. Oxybutynin

Zinner and colleagues¹⁴ evaluated darifenacin's efficacy in reducing symptoms of OAB compared to the non-selective anticholinergic oxybutynin and placebo. This study was a randomized, double-blind, placebo-controlled, four-way crossover study designed to assess the efficacy, tolerability, and safety of darifenacin compared to oxybutynin. Each patient received two weeks each of darifenacin 15 mg daily, 30 mg daily, oxybutynin 5 mg TID, and placebo in a random sequence at 10 day intervals. The primary outcome was an overall decrease in OAB symptoms broken down into four outcome variables: Mean number of incontinence episodes/week; mean number of urgency episodes/day; mean severity of urgency episodes; and mean number of micturitions/day. A total of 76 patients were randomized to receive one of the four treatments, but 16 withdrew before the study's end (only 5 because of AE's), leaving 58 patients in the final efficacy analysis. Darifenacin 15 mg daily was comparable to oxybutynin in overall improvement in OAB symptoms (p<0.05), meaning that both agents significantly reduced the number of incontinence episodes/week and the number and severity of urgency episodes at week 2 (**Table 2**). Sixty-one of the 76 patients were evaluated for drug tolerability. Rates of dry mouth were higher in patients taking darifenacin 15 mg compared with placebo, but were not significant. Dry mouth occurred in 13.1% of patients on darifenacin 15 mg compared to 34.4% in oxybutynin 5 mg TID

($p < 0.05$). Rates of constipation were higher among active treatments compared to placebo, but were comparable between darifenacin 15 mg and oxybutynin 5 mg TID at 9.8% and 8.2%. Blurred vision and dizziness occurred in 3.3% and 1.6 % of patients receiving oxybutynin, but did not occur with darifenacin or placebo.

Safety Trials

In the past decade, the most common cause of withdrawal or restriction of an approved and marketed drug has been the prolongation of the QT interval, which is associated with torsade de pointes.¹⁶ Because of this, increased regulatory scrutiny has focused on noncardiac drugs that affect cardiac function. Since anticholinergic agents have the potential to cause palpitations and tachycardia due to blockade of M₂ receptors in the myocardium, the possibility of effects at cardiac ion channels, and the subsequent change in cardiac conduction must be ruled out before these drugs are marketed.⁵ Serra et al.⁵ conducted a 7-day randomized, parallel-group study (n = 188) measuring the QT/QTc interval in healthy volunteers taking darifenacin at steady-state therapeutic (15 mg daily) and suprathreshold (75 mg daily) doses. Patients were compared to control groups receiving placebo or moxifloxacin (positive control, 400 mg daily). No significant increase in QTc interval was found with either dose of darifenacin when compared with placebo. Mean changes from baseline at T_{max} vs. placebo were -0.4 (p = 0.842) and -2.2 (p = 0.400) milliseconds in the darifenacin 15 mg and 75 mg groups. The positive control (moxifloxacin 400 mg daily), showed an increase of 11.6 milliseconds (p < 0.01). The results of this study demonstrate that darifenacin, even at suprathreshold doses, does not significantly prolong QT/QTc interval.

Another concern associated with anticholinergic medications is their potential to cause adverse CNS

effects. Older patients are more vulnerable due to reduced brain muscarinic receptor density and an increased sensitivity to antimuscarinic effects. Kay et al.¹⁵ compared darifenacin with oxybutynin ER on memory in patients ≥ 60 years old. This 3-week multicenter, double-blind, double dummy, parallel group study compared oxybutynin ER (10 mg once daily, increasing to 20 mg once daily by week 3) with darifenacin (7.5 mg once daily in weeks 1 and 2, then 15 mg in week 3). The primary end-point was accuracy on a delayed recall Name-Face Association Test at the end of week 3. Results showed no significant difference between darifenacin and placebo on delayed recall by the end of week three (mean difference, -0.06, p = 0.908). Oxybutynin ER, however, resulted in significant memory impairment, with lower scores than placebo and darifenacin for delayed recall (mean differences, -1.30, p = 0.011 and -1.24, p = 0.022). The magnitude of effect on memory impairment in the oxybutynin ER patients is comparable to 10 years of brain aging.

Dosing and Administration

Darifenacin doses ranging from 3.75-30 mg/day in a once daily dosing regimen have been investigated in clinical trials for treatment of OAB. The dose-response relationship begins to flatten at 15 mg/day, while the frequency of adverse effects increases. Data supports the manufacturer's recommended maximum daily dosage of 15 mg/day, since efficacy at 30 mg/day is minimally improved at the cost of a large increase in adverse events. The recommended starting dose of darifenacin is 7.5mg once daily. Based on response, the dose may be increased to 15 mg once daily after 2 weeks of therapy.⁸ The majority of the therapeutic effect is apparent by about 6 weeks of treatment, though some symptomatic improvement can be seen immediately.¹⁷ No studies have evaluated the use of darifenacin in combination

Table 2. Outcome variables at week 2¹⁴

Outcome variable	Darifenacin		Oxybutynin	
	15 mg daily	30 mg daily	5 mg TID	Placebo
Mean no. of incontinence episodes/week	10.93*	8.82*	9.45*	14.64
Mean no. of urgency episodes/day	7.95*	7.59*	8.12*	8.71
Mean severity of urgency episodes	1.93*	1.84*	1.89*	2.03
Mean no. of micturitions/day	9.33	8.85*	9.24*	9.62

*P < 0.05 vs. placebo, accounting from multiplicity by the least significant difference method; TID indicates three times daily

*All values are adjusted for sequence and period from the crossover analysis of variance

Table 3. Adverse events* reported in > 3% of patients treated with darifenacin⁴

Adverse Event	Darifenacin 7.5/15 mg, N = 268	Placebo, N = 127
Constipation	56 (20.9%)	10 (7.9%)
Dry Mouth	50 (18.7%)	11 (8.7%)
Headache	18 (6.7%)	7 (5.5%)
Dyspepsia	12 (4.5%)	2 (1.6%)
Nausea	11 (4.1%)	2 (1.6%)
Urinary Tract Infection	10 (3.7%)	4 (3.1%)
Accidental Injury	8 (3.0%)	3 (2.4%)
Flu Syndrome	6 (3.0%)	3 (2.4%)

*Regardless of causality

with other drugs used to treat OAB.

Toxicity and Safety

Data collected from Steers and colleagues⁴, showed adverse events of constipation, dry mouth, headache, dyspepsia, and nausea in patients receiving darifenacin once daily (**Table 3**). Other adverse events reported in phase III studies include abnormal vision, back pain, dry skin, vomiting, weight gain, sinusitis, and rash. These adverse effects occurred in $\geq 1\%$ of patients.⁸ Three different trials^{11,14,15} demonstrated that the incidence of dry mouth is significantly less frequent in patients taking darifenacin than those taking oxybutynin. Despite this, the most common reasons for discontinuation of darifenacin remain dry mouth and constipation.

Cost

Pricing data for darifenacin was obtained from averaging the cost of a one month prescription from three pharmacies located in Gainesville, FL. The average monthly cost (30 tablets) for both 7.5 mg and 15 mg is \$112.64 (range \$108.95 – \$118.99).

Summary

Darifenacin is a novel agent that selectively inhibits M₃ receptors and is indicated for the treatment of OAB. Darifenacin appears to be as effective as immediate release oxybutynin, in OAB treatment, while having a lower incidence of dry mouth and adverse CNS effects. It is unknown how darifenacin compares to other anticholinergic agents used for OAB, such as tolterodine or solifenacin, as no head-to-head trials have been completed. However, with the data available, darifenacin seems to have a place in the treatment of patients suffering from overactive bladder.

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SITAGLIPTIN: A DIPEPTIDYL PEPTIDASE IV INHIBITOR FOR DIABETES MELLITUS TYPE 2

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In recent years, the incidence of type 2 diabetes has steadily increased and the CDC now estimates there are approximately 20.8 million people with diabetes in the United States comprising 7% of the population. Globally, the burden of diabetes is expected to climb to 336 million by 2030.¹ Chronic hyperglycemia can give rise to a number of serious complications including heart disease, stroke, hypertension, blindness, kidney disease, and nervous system damage. The direct medical cost of these complications is estimated around \$24.6 billion annually in the U.S.²

Despite a number of medication options, controlling diabetes remains a huge challenge to health care professionals. Currently available oral options include sulfonylureas, thiazolidinediones, biguanides, meglitinides, and alpha-glucosidase inhibitors. The use of some of the oral agents is limited by side effects such as weight gain and hypoglycemia or contraindications including renal insufficiency or chronic heart failure. Due to the limitations of currently available medications, there is a need for additional options to manage patients with difficult to

control diabetes or for those with contraindications or side effects to traditional options.

Incretin hormones have recently become a target for treating diabetes. These hormones stimulate the release of insulin in response to elevated plasma glucose levels.³ Glucagon-like peptide 1, or GLP-1, is an incretin that is released from the small intestine in response to the ingestion of food.³ GLP-1 regulates glucose homeostasis by increasing insulin secretion and synthesis as well as by inhibiting glucagon release.⁴ Additionally, GLP-1's effects on glucose homeostasis and insulin release are glucose dependant, thus minimizing the likelihood of having hypoglycemia.⁵ Based on the benefits of GLP-1 augmentation, research has focused on creating a drug to increase GLP-1 levels in the body. One limitation to supplementing GLP-1 is that it has an extremely short half life due to rapid degradation in vivo by the enzyme dipeptidyl peptidase IV (DPP-IV).⁶

Sitagliptin is a novel medication that targets the DPP-IV enzyme and inhibits it from inactivating GLP-1. By inhibiting DPP-IV, the half-life of GLP-1 is increased; thus, allowing GLP-1 to regulate glucose homeostasis more efficaciously.

Sitagliptin (sīt ə glīp' tīn) is being marketed by Merck and Co. under the brand name Januvia[®] (jə nōō' vē ə). The FDA approved sitagliptin on October 17, 2006.³³

This article will review the mechanism of action for sitagliptin as well as the pharmacokinetics, safety, and efficacy

Pharmacology and Pharmacokinetics

The regulation of glucose levels via insulin is a complex mechanism involving many factors. Incretin hormones are one of the factors that play a central role in regulating the secretion of insulin. When glucose is administered orally, an increased secretion of insulin occurs as opposed to when it is administered intravenously. This increased response of insulin secondary to oral glucose administration is known as the incretin effect and is estimated to account for 50-70% of the insulin secreted by the body.⁷ The two incretin hormones most often associated with the incretin effect are GLP-1 and glucose-dependent insulinotropic peptide (GIP).⁸ Studies show that patients with type 2 diabetes have normal GIP concentrations but decreased levels of GLP-1.⁹ GLP-1 is associated with stimulating insulin synthesis and secretion, inhibiting glucagon release, slowing gastric emptying,

and reducing appetite.¹⁰ Additionally, GLP-1 has been associated with positive effects on beta cell function and thus may play a role in beta cell restoration and prevention of type 2 diabetes.^{10,32,28} The significance of the effects of GLP-1 are not fully understood; however, the observation that people with type 2 diabetes have decreased levels of GLP-1 stimulated research to correct these levels as an approach to managing diabetes. One challenge in increasing GLP-1 levels is that it is rapidly degraded in vivo by dipeptidyl peptidase-IV (DPP-IV), an enzyme that is primarily located in the brush border membrane of the intestines and kidneys.¹¹ As a result, GLP-1 has a half life of less than 2 minutes.¹¹ Inhibition of this enzyme should promote improvements in glucose homeostasis by increasing the concentration of GLP-1.

Sitagliptin is a selective, competitive, reversible inhibitor of the DPP-IV enzyme, which causes decreased deactivation of the incretin hormone GLP-1. Sitagliptin's effects are mediated through a number of mechanisms. The primary mechanism of action for sitagliptin is amplifying the effect of the incretin GLP-1 which in turn increases insulin biosynthesis and secretion and inhibits glucagon release. Sitagliptin also plays a potentially beneficial role on the function of beta cells and may have the potential to prevent or delay type 2 diabetes.^{10,12} GLP-1 slows gastric emptying and suppresses appetite.²⁰ Sitagliptin also inhibits T-cell activity in vitro and has been shown to affect substance P, certain chemokines, and neuropeptide Y, although the implications of these actions are currently unknown.³⁰

Most of the pharmacokinetic studies conducted to date for sitagliptin were performed in patients without diabetes. Bergman et al.¹³ conducted a multiple oral dose trial with sitagliptin in 70 healthy subjects (**Table 1**). This study demonstrated that sitagliptin inhibited the DPP-IV enzyme dose dependently. As a result, GLP-1 concentrations increased in a manner proportional to the dose. In this trial, the terminal half-life ($t_{1/2}$) was 11.8-14.4 hours. The renal

clearance, averaged across all doses (25-600 mg daily), was 349 mL/min, which is greater than the GFR indicating that an active secretion process is involved. This study concluded that sitagliptin exhibited pharmacokinetic/pharmacodynamic parameters consistent with a once daily dosing schedule.

Sitagliptin is readily absorbed following oral administration, with a bioavailability of 87%.³¹ Food does not interfere with the pharmacokinetics of sitagliptin.³¹ About 75% of sitagliptin is excreted in the urine unchanged.¹³ Steady state is achieved after 3 days.¹⁴ Additionally, the pharmacokinetics of sitagliptin are independent of age, gender, and obesity.¹⁶

Renally impaired patients experienced increased exposure to sitagliptin and thus will require a dose reduction.¹⁷ Hepatic impairment has no effect on the time to maximum concentration (T_{max}), $t_{1/2}$, renal clearance, or fraction of the oral dose excreted in the urine.¹⁸

Clinical Trials

Several clinical trials have been conducted to date on sitagliptin (**Table 2**). These studies were involved in the pre-marketing approval of sitagliptin and many are only available in abstract form. These articles include trials on: safety, dose-ranging, efficacy as monotherapy, combination therapy, and drug interaction studies.

In a randomized, double blind, placebo-controlled, 3-period, single-dose, crossover study, the safety, tolerability and glucose lowering ability of sitagliptin was evaluated in 56 type 2 diabetics. Oral glucose tolerance tests performed 2 hours after administration of sitagliptin demonstrated that the AUC was reduced by 22% and 26% for the 25mg and 200mg doses, respectively ($p < 0.001$). Additionally, GLP-1 concentrations were doubled by both sitagliptin doses, plasma insulin levels increased 22% and 23% ($p < 0.001$), and plasma glucose levels were decreased 8% ($p = 0.015$) and 14% ($p < 0.001$) for the 25mg and 200mg doses.¹⁹

Table 1. Pharmacokinetics of sitagliptin on day 10 in healthy men¹³

Parameter	50 mg daily of sitagliptin, N=8	100 mg daily of sitagliptin, N=8
AUC _{0-t} (mmol/L·h)	3.7	8.5
C _{max} (nmol/L)	366	941
T _{max} (h)	2.5	3.0
T _{1/2} (h)	14.2	14.4
f _{e,0-t}	0.70	0.76
Cl _R (ml/min)	369	363

Cl_R = renal clearance

f_{e,0-t} = the amount of sitagliptin excreted unchanged in the urine over the dosing interval

Raz et al.²¹ studied 521 people with type 2 diabetes who took sitagliptin to evaluate its efficacy as monotherapy in reducing hemoglobin A_{1c} (A1C) levels. Patients had A1C levels between 7-10% at baseline. Patients either received 100mg daily, 200mg daily, or placebo for 18 weeks. The patients receiving sitagliptin had decreased A1C levels when compared with the placebo group. The reductions in A1C were -0.60% [95% CI -0.82 to -0.39] and -0.48% [95% CI -0.70 to -0.26] for the 100mg and 200mg groups respectively. The group that received the greatest reduction was the patients who had a baseline A1C \geq 9%. Overall, sitagliptin was well tolerated.

Sitagliptin was compared to glipizide in a 12 week, double-blind, placebo-controlled, dose-range finding study conducted in 743 people with type 2 diabetes.²⁴ Patients were randomized to receive either sitagliptin 5mg, 12.5mg, 25mg, 50mg BID or glipizide 5mg titrated to 10, 15, and then to 20mg/day for 12 weeks. The reduction in A1C for sitagliptin was dose dependant and ranged from -0.4 to -0.8% (p values not reported), while the reduction in A1C in the glipizide group was -1.0% (p value not reported). However, the glipizide group experienced a mean weight gain of 1.1 kg, while the sitagliptin group did not. Additionally, the incidence of hypoglycemia was much higher in the glipizide treated group than in the sitagliptin treated group.

Karasik et al.²³ examined sitagliptin as add-on therapy to metformin. This trial had 701 patients inadequately controlled on doses of metformin \geq 1500mg/day alone. Patients were randomized to receive either sitagliptin 100mg daily or placebo for 24 weeks. The addition of sitagliptin provided an additional -0.65% (p<0.001) decrease in A1C. Fasting glucose levels improved (-25.4mg/dL, p<0.001) in the metformin plus sitagliptin group versus the metformin plus placebo group. Weight gain was not different between the sitagliptin group and the placebo treated patients, and the addition of sitagliptin was not associated with an increase in the hypoglycemic events compared to placebo.

The efficacy of sitagliptin in combination with pioglitazone for inadequately controlled diabetes was studied in a 24 week study by Rosenstock.²² Patients with an A1C between 7-10% were randomized to receive either 100mg of sitagliptin or placebo in addition to pioglitazone therapy. The addition of sitagliptin to pioglitazone resulted in a -0.70% decrease

in the A1C versus pioglitazone alone (p<0.001) and fasting plasma glucose levels decreased 17.7mg/dL (p<0.001) in the patients on combination therapy. Additionally, almost double the patients in the sitagliptin group achieved their goal A1C (<7%) versus the placebo group (45% versus 23%, p<0.001).

Dosing and Administration

A number of trials have been conducted evaluating the pharmacokinetics of sitagliptin. In these trials, several different doses were evaluated and the percent inhibition of DPP-IV recorded. An ideal dose of sitagliptin should inhibit at least 80% of DPP-IV enzyme activity.²⁵ Bergman et al.¹³ demonstrated that 50, 100, and 200 mg daily inhibited DPP-IV at levels greater than 80%. Doses of 25, 50 and 100 mg were approved by the FDA. A starting dose of 100 mg daily is recommended for monotherapy or add-on therapy in patients with normal renal function.³⁴ Although, doses up to 600 mg were well tolerated in healthy male subjects, the maximum approved dose is 100 mg daily.³¹

The majority of sitagliptin (>75%) is renally excreted unchanged and kinetic studies indicate that accumulation occurs in renally compromised patients. As such, lower doses are recommended for patients with renal insufficiency. Patients with moderate renal insufficiency (CrCl < 50 ml/min) should take 50 mg daily, while in severe renal insufficiency (CrCl < 30 ml/min), the 25 mg dose is suggested.^{26,34} Sitagliptin is administered once daily due to a favorable pharmacokinetic profile consistent with once daily administration.¹³

Toxicity and Safety

Sitagliptin appears to exhibit a promising side effect profile, especially when compared to many of the older oral antidiabetic medications. There are currently no contraindications to sitagliptin and the only warning in the package insert is for a dose reduction in patients with renal impairment.³⁴ Additionally, in the numerous pharmacokinetic trials performed, sitagliptin was associated with very few hypoglycemic events. The absence of hypoglycemia is expected since GLP-1 is dependant on glucose to stimulate the release of insulin.⁵ Sitagliptin has an appetite suppressant effect²⁰ and it initially was believed that it might possess weight loss properties. Clinical trials have failed to show weight loss in study participants; however, sitagliptin does appear

Table 2. Summary of sitagliptin trials

Trial	Design	Patients	Treatment	Duration	Outcome	Adverse effects
Herman (2005) ¹⁹	R, DB, PC, CO	N=56 T2DM	SIT 25mg or 200mg x 1	Single dose	AUC for glucose decreased 22% and 26%	No hypoglycemia reported
Raz (2006) ²¹	R, DB, PC, PGS	N=521 T2DM	SIT 100mg or 200mg qd vs. Pbo	18 weeks	A1C decreased 0.60% & 0.48%	hypoglycemia and GI adverse events no diff. than placebo. SIT weight neutral.
Aschner (2006) ²⁸	R, DB, PCS	N=741 T2DM	SIT 100mg or 200mg qd vs. Pbo	24 weeks	A1C decreased 0.79% & 0.94%	Hypoglycemia no diff. than placebo; weight neutral
Herman (2005) ²⁹	R, DB, PC, PGS	N=552 T2DM	1 of 5: Pbo, SIT 25, 50, 100mg QD or 50mg BID	12 weeks	0.6% to 1.1% decrease in A1C for 100mg depending on the initial A1C	One event of hypoglycemia in each sitagliptin group; no wt. gain
Scott (2005) ²⁴	R, DB, PC, AC, PGS	N=743 T2DM	1 of 6: Pbo, SIT 5, 12.5, 25, 50mg BID, or GLIP 5mg QD (titrated to 20mg/d)	12 weeks	0.4 to 0.8% decrease in A1C (up to 50mg bid); 1.0% A1C decrease in glipizide	No weight gain in sitagliptin groups; 1.1kg weight gain for glipizide.
Nonaka (2006) ²⁷	R, DB, PC, PGS	N=151 T2DM	SIT 100mg qd vs. Pbo	12 weeks	Decrease in A1C of 0.65% as compared with a 0.41% increase in placebo	No weight gain or hypoglycemia reported
Rosenstock (2006) ²²	R, DB, PC	N=353 T2DM on PIO	PIO + SIT 100mg qd vs. PIO + Pbo	24 weeks	Addition of SIT to PIO caused A1C to decrease 0.7%	Incidence of hypoglycemia similar to Pbo. Slightly more abdominal pain. No change in body weight
Karasik (2006) ²³	R, DB, PC	N=701 T2DM on MET	MET + SIT 100mg qd vs. MET + Pbo	24 weeks	Addition of SIT to MET caused A1C to decrease 0.65% when compared with placebo	No change in body weight or increased hypoglycemia or GI adverse events when compared with placebo

AC= active control; CO= crossover; DB= double-blind; GLIP= glipizide; MET= metformin; PC= placebo controlled; PGS= parallel group study; Pbo= placebo; PIO=pioglitazone; QD= once daily; R= randomized; SIT=sitagliptin; T2DM= type 2 diabetes

to be weight neutral.^{27, 28, 29}

Sitagliptin's effect on inhibiting T-cell activity initially raised concerns that immune function might be compromised as a consequence. However, data from clinical trials in humans have failed to confirm this and to date this effect has only been exhibited in vitro.³⁰

The most common adverse effects from treatment with sitagliptin reported in the package insert are nasopharyngitis (5.2% vs. 3.3% in placebo), upper respiratory tract infections (6.3% in patients receiving sitagliptin plus pioglitazone versus 3.4% in patients receiving pioglitazone alone), and headache (5.1% in patients receiving sitagliptin plus pioglitazone versus 3.9% in patients receiving pioglitazone alone).³⁴ Additionally, the incidence of gastrointestinal adverse events does not appear to be higher than placebo (abdominal pain: 2.3% in sitagliptin; 2.1% in placebo, nausea: 1.4% in sitagliptin; 0.6% in pla-

cebo, and diarrhea: 3.0% in sitagliptin; 2.3% in placebo).³⁴

Drug Interactions

Limited data is currently available concerning sitagliptin's drug interaction profile. Sitagliptin does not appear to be metabolized by the CYP450 enzymes. Sitagliptin has been studied in pharmacokinetic trials with pioglitazone and metformin and did not show any significant interactions with either.^{22, 23} When digoxin was administered concomitantly with sitagliptin for ten days, a slight increase in the area under the curve (AUC) for digoxin was observed. However, no dosage adjustment is recommended when sitagliptin is administered with digoxin.³⁴ Sitagliptin has also been studied with warfarin³⁵, glyburide³⁶, rosiglitazone³⁷, cyclosporine³⁸, and simvastatin³⁹ and no significant drug interactions were identified. In the future, additional trials are needed to

assess the interaction between sitagliptin and other drugs commonly used in diabetic patients.

Cost

Pricing data for sitagliptin was obtained for a one month prescription from three pharmacies located in Gainesville, FL. The average monthly cost (30 tablets) for all strengths was \$191 (range \$180 – \$203).

Summary

Sitagliptin is a novel oral medication that raises levels of the naturally occurring incretin hormone, GLP-1, which functions to increase insulin secretion and inhibit glucagon release in a glucose-dependant manner. Sitagliptin provides up to a 1% A1C decrease, depending on the patient's baseline. Sitagliptin has a favorable side effect profile when compared to available second line oral agents, since it is weight neutral and induces minimal to no hypoglycemia. While sitagliptin's exact place in therapy is not yet established, it appears to be efficacious as either monotherapy or combination therapy with metformin or pioglitazone. Additional trials will aid in defining sitagliptin's role in treating type 2 diabetes, but it appears that it will provide a useful option for patients with contraindications to traditional oral antidiabetic medications or for those wishing to minimize hypoglycemia or weight gain.

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