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Fluticasone Furoate: A Once Daily Inhaled Corticosteroid for the Treatment of Asthma

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Asthma, a common chronic disorder of the airways, affects 35.9 million people in the United States.[1] Healthcare costs associated with asthma were estimated at $56 billion in the United States in 2007, which was a 6% increase from the $53 billion that was spent on asthma in 2002. According to the Centers for Disease Control (CDC), asthma prevalence in the U.S. has increased from 3% in 1970, to 5.5% in 1996, and 7.8% between 2006 to 2008.[1] The cause of asthma is unknown but multiple sources can contribute to the development and worsening of asthma such as exercise, airway infections, airborne allergens, occupation and air pollution. Although no cure for asthma is available, exposure to asthma triggers can be prevented and asthma can be controlled with appropriate asthma education and medical care.[1]

Persistent asthma is most effectively controlled with daily long-term controller medications, most often inhaled corticosteroids (ICSs), directed toward suppressing inflammation. If additional asthma control is needed, options include long-acting β_2 agonists (LABAs), leukotriene modifiers, immunomodulators, mast cell stabilizers, and combination products (ICS/LABA).[2] Selection among these treatment options is based on consideration of patient's history of previous responsiveness to different asthma medications. Because asthma is a chronic inflammatory disorder, a stepwise approach to managing asthma is recommended to gain and maintain control of asthma in both the impairment and risk domains.[2]

A new ICS, fluticasone furoate (FF; Arnuity™ Ellipta®; GlaxoSmithKline; Research Triangle Park, NC) was granted an approved indication for maintenance treatment of asthma by the Food and Drug Administration (FDA) in August 2014. In contrast to most other available ICSs used in patients with asthma, FF requires only once-daily administration and thus may represent an improvement over standard agents. The purpose of this article is to review the mechanism of action, pharmacokinetics, approved dosages, adverse reactions, and clinical studies associated with fluticasone furoate as an asthma treatment option in patients with persistent asthma.

IN THIS ISSUE

Clinical Pharmacology

A major component in the pathogenesis of asthma is chronic inflammation, characterized by increased expression of multiple inflammatory genes regulated by proinflammatory transcription factors such as nuclear factor kappaB and activator protein-1.[3] Corticosteroids suppress the multiple inflammatory genes that are activated in chronic inflammatory diseases such as asthma by reversing histone acetylation of activated inflammatory genes through the binding of liganded glucocorticoid receptors to coactivators and recruitment of histone deacetylase-2 to the activated transcription complex.[3]

Similar to fluticasone propionate (FP), fluticasone furoate is a synthetic tri-fluorinated corticosteroid associated with anti-inflammatory activity. The esters derived from FF yield higher affinity for both nasal and lung tissue than FP's metabolites, leading to enhanced drug residency.[4] *In vitro* studies have shown that FF's binding affinity for the human glucocorticoid receptor is approximately 29.9 times that of dexamethasone and 1.7 times that of FP.[5]

Trials in subjects with asthma have shown that FF has a high local anti-inflammatory effect and negligible oral systemic bioavailability.[5] Furthermore, FF's metabolites have minimal pharmacologic activity.[5] Pharmacokinetic effects of FF were characterized in trials where FF was given as a single component and in combi-

Table 1 | Pharmacokinetic properties of fluticasone furoate.[5-7]

Parameter	Fluticasone Furoate
Absorption	
Bioavailability	13.9%
C_{max}	4224 pg/mL
T_{max}	0.5 to 1 hour
Distribution	
V_d[a]	661 L
Protein binding	99.6%
Metabolism	Liver via CYP3A4 to metabolites with significantly reduced corticosteroid activity
Elimination	
Route	Primarily through feces
$t_{1/2}$	23.7 hours

[a]Following I.V. administration.
C_{max} = maximum concentration; **$t_{1/2}$** = half-life; **T_{max}** = time to maximum concentration; **V_d** = volume of distribution.

TABLE 2 | Characteristics and results of select clinical trials of fluticasone furoate in the treatment of asthma.

Reference	Patient Population	Treatment Arms	Primary Endpoint	Results
Bateman, et al.[8] (2010)	• Age ≥12 years • Persistent asthma not controlled by non-ICS therapy	1. FF 25 mcg (n=97) 2. FF 50 mcg (n=100) 3. FF 100 mcg (n=110) 4. FF 200 mcg (n=95) 5. FP 100 mcg twice daily (n=102) 6. Placebo (n=94)	Change in trough FEV_1 from baseline to week 8	Treatment differences in FEV_1 (FF or FP minus placebo): • FF 25 mcg OD: 0.101 L (95% CI -0.018 to 0.221) • FF 50 mcg OD: 0.129 L (95% CI 0.011 to 0.247) • FF 100 mcg OD: 0.204 L (95% CI 0.089 to 0.319) • FF 200 mcg OD: 0.230 L (95% CI 0.111 to 0.349) • FP 100 mcg BID: 0.106 L (95% CI -0.010 to 0.223)
Woodcock, et al.[9] (2011)	• Age ≥12 years • Moderate asthma • No ICS ≥8 weeks prior • Pre-bronchodilator FEV_1 40%-85% predicted • FEV_1 reversibility ≥12% and ≥200 mL in response to salbutamol	1. FF 200 mcg q PM with placebo in the AM (n=140) 2. FF 100 mcg BID and placebo BID (n=142) 3. FP 200 mcg q PM with placebo in the AM (n=42) 4. FP 100 mcg BID and placebo BID (n=43) 5. Placebo (n=187)	Pre-dose, pre-rescue bronchodilator FEV_1 on evening of day 28	Treatment differences in FEV_1 (FF minus placebo): • FF 200 mcg q PM: 108 mL (95% CI 64 to 153) • FF 100 mcg BID: 98 mL (95% CI 54 to 142) • FP 200 mcg q PM: 87 mL (95% CI 14 to 161) • FP 100 mcg BID: 132 mL (95% CI 59 to 205) Treatment difference in FEV_1 for FF 200 mcg q PM minus FP 100 mcg BID: • 11 mL (95% CI -35 to 56)
Woodcock, et al.[10] (2011)	• Age ≥12 years • Mild-moderate Asthma • Taking ICS ≥3 months prior (max of FP 200 mcg) • Morning FEV_1 50-80% of predicted normal value • Reversibility of baseline FEV_1	1. FF 400 mcg q PM (n=113) 2. FF 400 mcg q AM (n=111) 3. FF 200 mcg q PM (n=103) 4. FF 200 mcg q AM (n=105) 5. FF 200 mcg twice daily (n=113) 6. Placebo twice daily (n=101)	Mean change from baseline pre-dose, pre-rescue bronchodilator FEV_1 (week 8)	Treatment differences in FEV_1 (FF minus placebo): • FF 200 mcg q PM: 0.124 L (95% CI 0.010 to 0.238) • FF 400 mcg q PM: 0.240 L (95% CI 0.129 to 0.351) • FF 200 mcg q AM: 0.174 L (95% CI 0.067 to 0.282) • FF 400 mcg q AM: 0.202 L (95% CI 0.096 to 0.307) • FF 200 mcg BID: 0.235 L (95% CI 0.123 to 0.346)

BID = twice daily; **FEV_1** = forced expiratory volume; **FF** = fluticasone furoate; **FP** = fluticasone propionate; **ICS** = inhaled corticosteroid.

nation with vilanterol resulting in linear pharmacokinetics at 200 mcg doses of FF.[5] Once-daily repeated administration showed stable FF plasma concentration after 6 days. The bioavailability of FF increases nearly 2.6-fold after repeated administrations compared to single dose administration, presumably because of drug accumulation.[5] The pharmacokinetics of FF are summarized in Table 1.[5,6]

CLINICAL TRIALS

Table 2 summarizes several of the key clinical studies of FF in the treatment of mild-to-moderate persistent asthma. A randomized, double-blind, placebo-controlled, parallel group study of 598 patients randomly assigned to one of with six treatment groups including FF at varying doses (25 mcg, 50 mcg, 100 mcg, or 200 mcg) once daily, FP 100 mcg twice daily, and placebo was conducted in order to examine FF efficacy in treating asthma.[8] Eligible patients were those with persistent asthma defined by the Expert Panel on Asthma,[2] who were symptomatic while on treatment with a short-acting ß$_2$ agonist or other non-steroid agents, and who had 40% to 90% evening or 40% to 85% morning predicted FEV_1 with a FEV_1 reversibility of ≥12% and ≥200 mL when administered albuterol/salbutamol via metered-dose inhaler. Patients were considered symptomatic if they had used albuterol/salbutamol >4 times during the last 7 days of a 4-week run-in period while taking usual asthma medications. The primary endpoint was mean change from baseline in trough (pre-dose, pre-rescue bronchodilator) evening FEV_1 at week 8 in each treatment group. Changes in evening FEV_1 after 8 weeks of treatment with each of the four FF doses suggested that a linear dose-response relationship existed for increasing doses of FF. Linearly predictable increases in least square differences in FEV_1 from the placebo

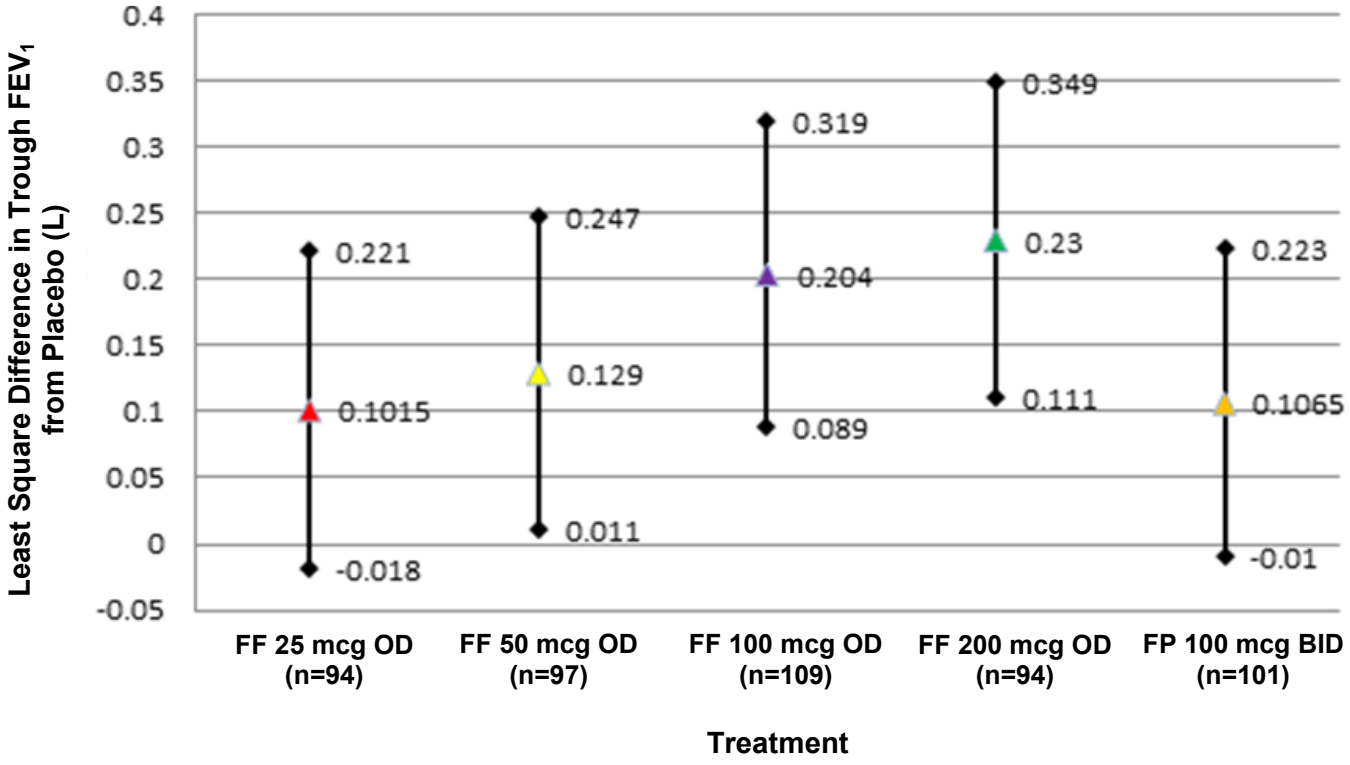

FIGURE | Least-square differences in FEV_1 comparing various dosing strategies of fluticasone furoate and fluticasone propionate.[8] Solid black lines represent 95% confidence intervals for the least square differences between each treatment group and placebo. The least square difference in FEV_1 for FP 100 mcg twice daily was examined as depicted above to compare efficacy of FF at each dose to an active treatment.

group (no steroid treatment) were evident with increasing doses of FF (linear trend $p<0.001$).[8] After 8 weeks, patients that had received treatment with FF 50 mcg or more had significantly greater increases in trough FEV_1 from baseline than placebo. Treatment with FF 100 mcg and 200 mcg achieved trough FEV_1 increases ≥200 mL, which were considered clinically significant improvements. The **Figure** depicts the dose-response relationship for increasing doses of FF (25-200 mcg) and includes the response for FP 100 mcg twice daily as a reference point for comparison.

Fluticasone furoate dosed once daily in the evening was compared to twice-daily dosing in a separate double-blind, crossover study by Woodcock, et al.[9] Patient inclusion criteria included moderate asthma according to the Expert Panel on Asthma,[2] age ≥12 years, pre-bronchodilator FEV_1 40% to 85% predicted, and FEV_1 reversibility ≥12% or ≥200 mL.[9] Patients were excluded from this study if they had used any ICS during the 8 weeks prior to enrollment. Patients were assigned to 1 of 12 possible treatment sequences, each sequence comprising three 28 day treatment periods separated by two 2-week washout periods. Six sequences contained FF 200 mcg once daily in the evening with placebo in the morning. The other sequences included FF 100 mcg twice daily with placebo administered twice daily and FP administered twice daily with placebo administered twice daily. Different delivery devices were used between FF and FP sequences, but investigators were double-blinded to whether a patient was receiving treatment, placebo, or either FF or FP. Of 190 patients randomly assigned to study treatment, 147 patients were assigned to 1 of 6 possible FF sequences and 43 patients were assigned to 1 of 6 possible FP sequences.[9] After an 8-week run-in period, patients were randomly assigned to receive FF 200 mcg once in the evening (n=140), FF 100 mcg twice daily (n=142), FP 200 mcg once in the evening (n=42), FP 100 mcg twice daily (n=43), or placebo (n=187). On day 28, least square mean treatment differences (active treatment minus placebo) in pre-dose FEV_1 from baseline were 108 mL for the FF 200 mcg once daily group and 98 mL for the FF 100 mcg twice-daily group. The FP 100 mcg twice-daily group had a mean difference of 132 mL while the FP 200 mcg once daily group had a difference of 87 mL.[9] All treatment groups produced significant differences in baseline trough (pre-dose, pre-rescue bronchodilator) FEV_1 from placebo. Furthermore, FF 200 mcg once in the evenings was non-inferior to FP 100 mcg twice daily (mean treatment difference, 11 mL, 95% CI -35 to 56).[9]

Another multicenter, randomized, double-blinded, parallel group, placebo-controlled 8-week study by Woodcock et al., evaluated FF 200 mcg twice daily (n=113), FF 200 mcg once each morning (n=105), FF 400 mcg once each morning (n=111), FF 200 mcg once each evening (n=103), and FF 400 mcg once each evening (n=113), compared with placebo (n=101).[10] Patient eligibility criteria for this study included persistent asthma with use of an ICS for ≥3 months prior to study entry and maintained on a stable dose for 4 weeks prior to study visit 1, baseline FEV_1 50% to 80% of predicted normal value during visit 1, and demonstrating ≥12% reversibility of FEV_1 within 30 minutes of inhalation of albuterol/salbutamol aerosol (2-4 puffs). The primary endpoint was the mean change from baseline at week 8 in trough (AM or PM) FEV_1. Baseline characteristics between patient groups were very similar in the 6 treatment groups. Each group had a mean

Table 3 | Adverse events occurring at a ≥3% incidence in trials of fluticasone furoate 100 mcg or 200 mcg.[11]

Adverse Event	Fluticasone furoate 200 mcg (n=119)	Fluticasone furoate 100 mcg (n=119)	Placebo (n=115)
Bronchitis	7%	12%	6%
Headache	13%	10%	4%
Nasopharyngitis	13%	12%	5%
Upper Respiratory Tract Infection	6%	2%	5%
Pharyngitis	3%	6%	3%
Sinusitis	4%	7%	1%
Oropharyngeal Pain	4%	3%	0%
Oral Candidiasis	3%	<1%	0%
Influenza	7%	4%	n/a
Back Pain	3%	3%	0%
Dysphoria	3%	2%	0%
Procedural Pain	3%	<1%	0%
Rhinitis	3%	<1%	0%
Throat Irritation	3%	<1%	0%
Abdominal Pain	3%	0%	0%
Cough	3%	0%	0%

n/a = data not available.

age of approximately 45 years. The majority of patients in each treatment arm were White (60% to 70%), and women (60% to 70%). Lastly, approximately 60% of patients in each treatment arm had a ≥10-year history of asthma, whereas 25% had a 5- to 10-year history of asthma and 15% had a 1- to 5-year history. Baseline mean pre-bronchodilator FEV_1 across the groups was 67% of predicted and mean FEV_1 reversibility was 29%. Significantly greater improvements in trough FEV_1 were evident in each FF treatment group compared with placebo: the least squares mean difference from placebo for FF 200 mcg once daily in the evening dosing was 124 mL (95% CI 10 to 238; p=0.033). Similar improvements were seen in the FF 200 mcg once each morning with a difference from placebo of 174 mL (95% CI 67 to 282; p=0.002). Placebo-adjusted trough FEV_1 improvement for the FF 200 mcg once daily group was 202 mL while the FF 200 mcg twice daily group had a mean improvement of 315 mL.[10] Moreover, FF 400 mcg once every evening showed similar placebo-adjusted improvements in evening trough FEV_1 versus FF 200 mcg twice daily (240 mL vs. 235 mL).[10]

Adverse Events

Two percent of subjects discontinued FF treatment because of adverse events in phase 3 trials. Adverse events are summarized in **Table 3**. Serious adverse events, whether drug-related or not, occurred at rates ≤1%.[11]

Safety data ranging from 52 to 76 weeks in duration comes from two FF clinical trials in adolescent and adult subjects with asthma. One trial had patients inhale FF 100 mcg/day over a 24- to 76-week period. Patients included in this study had a history of one or more asthma exacerbations requiring treatment with systemic corticosteroids, ER visits, or inpatient hospitalization over the past 12 months.[11] The major adverse events occurring in 3% or more of subjects enrolled in this study are summarized in **Table 3**.[11] In a separate, 52-week trial, subjects receiving FF 100 mcg or 200 mcg in combination with a LABA presented with the following adverse events at incidence rates ≥3%: pyrexia, extrasystoles, upper abdominal pain, respiratory tract infection, diarrhea, and allergic rhinitis.[11] These adverse events were considered clinically more severe than common complaints such as throat irritation where FF use could be a potential contributor to their incidence rates.[11]

Hypothalamic-pituitary-adrenal (HPA) axis function does not appear to be significantly affected in those taking FF. Healthy subjects taking FF at repeat doses up to 400 mcg/day showed no significant decrease in serum or urinary cortisol concentrations.[12] In dose ranging studies examining FF doses ranging from 25 mcg to 800 mcg, there was no significant 24 hour cortisol excretion suppression after 8 weeks of once-daily dosing relative to placebo, except for in patients who took FF 800 mcg daily.[13]

Dosing and Administration

The commercially-available doses of FF are 100 mcg and 200 mcg. FF should be administered by inhalation at the same time every day, preferably in the evening, and no more than once every 24-hour period.[9, 14] Starting doses for FF are based on a patient's asthma severity and previous asthma drug therapy. The usual recommended starting dose of FF is 100 mcg every evening.[9, 11] Typically patients who have never used an ICS for asthma control would start on the 100 mcg dose while patients who have previously tried other ICS agents would start on the 200 mcg dose.[11, 14] For patients taking FF 100 mcg every evening with an inadequate response after 2 weeks of therapy, the dose can be titrated to 200 mcg every evening.[9, 11] If FF fails to provide adequate asthma control, the therapeutic regimen should be re-evaluated with consideration of other options such as initiating a combination product or initiating oral corticosteroids.[2, 11] Titration to the lowest effective dose of FF is desirable, to reduce unnecessary adverse effects, after asthma stability has been achieved.[11] Caution should

be exercised when considering co-administration of FF (a CYP3A4 substrate) with long-term ketoconazole or other strong CYP3A4 inhibitors (e.g, ritonavir, clarithromycin, indinavir, lopinavir, nefazodone, troleandomycin, voriconazole, etc.) because of increased systemic exposure to FF.[11]

Cost

The average retail costs of FF and alternative therapies used in asthma maintenance are summarized in **Table 4**. Fluticasone furoate is not available generically at this time, but several patient assistance programs are offered by the manufacturer (http://www.bridgetoaccess.com/ or http://gsk-access.com/). If patients do not qualify for either assistance program, they may apply for reimbursement online through GSK (http://www.gskforyou.com/patient-assistance-programs/reimbursement-resource-center.html).[15]

Conclusion

Asthma is a growing epidemic with increasing economic burden and healthcare costs.[2] Inhaled corticosteroids represent a major treatment modality for patients with persistent asthma and adherence to ICS therapy is paramount to successful asthma treatment.[1, 2] Fluticasone furoate is a newly approved ICS that may offer a potential advantage in this regard because it is administered only once daily in contrast to most other ICS medications. Once daily evening administration of FF 100 mcg or FF 200 mcg is effective and generally well tolerated.[12, 14] Phase 3 clinical trials of FF 100 to 200 mcg/day showed improvements in trough FEV_1 ≥200 mL, which was clinically significant.[9, 10] Additionally, FF 100 to 200 mcg/day was noninferior to fluticasone propionate 100 mcg twice daily.[8, 9] Additional research is needed to elucidate the precise role of FF among other ICS agents in the treatment of persistent asthma.

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Table 4 | Average retail cost of fluticasone furoate and other inhaled corticosteroids for asthma.[16-21]

Medication	Cost[a]
fluticasone furoate (Arnuity Ellipta®)	
100 mcg inhaler	$142.35
200 mcg inhaler	$187.88
budesonide (Pulmicort®) 180 mcg	$197.37
fluticasone propionate (Flovent®) 110 mcg	$222.72
mometasone (Asmanex®) 220 mcg	120 doses: $308.31
beclomethasone (Qvar®) 80mcg	8.7g: $214.08
ciclesonide (Alvesco®) 80 mcg	$239.33

Average pricing represents cash price (i.e. without insurance) from Walgreens, CVS, Publix, Target, and Walmart stores in the Gainesville, FL area on 06/11/2015.
[a]Per 30-day supply.

Liraglutide (Saxenda®): Familiar Name, New Use for Weight Management

Lance Springfield, PharmD Candidate

Obesity, defined by a body mass index (BMI) ≥30 kg/m², is one of the most pervasive chronic conditions in the world. Globally, 1.9 billion adults are either overweight or obese and this number is expected to increase to 3 billion by 2030.[1] In the U.S., obesity affects 1 in 3 adults and 1 in 5 children and adolescents.[2] Obesity has become a major public concern and one of the most difficult public health issues in our society.[3] Obesity is associated with an increase risk for diabetes, hypertension, hypercholesterolemia, heart disease and death.[4] According to the most recent Calorie Control Council National Consumer Survey, almost 60% of Americans are attempting to lose weight yet most are projected to fail.[5,6]

Obesity, previously considered the result of poor personal choices and primarily affecting appearance, is now considered a chronic disease that requires treatment.[6] The cause of obesity is multifactorial including genetics, environmental factors, and medications.[6,7] Consequently, patients often require a multi-modal and multi-disciplinary approach to successfully lose weight and keep weight off.[4] The number of pharmacologic treatment for obesity are increasing and constitute one prong of a comprehensive plan that includes diet, exercise, and behavior modification.

Liraglutide (Saxenda®; Novo Nordisk A/S; Bagsvaerd, Denmark) is a new pharmacologic treatment option for weight loss. Liraglutide was granted an FDA-approved indication in December 2014 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of ≥30 kg/m² or ≥27 kg/m² in the presence of at least one weight-related comorbidity (osteoarthritis, sleep apnea, hypertension, dyslipidemia, type 2 diabetes mellitus, or venous stasis disease). This review will discuss the pharmacology, supporting clinical evidence, adverse effects, and dosing of liraglutide in the treatment of obesity.

Pharmacology

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist similar to exenatide, dulaglutide, and albiglutide. GLP-1 agonists act as incretin mimetics, a group of metabolic hormones released from the gut into the blood in response to eating. Endogenous GLP-1 is made primarily in the intestines and secreted from L-cells;[8] once in circulation, the half-life of GLP-1 is very short (<2 minutes) due to rapid degradation primarily by the enzyme dipeptidyl peptidase 4 (DPP-4).[9-12] Liraglutide shares a 97% structural homology to human GLP-1, but has a much longer half-life (about 13 hours). When injected subcutaneously, liraglutide mimics natural GLP-1 and increases insulin release in the presence of elevated blood glucose. Additionally, liraglutide decreases glucagon secretion in a glucose-dependent manner and delays gastric emptying.[11] Research has strongly suggested liraglutide effects the gastrointestinal system to delay gastric emptying as well as effects the CNS to increase satiety contributes to the reduction in meal intake.[12] Weight loss with liraglutide occurs due the reduction of visceral and subcutaneous fat.[13] A review of several studies that have examined the effects of GLP-1 agonist have also reported additional benefits that include neuroprotection, cardiovascular improvements, and renal protection.[14]

One of the notable effects of liraglutide when used as antidiabetic medication was weight-loss. Liraglutide was shown to have significant weight reduction when titrated to a 1.2 and 1.8 mg daily dose compared to placebo, resulting in a 2.6 to 2.8 kg weight reduction, on average, which occurred predominantly in the first 16 weeks of treatment and was maintained throughout at least 52 weeks of continuous use.[15]

Pharmacokinetics

The pharmacokinetic properties of liraglutide are summarized in Table 1. Liraglutide is metabolized endogenously by dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidases (NEP), but is partially stable to degradation. After subcutaneous administration, liraglutide self-associates, delaying absorption time, and results in a time to maximum concentration (t_{max}) of 11 hours. No specific organ is responsible for the elimination of liraglutide. Between 5-6% of liraglutide metabolites are found in urine and feces.[14]

Liraglutide may alter the pharmacokinetics of other drugs due to delayed gastric emptying, resulting in potentially slowed absorption of some oral medications (i.e., oral contraceptives, digoxin, lisinopril, atorvastatin, and acetaminophen).[14]

Clinical Trials

The FDA-approved indication for liraglutide for chronic weight management was based on three phase 3, 56-week, randomized, double-blind, placebo-controlled trials. At the time of this writing, one of these trials have been presented in abstract form only,[17] whereas the other two trials has been published with full peer review.[16, 18] In all 3 trials, liraglutide was titrated up to 3 mg/day by week 5. In addition to administering daily liraglutide injections, all subjects received instructions on a reduced calorie diet (about 500 kcal deficit) and were counseled on exercise (at least 150 minutes/week).[14]

Pi-Sunyer, et al., enrolled 3,731 patients with a BMI ≥30 kg/m² or a BMI 27-29.9 kg/m² and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded.[16] Patients were randomly assigned to treatment with liraglutide

Table 1 | Pharmacokinetic properties of liraglutide.

Property	Liraglutide
Absorption	
C_{max}	11 hours
C_{ss}	116 ng/mL
Bioavailability (SQ)	55%
Distribution	
V_d	20-25 L
Plasma protein binding	>98%
Metabolism	Degraded endogenously by DPP-4 and NEP
Elimination	
Plasma $t_{1/2}$	13 hours

C_{max} = maximum concentration; **C_{ss}** = steady-state concentration; **DPP-4** = dipeptidyl peptidase-4; **NEP** = neutral endopeptidase; **SQ** = subcutaneous; **$t_{1/2}$** = half-life; **V_d** = volume of distribution.

3 mg or placebo, each administered daily. Major inclusion/exclusion criteria and baseline characteristics of this study are summarized in Table 2. After 56 weeks of treatment, the authors concluded that liraglutide 3.0 mg, as adjunct to diet and exercise, was superior to placebo in reducing body weight, with an average loss of 8.0% (8.4 kg) of body weight compared to 2.6% (2.8 kg) on placebo (Table 3). Additionally, waist circumference was reduced from baseline (mean, 109.4 cm) by 8.2 cm in the liraglutide group compared with 3.9 cm from baseline (mean, 107.8 cm) in the placebo group ($p<0.001$). Mean systolic blood pressure (SBP) was reduced more at 56 weeks in liraglutide-treated patients (4.2 mm Hg reduction) than placebo-treated patients (1.5 mm Hg reduction; $p=0.007$). Furthermore, liraglutide recipients experienced significantly greater improvements in lipid parameters compared to placebo, including total cholesterol (-3.1% vs. -1.0%, respectively), LDL-C (- 3.0% vs. -1.0%), HDL-C (+2.3% vs. +0.7%), VLDL-C (-13.1% vs. -5.5%) and triglyceride (-13.3% vs. -5.5%) levels.[14,16]

In a 56-week trial, DeFronzo, et al., enrolled 635 patients with type 2 diabetes who were either obese (with or without weight-related comorbidities) or overweight with at least one weight-related comorbid condition.[17] Patients must have had an HbA1c of 7% to 10% and must have been receiving treatment with metformin, a sulfonylurea, or a glitazone as single agent or in any combination, or with diet and exercise alone. Patients were randomly assigned to treatment with liraglutide 3 mg or placebo, each administered daily (Table 2). The authors found that liraglutide 3.0 mg, as adjunct to diet and exercise, was efficacious and well tolerated for weight management over 56 weeks in obese/overweight individuals with type 2 diabetes (Table 3). Liraglutide also significantly decreased SBP versus placebo (-3.0 vs. -0.4 mmHg, respectively); liraglutide 3 mg/day also was shown to significantly reduce total cholesterol (-1.4% vs. +2.4%, respectively) and triglycerides (-14.5% vs. -0.7%, respectively) and increase HDL to a greater extent (+4.8% vs. +1.9%, respectively). Not surprisingly, patients treated with liraglutide 3 mg daily achieved superior glycemic control compared to those treated with placebo or liraglutide 1.8 mg, in terms of change in HbA1c and fasting plasma glucose, and proportion of patients reaching HbA1c ≤6.5%.[14,17]

In another 56-week trial, Wadden, et al., enrolled 422 patients who were obese (BMI ≥30 kg/m^2) or overweight (BMI 27-29.9 kg/m^2) with at least one weight-related comorbid condition.[18] Patients with type 2 diabetes were excluded. All patients were first treated with a low-calorie diet (total energy intake 1200-1400 kcal/day) in a run-in period lasting 4 to 12 weeks. Patients who lost ≥5% body weight during the run-in period were then randomly assigned to treatment with either liraglutide (titrated to 3 mg over 5 weeks) or placebo (administered daily) for 56 weeks. Liraglutide, as an adjunct to diet and exercise, maintained weight loss achieved by caloric restriction and induced further weight loss over 56 weeks (Table 3).[14,18]

ADVERSE EFFECTS

Most treatment-related adverse events in clinical trials of liraglutide were of gastrointestinal nature and were transient and mild. Gastrointestinal events, including nausea, vomiting, and diarrhea, led to discontinuation of therapy in 6.2% of liraglutide-treated subjects compared to 0.8% of subjects treated with placebo.[14] About 68% of subjects treated with liraglutide and 39% of subjects treated with placebo reported gastrointestinal effects, with the most frequent being nausea (39.3% of patients treated with liraglutide). The percentage of patients reporting nausea declined as treatment continued. Adverse reactions that occurred in ≥2% of subjects are summarized in Table 4.

Liraglutide decreases blood glucose concentration and can cause hypoglycemia. Patients receiving concomitant sulfonylureas had higher rates of symptomatic hypoglycemia, compared with those not receiving sulfonylureas in one trial.[14,16] Therefore, patients with type 2 diabetes may need a lower dose of sulfonylureas when taken concomitantly with liraglutide. Also, monitoring blood glucose before starting and during treatment with liraglutide is a mainstay in patients with type 2 diabetes. Hypoglycemia has

TABLE 2 | Study features and baseline characteristics from selected phase 3 trials of liraglutide for weight loss.

Study	Treatment Arms	Inclusion Criteria	Major Exclusion Criteria	Baseline Characteristics
Pi-Sunyer, et al.[16] (2014)	• liraglutide 3 mg (n=2487) • placebo (n=1244)	• Obese or BMI ≥27 and ≥1 comorbid condition	• T2DM	• 79% female • 85% Caucasian • 10% African American • 11% Hispanic/Latino • Mean age: 45 yrs (range, 18-78)
DeFronzo, et al.[17] (2014)	• liraglutide 3 mg (n=423) • placebo (n=212)	• T2DM (A1c: 7%-10%) • Obese or BMI ≥27 and ≥1 comorbid condition	• Treatment with GLP-1 agonist or DPP-4 inhibitor	• 50% female • 83% Caucasian • 12% African American • 10% Hispanic/Latino • Mean age: 55 yrs (range, 18-82)
Wadden, et al.[18] (2013)	• liraglutide 3 mg (n=212) • placebo (n=210)	• Obesity or BMI ≥27 and ≥1 comorbid condition • First treated with 1200-1400 kcal/day diet and lost ≥5% BW in 4-12 weeks (run-in period)	• T2DM	• 81% female • 84% Caucasian • 13% African American • 7% Hispanic/Latino • Mean age: 46 yrs (range, 18-73)

BMI = body mass index; **BW =** body weight; **DPP-4 =** dipeptidyl peptidase-4; **GLP-1 =** glucagon-like peptide-1 **T2DM =** type 2 diabetes mellitus.

not been reported in patients without diabetes.

Rare but serious conditions have been observed with liraglutide use and include acute pancreatitis, gallbladder disease, and renal impairment.[14] Tachycardia has been observed in clinical trials. The mean heart rate increase from baseline averaged 2.5 beats/min (range 1.6–3.6 beats/min) in liraglutide recipients in one trial.[19] The increase in heart rate peaked at 6 weeks and resolved during continued treatment. Patients should have their heart rate monitored throughout treatment with liraglutide.[14,20]

Warnings, Precautions, and Contraindications

Liraglutide has a boxed warning stating that tumors of the thyroid gland (thyroid C-cell tumors) have been observed in rodent studies with liraglutide, although this possible carcinogenic effect has not been observed in humans. Consequently, liraglutide should not be used in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (a disease in which patients have tumors in more than one gland in their body, which predisposes them to MTC).[14] The FDA requires the manufacturer to have a Risk Evaluation and Mitigation Strategy (REMS) to inform providers about the serious risks associated with liraglutide.

Dosing and Administration

Liraglutide is administered as a once daily subcutaneous injection in the upper arm, abdomen, or thigh. During the first week of treatment, the patient should be instructed to inject a daily dose of 0.6 mg per day. On week 2, the patient should titrate to a dose of 1.2 mg daily, followed by 1.8 mg daily starting on week 3, 2.4 mg daily starting on week 4, and 3 mg daily starting week 5.[14] Each pen is a prefilled dial-a-dose pen that contains 18 mg of liraglutide. Patient can select doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3 mg. The pen is made to be used with NovoFine® or NovoTwist® disposable needles up to a length of 8 mm. Patients can reduce GI side effects by eating smaller meals and titrating daily doses of liraglutide from 0.6 mg to 3 mg dose over 5 weeks.

No specific duration of therapy has been established for liraglutide for chronic weight management in conjunction with a reduced-calorie diet and increased physical activity. Clinical trials have only evaluated treatment for up to ~1 year. Patients using liraglutide should be evaluated after 16 weeks to determine if the treatment is working. If a patient has not lost at least 4% of baseline body weight, the patient may be considered a "non-responder," in which case liraglutide should be discontinued.[14]

Use in Special Populations

No dose adjustments are required based on age, sex, race, ethnicity, or renal or hepatic impairment. Safety and effectiveness of liraglutide have not been established in pediatric patients. As such, liraglutide is not recommended for use in pediatric patients. Liraglutide is classified as pregnancy category X and is absolutely contraindicated in pregnancy. Liraglutide is not known to be excreted in human milk. In lactating rats, liraglutide was excreted unchanged in milk at concentrations approximately 50% of maternal plasma. Thus, liraglutide use in nursing mothers must be used with caution.[14]

Place in Therapy

Liraglutide joins orlistat (inhibitor of pancreatic and gastric lipases), lorcaserin (selective serotonin C2 receptor agonist), phentermine/topiramate (sympathomimetic anorectic/anti-epileptic combination), and naltrexone/bupropion extended-release (opioid antagonist plus a norepinephrine and dopamine reuptake inhibitor) as the fifth drug with an FDA-approved indication for chronic weight management. Liraglutide causes a placebo-adjusted weight loss of about 4.5%, which is greater than that found with orlistat, or lorcaserin and is comparable to naltrexone/bupropion extended-release, but less than phentermine/topiramate.[20] However, liraglutide has not been compared head-to-head with the other FDA-approved weight loss medications; thus, comparisons across trials are difficult. Liraglutide is the only FDA-approved weight-loss medication administered via injection. Thus, patients may be less like to prefer daily injections over effective oral alternatives.

Table 3 | Phase 3 clinical trial results for liraglutide 3 mg used for weight-management.

	Pi-Sunyer 2014[16]		DeFronzo 2014[17]		Wadden 2013[18]	
	Liraglutide (n= 2487)	**Placebo** (n=1244)	**Liraglutide** (n=423)	**Placebo** (n=212)	**Liraglutide** (n=212)	**Placebo** (n=210)
Weight (kg)						
Baseline mean ± SD	106.2 ± 21.2	106.2 ± 21.7	105.7 ± 21.9	106.5 ± 21.3	100.4 ± 20.8	98.7 ± 21.2
% change over 56 weeks	-8.0%	-2.6%	-5.4%	-1.7%	-4.9%	+0.3%
Difference	-5.4% (95% CI -5.8% to -5.0%)		-3.7% (95% CI -4.7% to -2.7%)		-5.2% (95% CI -6.8% to -3.5%)	
Achieved ≥5% weight loss (%)	63.2%	27.1%	49.0%	16.4%	44.2%	21.7%
Difference	4.8% (95% CI 4.1%–5.6%)[a]		32.6% (95% CI 25.1%–40.1%)		22.6% (95% CI 13.9%–31.3%)	
Achieved ≥10% weight loss (%)	33.1%	10.6%	22.4%	5.5%	25.4%	6.9%
Difference	4.3% (95% CI 3.5%–5.3%)[a]		16.9% (95% CI 11.7%–22.1%)		18.5% (95% CI 11.7%–25.3%)	

[a]Loss of at least 5% and more than 10% of body weight were analyzed by logistic regression with data from the full-analysis set, with LOCF imputation, and are presented as the proportions of patients (%) and odds ratios.

Table 4 | Adverse effects reported in at least 2% of subjects in phase 3 liraglutide trials for weight loss.

Adverse Effect	Liraglutide	Placebo
Gastrointestinal		
Nausea	39.3%	13.8%
Diarrhea	20.9%	9.9%
Constipation	19.4%	8.5%
Vomiting	15.7%	3.9%
Dyspepsia	9.6%	2.7%
Abdominal Pain	5.4%	3.1%
Upper Abdominal Pain	5.1%	2.7%
GERD	4.7%	1.7%
Abdominal Distension	4.5%	3.0%
Eructation	4.5%	0.2%
Flatulence	4.0%	2.5%
Dry Mouth	2.3%	1.0%
Metabolism and Nutrition Disorders		
Hypoglycemia in T2DM	23.0%	12.7%
Nervous System Disorders		
Headache	13.6%	12.6%
Dizziness	6.9%	5.0%
General Disorders and Administration Site Conditions		
Fatigue	7.5%	4.6%
Injection site Erythema	2.5%	0.2%
Injection Site Reaction	2.5%	0.6%
Asthenia	2.1%	0.8%
Infections		
Gastroenteritis	4.7%	3.2%
Urinary Tract Infection	4.3%	3.1%
Viral Gastroenteritis	2.8%	1.6%
Laboratory Abnormalities		
Increased Lipase	5.3%	2.2%
Psychiatric Disorders		
Insomnia	2.4%	1.7%
Anxiety	2.0%	1.6%

Cost

Saxenda® is expected to be available in U.S. pharmacies by mid-2015. Anticipated retail cash pricing (i.e., without insurance) for liraglutide is about $1000 per month, approximately double the cost of Victoza® (liraglutide). For comparison, Contrave® (Bupropion/naltrexone), Belviq® (Lorcaserin), and Qsymia® (Phentermine/topiramate) all cost around $200 per month (**Table 5**).[21]

Conclusion

Liraglutide is the latest FDA-approved chronic weight-management medication and is available as a once daily subcutaneous injection. Liraglutide was first approved for use in glycemic control in patients with type 2 diabetes, however studies in these patients, most of whom were overweight or obese, revealed that liraglutide produced significant weight loss. Liraglutide is a GLP-1 receptor agonist and is believed to reduce bodyweight by slowing gastric emptying, increasing satiety and reducing calorie intake. Studies have shown liraglutide reduces bodyweight to a significantly greater extent than placebo at 56 weeks in obese adults or overweight adults with ≥1 bodyweight-related comorbidity. In clinical trials, significantly more liraglutide-treated patients achieved ≥5% and ≥10% weight loss compared with placebo; liraglutide also maintains bodyweight reductions for at least 1-year with continuous treatment. Liraglutide is generally well tolerated; most adverse events are gastrointestinal in nature, and are transient and of mild intensity. Saxenda® (liraglutide) for chronic weight management is expected to be available in U.S. pharmacies by the end of the first half of 2015 and is expected to cost patients $1000 per month without insurance.

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Table 5 | Estimated retail cost of available weight-management drugs.

Drug	Cost[a]
Contrave® (bupropion/naltrexone)	$240
Belviq® (lorcaserin)	$225
Qsymia® (phentermine/topiramate)	$205
Xenical® (orlistat)	$165
Saxenda® (liraglutide)	$1,090

[a]Cash price per 1-month supply. Cost data were retrieved from GoodRx, Inc. as of June, 2015.

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Editor's Corner

Intensive Blood Pressure Management May Decrease Morbidity and Mortality

The National Institutes of Health (NIH) has recently announced the early cessation of a landmark study (SPRINT) investigating the cardiovascular (CV) and mortality benefits of targeting a lower than recommended systolic blood pressure (BP) goal. The study aimed to evaluate the benefits of maintaining a lower target BP through intensive BP management.

The SPRINT study, which was initiated in 2009, includes more than 9,300 patients aged 50 years or older. The study population was diverse; however, patients with diabetes, prior stroke, or polycystic kidney disease were not included in the study. Participants of the study were randomized to standard treatment targeting a goal systolic BP <140 mmHg or intensive treatment targeting a goal systolic BP <120 mmHg. According to the initial results, intensive management of high BP significantly reduced CV events by almost a third and the risk of death by almost a quarter, when compared to standard treatment. Primary results of the study are expected to be published within the next few months.

For additional information:
Landmark NIH study shows intensive blood pressure management may save lives. http://www.nih.gov/news/health/sep2015/nhlbi-11.htm. Published September 11, 2015. Accessed September 25, 2015.

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