



Keeping pharmacy students informed on current and pertinent diabetes information!

New SGLT-2 Inhibitor on the Block: Steglatro™

By: Emily Harden, 3rd Year Pharm.D. Candidate

Steglatro™ (ertugliflozin) is the newest member of the SGLT-2 inhibitor family to achieve FDA approval as of December 2017. SGLT-2 inhibitors work by inhibiting the sodium glucose co-transporter 2 (SGLT-2) to reduce renal reabsorption of filtered glucose thereby increasing urinary excretion of glucose.¹ Steglatro™ is approved in 5 mg and 15 mg tablets to be taken once daily as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹

Steglatro™ has similar side effect profile as other SGLT-2 inhibitors. The most common adverse reaction associated with Steglatro™ is yeast infections which occur in ≥ 5% of female patients.¹ Steglatro™ is contraindicated in patients with severe renal impairment, end-stage renal disease, dialysis, and is not recommended for pregnant or breastfeeding females.¹

The VERTIS mono trial was a 26-week placebo-controlled, randomized, double-blind multicenter study which evaluated the safety and efficacy of Steglatro™ as monotherapy.² The trial followed 461 patients with type 2 diabetes with a HbA1c between 7% and 10.5% inadequately controlled with diet and exercise alone. At week 26, treatment with Steglatro™ with 5 mg or 15 mg daily achieved statistically significant reductions in HbA1c from baseline, -0.99% and -1.16% respectively, compared to placebo. A greater proportion of patients in the ertugliflozin groups achieved a HbA1c < 7% compared to placebo.²



Steglatro™ was also studied in combination with metformin in the VERTIS MET trial and in combination with sitagliptan in the VERTIS SITA trial.^{3,4} Both trials met primary endpoints to achieve statistically significant reductions in HbA1c when Steglatro™ was added to either metformin or sitagliptin.^{3,4} Secondary endpoints also proved statistically significant with reductions in weight, fasting plasma glucose, systolic blood pressure and diastolic blood pressure compared to placebo.³

In addition to Steglatro™, Steglujan (ertugliflozin and sitagliptan) and Segluromet™ (ertugliflozin and metformin hydrochloride) are also FDA-approved fixed-dose combinations.⁵ Steglujan combines 5mg or 15mg of ertugliflozin with 100 mg of sitagliptan. Segluromet™ combines 2.5 mg or 7.5 mg of ertugliflozin with 500mg or 1000 mg of metformin hydrochloride.⁵

References

1. Merck. https://www.merck.com/product/usa/pi_circulars/s/steglatro/steglatro_pi.pdf. Updated December 2017. Accessed February 2018.
2. Terra S, et al. Phase III efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. *Diabetes Obes Metab*. 2017 May; 19(5):721-728
3. Rosenstock J, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). *Diabetes Obes Metab*. 2018 Mar;20(3):520-529. Doi: 10.1111/dom.13103. Epub 2017 Oct.
4. Dagogo-Jack S, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptan: the VERTIS SITA2 placebo-controlled randomized study. *Diabetes Obes Metab*. 2017. <https://doi.org/10.1111/dom.13116>
5. Pfizer. https://www.pfizer.com/news/press-release/press-release-detail/fda_approves_sglit2_inhibitor_steglatro_ertugliflozin_and_fixed_dose_combination_steglujan_ertugliflozin_and_sitagliptin_for_adults_with_type_2_diabetes. Updated December 2017. Accessed February

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Diabetes Management in Women

By: Sydney Finder, 2nd Year Pharm.D. Candidate

Currently, the accepted standard of care for both men and women with diabetes is the American Diabetes Association guidelines. The only female-specific guidelines are for pregnant women or those planning on becoming pregnant. However, data suggests that current therapies are not working as well for women as they are for men¹. Studies show a striking difference in outcomes in diabetes control between men and women.

Among diabetic women, there is a 40% higher risk and a 50% increase in mortality due to coronary heart disease. Diabetic women also have a 30% higher chance of having a stroke than their male counterparts. Studies that explored gender differences in the treatment of type 2 diabetes found lower rates of aspirin and anticoagulation use in eligible diabetic women. When comparing men to women, women on antihypertensive therapy at equal or greater treatment intensity to men, are less likely to be at treatment goals.¹

While the discrepancy in therapeutic outcomes is clear in the data, few studies have been performed to explain these differences. The FDA postulated a few hypotheses including differences in body fat, liver metabolism, and hormones being the influencing factors, but they concluded more definitive research is needed. Due to differences in metabolism between men and women, medications have been shown to yield different results in women and men taking the same regimens. For example, women taking thiazolidinediones, such as pioglitazone and rosiglitazone, have higher plasma levels than men taking the same amount of medication. Women taking rosiglitazone have higher mortality and higher risk of hypoglycemia and bone fracture.² Another study shows women on exenatide, a GLP-1 agonist, are less likely to reach their HbA1c lowering target than men taking the same medication.² SGLT-2 inhibitors such as apagliflozin, canagliflozin and empagliflozin have the common side effect of genital mycotic infection and women are more likely to experience this adverse effect.

Pregnant women with type 2 diabetes or gestational diabetes are at higher risk for adverse reactions that can affect both the child and the mother. Because of this, the ADA recommends that all diabetic women of childbearing age be educated on the risks associated with pregnancy.⁶ Pregnant diabetic women have a higher red blood cell turnover rate that must be taken into consideration. Due to the higher turnover, their HbA1c levels could be slightly lower. Therefore, HbA1c targets for pregnant diabetic women should be between 6 and 6.5 %, more stringent than the ADA goal of 7%. When pregnant, insulin is the preferred treatment. NPH insulin and fast-acting insulins are used to maintain recommended blood glucose levels. If insulin is not possible or rejected by the patient, metformin and glyburide are the best oral agents for type 2 and gestational diabetes. However, both cross the placenta and should be avoided if possible. Women will need higher doses of insulin as pregnancy progresses. After delivery, insulin sensitivity increases and may remain this way in the postpartum period. Pregnant women are at an increased risk for hypoglycemia and ketoacidosis and they should be educated on the signs of both disease states, as well as maintaining regular blood sugar testing and urine ketone testing⁶.

In conclusion, there are potential gender differences to be taken into consideration when planning a treatment regimen for diabetic men and women. While data on the topic is lacking, healthcare providers should be encouraged to research available data on each prescribed medication. Gender-specific education is recommended amongst physicians and pharmacists on the side effects and outcomes to be expected. Taking gender into account could reduce adverse reactions and improve therapeutic outcomes in diabetic women.

References

1. Kautzky-Willer A, Harreiter J. Sex and gender differences in therapy of type 2 diabetes. *Diabetes Research & Clinical Practice* [serial online]. September 2017;131:230-241. Available from: Academic Search Complete, Ipswich, MA. Accessed February 18, 2018.
2. Campesi I, Franconi F, Seghieri G, Meloni M. Sex-gender-related therapeutic approaches for cardiovascular complications associated with diabetes. *Pharmacological Research* [serial online]. May 2017;119:195-207. Available from: MEDLINE, Ipswich, MA. Accessed February 18, 2018.
3. De Melo M, de Sa E, Gucciardi E. Exploring differences in Canadian adult men and women with Diabetes management: results from the Canadian community health survey. *BMC Public Health* [serial online]. December 2013;13(1):1-19. Available from: Food Science Source, Ipswich, MA. Accessed February 18, 2018.
4. Scheen A. Pharmacodynamics, Efficacy and Safety of Sodium-Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes Mellitus. *Drugs* [serial online]. January 2015;75(1):33-59. Available from: Academic Search Complete, Ipswich, MA. Accessed February 21, 2018
5. Miller M. Gender-Based Differences in the Toxicity of Pharmaceuticals—The Food and Drug Administration's Perspective. *International Journal Of Toxicology* (Taylor & Francis) [serial online]. May 2001;20(3):149-152 American Diabetes Association. 13. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes

SDC Highlights



Students presenting during the Low Glycemic Index Food fundraiser in Athens.



Dawgtoberfest 2017

- ◆ Diabetes education classes at Barney Pharmacy take place once a month.
- ◆ Raised \$53.91 during the spring fundraisers.

Congratulations to the 2018-2019 officers!!

- ◆ **President:** Nikesh Patel
- ◆ **VP:** Seth Garner
- ◆ **Secretary:** Sonam Patel
- ◆ **Treasurer:** Laura Pyronneau
- ◆ **Fundraising Chair:** Emily Harden

FDA Drug Approval: Ozempic®

By: Michael Mgbemena, 3rd Year Pharm.D. Candidate

In December 2017 the FDA approved the newest glucagon like peptide-1 (GLP-1) receptor agonist, Ozempic® (semaglutide), to the market for the treatment of type 2 diabetes in adults. Ozempic® is a long-acting GLP-1 receptor agonist that is administered once weekly on the same day via an injectable pen device. The pen will be available in two dosages: 0.5 mg and 1 mg. It is indicated for the improvement of glucose control in adult type 2 diabetic patients in conjunction with diet and exercise.¹

Ozempic® works by decreasing blood glucose levels by simultaneously stimulating the secretion of insulin and reducing the secretion of glucagon in a glucose-dependent manner. Because of its high albumin binding ability, a once-weekly dosing regimen is possible. This factor decreases its renal clearance and protects it from being metabolically degraded.

Ozempic®'s FDA approval was based on significant findings from eight SUSTAIN phase 3a trials which included over 8000 adults who had type 2 diabetes.¹ These trials included a 2-year FDA mandated cardiovascular-outcomes trial (SUSTAIN-6) which involved 3,297 type 2 diabetic patients who were at high risk for cardiovascular events.² The five efficacy trials that were performed showed a HbA1c reduction between 1.4 to 1.8 percentage points, significantly higher than some of its competitors like Bydureon® (exenatide extended-release) and Januvia® (sitagliptin).¹ In addition to allowing more patients to reach their HbA1c goals, patients treated with Ozempic® also noticed a 10 to 14 pound weight loss.^{1,4} Many will consider this an added benefit especially in the treatment of obesity.

While Ozempic® boasts many promising benefits, there are safety concerns with the new drug, particularly the increased risk for diabetic retinopathy. This increased risk was seen almost exclusively in patients who already had retinopathy. Despite this, the drug was approved by the overwhelming majority of panel members. Recommendations about possible worsening of retinopathy and alerting physicians to advise patients on the importance of getting routine eye examinations were included in the prescribing information guide.^{3,5} Panel members also supported the cardiovascular safety of Ozempic® despite its inability to achieve sufficient statistical significance. The focus was placed on data showing sustained HbA1c lowering, safety, and weight loss.³

Overall, Ozempic® shows a great deal of promise for the treatment of type 2 diabetes. Weight loss is also an exciting added benefit since weight loss can contribute to better diabetic control. Ozempic® is now 1 of only 3 GLP-1 receptor agonists dosed once weekly and the seventh GLP-1 receptor agonist on the US market.

Currently, Ozempic® is under review by several other regulatory agencies and is set to be studied for use in patients under the age of 18.

References

1. "FDA Approves Semaglutide for Type 2 Diabetes." Medscape, 5 Dec. 2017, www.medscape.com/viewarticle/889631?nlid=119443_3901&src=wnl_newsairt_171205_MSCPEdT&uac=239347EG&implid=1501057&faf=1.
2. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2016;375(19):1834-1844. doi:10.1056/nejmoa1607141.
3. Medscape. (2018). FDA Advisory Panel Endorses Semaglutide for Type 2 Diabetes. [online] Available at: <https://www.medscape.com/viewarticle/887279> [Accessed 13 Jan. 2018]
4. Ahren B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol*. 2017;5(5):341-354.
5. Sorli C, Harashima SJ, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(4):251-26.

New Drug Update: Qtern®

By: Laura Pyronneau, 2nd year Pharm D Candidate

In September 2017, the FDA approved a new combination medication for the treatment of type 2 diabetes called Qtern® by AstraZeneca. Qtern® combines dapagliflozin and saxagliptin. Dapagliflozin is a sodium-glucose cotransporter - 2 (SGLT-2) that increases the urinary glucose excretion by reducing the reabsorption of glucose. Saxagliptin is a dipeptidyl peptidase - 4 (DPP-4) inhibitor that reduces activity of the incretin hormone and helps with insulin secretion after eating. The medication is supplied as an oral tablet of dapagliflozin 10 mg and saxagliptin 5 mg tablet that is to be taken once daily with or without food and should be swallowed whole.¹



Qtern® approval was based on three double blind placebo-controlled trials in 324

patients. The average A1c of patients in the trials was between 7% to 10%. In two trials, a placebo was compared against Qtern® with metformin and resulted in a statistically significant reduction of A1c. The third trial compared Qtern® and metformin against metformin and Farxiga® (dapagliflozin) and metformin and Onglyza® (saxagliptin). Qtern with metformin had a clinically significant reduction in A1c compared to metformin with saxagliptin or dapagliflozin alone.²

Minimal adverse effects were seen with Qtern®. The most common side effects were upper respiratory tract infections, urinary tract infections, and dyslipidemia. Qtern® is contraindicated in patients with heart failure, renal impairment with a GFR <45 mL/min/1.73m², and end stage renal disease requiring dialysis. A risk benefit analysis should be done before initiating Qtern® in patients with known risk factors for heart failure. Overall both SGLT-2 inhibitors and DPP-4 inhibitors are very well tolerated and widely prescribed medications.³

Qtern® will be considerably more helpful than alternative regimens due to the combination of two commonly prescribed medications. Combining two medications will help reduce a patient’s pill burden and increase medication adherence. According to the American Association of Clinical Endocrinologists, Qtern® is 3rd line to be used after a patient has failed monotherapy metformin and metformin with a SGLT-2 inhibitor.³

Qtern® is the 2nd medication in the US and the 1st in Europe to combine two agents of these classes in one tablet with the first being Glyxambi (linagliptin and empagliflozin).⁴ Currently, Qtern® is indicated to be used as an adjunct to diet and exercise for those with uncontrolled blood glucose.¹

References

- Holmberg M. Qtern. Pharmacy Times [serial online]. 2017; Available from: InfoTrac Health Reference Center Academic, Ipswich, MA. Accessed April 1, 2018.
- Chaplin S. Qtern: DPP-4 and SGLT2 inhibitor combination for type 2 diabetes. Prescriber [serial online]. 2017;(4):47. Available from: InfoTrac Health Reference Center Academic, Ipswich, MA. Accessed April 1, 2018.
- Dosing & Administration | QTERN® (dapagliflozin and saxagliptin) - For HCPs. <https://www.qtern-hcp.com/dosing-and-administration.html>. Accessed April 1, 2018.
- Yu H, Woo VC. Emerging use of combination therapies for the management of type 2 diabetes – focus on saxagliptin and dapagliflozin. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC55335>

Steroid Induced Hyperglycemia

By: Camille Haile-Selassie, 2nd Year Pharm.D. Candidate

Management of hyperglycemic episodes in patients with diabetes is important to reduce cardiovascular risk. Hyperglycemia commonly occurs during the fasting or postprandial states and a key factor to keep in consideration is that hyperglycemia can be influenced not only by diet but other medications as well. Steroids are the main cause of drug-induced hyperglycemia occurring in patients with and without diabetes.²

Currently the American Diabetes Association (ADA) guidelines do not differentiate between hyperglycemia and steroid-induced hyperglycemia (SIHG). Both are defined as a random blood glucose level of ≥ 200 mg/dL, or an HbA1c $> 6.5\%$. Hyperglycemia is detected optimally in the postprandial state. Therefore, fasting blood sugars should not be used for detection. Steroids increase blood sugar through invoking insulin resistance.

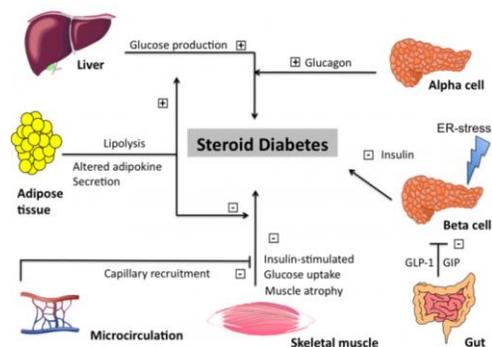
Patients most at risk for SIHG include^{2,4}:

- Pre-existing diabetes
- History of gestational or familial diabetes
- Overweight
- Caucasians above age 40
- African Americans, Middle Easterners, and South Asians above age 25.⁴
- Concomitant use of mycophenolate or calcineurin inhibitors (tacrolimus, pimecrolimus)
- The risk for hospitalized patients is also significant, as more than half develop hyperglycemia while receiving a high dose steroid; 48% of these patients show a mean glucose level of ≥ 140 mg/dL.^{2,5}

Studies including but not limited to the Hoorn Study, Honolulu Heart Study, and Chicago Heart Study show that when comparing

fasting and postprandial hyperglycemia, CVD risk mainly arises from the postprandial period. In type 2 diabetes patients, this happens because of increased LDL oxidation after meals, which is directly correlated with the severity of hyperglycemia. Less is known about the extent of CVD risk in SIHG, although fluctuations in blood

glucose are associated with higher overall cardiovascular mortality.¹ This risk is especially prevalent for patients who use steroids in the



management of rheumatoid arthritis. This disease state carries a risk of cardiovascular complications, which can be intensified by hyperglycemia from steroid use.² Only oral steroids have demonstrated increased risk of diabetes development. There is minimal to no risk from steroid-containing inhalers, eye drops, topical creams/ointments, or infrequent injections.² All patients taking oral steroids should be counseled to be aware of the three P’s of hyperglycemia: polyphagia, polydipsia polyuria.³ Proper dietary choices and exercise should also be reinforced.⁶

Management of patients with steroid induced hyperglycemia

Non-diabetic Patients	Diabetic patients
<ul style="list-style-type: none"> • If blood glucose does rise to hyperglycemic levels (pre-prandial >200 mg/dl), the first line therapy choice is sulfonylureas.⁶ • For persistent hyperglycemia ≥ 200 mg/dL, insulin is the preferred treatment.^{2,6} • As the steroid is discontinued, lower the insulin dose by similar increments • Self-monitor blood glucose up to 4 times daily.⁶ 	<ul style="list-style-type: none"> • Individualized therapy adjustments should be made based on duration of steroid treatment and severity of hyperglycemia. ⁵ • If not meeting BG goals, initiate a sulfonylurea (if not already taking) and titrate up as necessary. • If on maximum dose and still not at goal, add basal insulin in the morning.⁶

In the community setting, it is important for pharmacists to quickly identify patients most at risk for hyperglycemia when dispensing steroids. Counseling on the 3 P’s, lifestyle habits, and self-monitored blood glucose can help patients be more aware of and proactive in maintaining their health status.

References

- Ceriello A. Postprandial Hyperglycemia and Diabetes Complications: Is It Time to Treat? *Diabetes*. 2004;54(1):1-7. doi:10.2337/diabetes.54.1.1.
- Tamez-Pérez HCAE. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World Journal of Diabetes*. 2015;6(8):1073. doi:10.4239/wjcd.v6.i8.1073.
- High Blood Sugars Caused by Steroids. Hamilton Health Sciences <http://www.hamiltonhealthsciences.ca/Workfiles/Diabetes/HighBloodSugarCausedBySteroids-trh.pdf>. Published February 12, 2013. Accessed February 20, 2018.
- Steroid Induced Diabetes. Diabetes.co.uk. <https://www.diabetes.co.uk/steroid-induced-diabetes.html>. Accessed February 2018