Drug & Poison Information Center—Faculty of Pharmacy—Tanta University

Drug & Poison Information Bulletin

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Dear healthcare professionals.. a valuable letter!

In this issue:

Last year, Bristol-Myers-Squibb company announced about the discontinuation of Daklinza® *(daclatasvir)* tablets in all of its available doses, 30 mg, 60 mg & 90 mg. The 90 mg dose distribution was stopped last December 2018, whereas the 30 mg and 60 mg doses distribution will be stopped in June 2019.

Daklinza® belongs to non-structural protein 5A(NS5A) inhibitors, and is indicated for use with sofosbuvir for chronic hepatitis C virus (HCV) genotypes (1&3) infections.

The manufacturer, Bristol-Myers-Squibb said in a statement concerning the discontinuation that "The global discontinuation of Daklinza® is voluntary and is not the result of any quality, safety or efficacy issues regarding the product". The company added that it has carefully evaluated the potential impact of discontinuing Daklinza®,which has been available since 2015 and concluded there would be limited clinical impact given the availability of numerous preferred alternative medications for HCV."

References:

- ***Daklinza Monograph:*** ***https://reference.medscape.com/drug/daklinza-daclatasvir-1000013. Accessed in March 2019.***
- ***Bristol-Myers-Squibb Letter Concerning the Discontinuation:*** ***https://www.bms.com/assets/bms/ca/documents/productmonograph/DaklinzaHCPletter20sept2018EN.pdf. Accessed in March 2019.***

By: Amr Noweir, B.Sc

First oral add-on drug therapy for type 1 diabetes

For the first time, regulators are reviewing two pills of sodium–glucose co-transporter (SGLT) inhibitors as adjunctive therapies to insulin in type 1 diabetes (T1D):

Dapagliflozin: an SGLT-2 inhibitor, which has been approved for (T2D) since 2012 in Europe and since 2014 in the united states (USA).

Sotagliflozin: is a new SGLT-1/SGLT-2 dual inhibitor, and T1D will be the first population in which it is used.

These medications cannot replace insulin in T1D care, but they do usually lower insulin dose requirements while exerting favorable effects on blood pressure and contributing to weight loss.

In the first half of 2019, the European Medicines Agency (EMA) approved dapagliflozin for use in T1D as an adjunct to insulin in patients with a body mass index (BMI) ≥ 27 kg/m2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy. Dapagliflozin is the first approval of an oral T1D therapy in Europe and it is under regulatory review in USA and Japan.

Clinical data:

⇒ Dapaglifozin's approval is based on data from the Phase III DEPICT (Dapagliflozin Evaluation in Patients with Inadequately Controlled T1D) clinical program in T1D.

⇒ The short-term (24 weeks) and long-term (52 weeks) data from DEPICT-1, along with the short-term data from DEPICT-2, showed that 5 mg daily (when given as an oral adjunct to adjustable insulin in patients with inadequately-controlled glucose demonstrated significant and clinically-meaningful reductions from baseline in average glycated hemoglobin (HbA1c), weight, and total daily insulin dose at 24 and 52 weeks.

Safety issues:

⇒ The U.S. Food and Drug Administration (FDA) has rejected sotagliflozin as an adjunct to insulin for the treatment of T1D based on the increased risk of diabetic ketoacidosis (DKA) with the drug in T1D. Important to note that DKA is a risk that's seen across all SGLT inhibitors in T1D, including dapagliflozin.

⇒ However, sotagliflozin secured positive opinions from the EMA for lowering HbA1c levels and reducing body weight, despite a 3-4 % DKA rate. The control group had less than 1% in its Phase III study. Marketing authorization has not yet been granted by the European Commission.

References:

- ***International Diabetes Federation. First approval of oral type 1 diabetes therapy in the EU. Available at: https://diabetesvoice.org/en/news/first-approval-of-oral-type-1-diabetes-therapy-in-the-eu/. Accessed on May 2, 2019.***
- ***European Medicines Agency. First oral add-on treatment to insulin for treatment of certain patients with type 1 diabetes. Available at: https://www.ema.europa.eu/en/news/first-oral-add-treatment-insulin-treatment-certain-patients-type-1-diabetes. Accessed on April 30,***

By: Bassant Maher, B.Sc

New drug approval for osteoporosis

The FDA has recently approved ***romosozumab*** to treat osteoporosis in postmenopausal women at high risk of bone fracture.

These are women with a history of osteoporotic fracture or multiple risk factors for fracture, or those who have failed or are intolerant to other osteoporosis therapies.

Romosozumab is a monoclonal antibody that blocks the effects of the protein sclerostin and works mainly by increasing new bone formation.

Dosage & Administration:

⇒ It is available as: 105 mg/1.17 mL (single-use prefilled syringe). Syringe is not made with natural rubber latex.

⇒ One dose of the drug consists of two injections, one immediately following the other, given once a month by a health care professional. The bone forming effect of this drug decreases after 12 doses so more than 12 doses should not be used.

Clinical data:

The efficacy of romosozumab were demonstrated in two clinical trials involving a total of more than 11,000 women with postmenopausal osteoporosis. Results showed that it can reduce the risk of a new fracture in the spine (vertebral fracture) by 73% & 50% compared to placebo & alendronate respectively.

Safety issues:

⇒ Romosozumab contains a boxed warning on its labeling stating that it may increase the risk of heart attack, stroke and cardiovascular death and should not be used in patients who have had a heart attack or stroke within the previous year.

⇒ Health care professionals should also consider whether the benefits outweigh its risks in those with other risk factors for heart disease and should discontinue romosozumab in any patient who experiences a heart attack or stroke during treatment.

⇒ Common side effects includes: joints pain and headache. Injection site reactions were also observed

Reference:

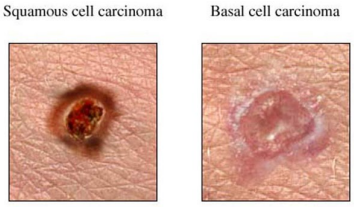
- ***FDA approves new treatment for osteoporosis in postmenopausal women at high risk of fracture:https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635653.htm.Accessed in April 2019.***
- ***romosozumab(Rx): https://reference.medscape.com/drug/evenity-romosozumab-1000158. Accessed in April, 2019.***

By: Mai Mousa, PharmD.

Hydrochlorothiazide Safety Alert

Hydrochlorothiazide is routinely used to treat high blood pressure and excess build-up of fluid in the body. It is known to increase the sensitivity of the skin to light (e.g., sunburns easily).

Two studies have concluded that, prolonged use *(3 years or more)* of hydrochlorothiazide may increase the risk for squamous cell carcinoma up to 4 times and increase the risk for basal cell carcinoma up to 1.25 times compared to the risk in patients not treated with hydrochlorothiazide.



Exposure to sun, ultraviolet light and/or drugs that increase the sensitivity of the skin to light are important risk factors for non-melanoma skin cancer (NMSC). Light colored skin and a personal or family history of skin cancer are also important risk factors.

Recommendations for consumers:

⇒ Check your skin for new marks or growths or any changes to existing ones.

⇒ Report any suspicious skin marks or growths to your healthcare professional.

⇒ Try to limit exposure to sunlight, avoid the use of tanning equipment, and use adequate sun protection (e.g., SPF 30 or higher, clothing, and a hat) to minimize the risk of skin cancer.

⇒ Alternative treatment may be considered for risky patients (Light colored skin, ongoing immunotherapy, family history).

⇒ It is required that manufacturers should update the product safety information for all hydrochlorothiazide-containing products.

References:

- ***Pedersen SA, Gaist D, Schmidt SAJ, Holmich LR, Friis S, Pottegard A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. J Am Acad Dermatol 2018;78(4):673-681.***
- ***Pottegard A, Hallas J, Olesen M et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med 2017;282(4):322-331***

By: Marwa EL-Hefnawy, M.Sc

"*Combo*" therapy with GLP-1 receptor agonists (GLP-1)-RA

"*Connect your information*"

A stepwise approach involving dietary & lifestyle changes along with medications is recommended for the management of patients with type 2 diabetes (T2D). Metformin is the first-line therapy unless contraindicated & if tolerated. After metformin, medications selection is determined by a variety of factors including glucose control, prescence of cardiovascular (CV) diseases, other patient-specific factors (e.g., comorbidities, renal function, or risk for hypoglycemia), patient preference, and cost. Glucagon-like peptide-1 receptor agonists(GLP-1)-RA (dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide) together with sodium-glucose co-transporters 2 (SGLT2) inhibitors have been shown to positively impact cardiovascular outcomes. Many times, combination therapy may be required to achieve glucose control. The tables below review combination therapy with the (GLP-1) RA, including potential clinical benefits and practical issues to consider.

Combo 1:	(GLP-1) RA plus insulin.
Rational for combo:	• **(GLP-1)-RA:**glucose-dependent increase in insulin secretion. • **Insulin:** Facilitates elimination of glucose and reduces hepatic glucose production.
Benefits of combo:	Adding a (GLP-1)-RA to patients on insulin may improve glycemic control with less weight gain and a lower risk of hypoglycemia compared to increasing insulin doses.
When to consider:	Consider adding a (GLP-1)-RA to patients on basal insulin (with or without metformin) requiring additional glucose lowering (with a mealtime insulin) who are at risk for hypoglycemia or who wish to avoid weight gain.
Combo 2:	(GLP-1)-RA plus metformin.
Rational for combo:	• **(GLP-1)-RA:**glucose-dependent increase in insulin secretion. • **Metformin:** reduces hepatic glucose production.
Benefits of combo:	Adding a (GLP-1)-RA to metformin may cause less hypoglycemia and less weight gain than adding other medications (e.g., insulin, meglitinides, or sulfonylurea).
When to consider:	Consider adding a (GLP-1)-RA to patients on metformin requiring additional glucose lowering who are at risk for hypoglycemia or who wish to avoid weight gain.

Combo3:	(GLP-1)-RA plus sulfonylureas.
Rationale for combo:	• **(GLP-1)-RA:** glucose-dependent increase in insulin secretion. • **Sulfonylureas:** increase insulin secretion (non-glucose dependent).
Benefits of combo:	Adding a (GLP-1)-RA especially (liraglutide or exenatide) to patients on a sulfonylurea (with or without metformin) can improve glycemic control and possibly lead to weight loss, with limited incidence of major hypoglycemia.
When to consider combo:	Consider this combination for patients on a sulfonylurea requiring additional glucose lowering who are at risk for hypoglycemia or who wish to avoid weight gain. Use a GLP-1 agonist with proven CV benefits (e.g., liraglutide) in patients with CV disease or at high CV

Combo 4:	(GLP-1)-RA plus Thiazolidinediones ("TZDs" or "Glitazones").
Rationale for combo:	• **(GLP-1)-RA**: Glucose-dependent increase in insulin secretion. • **TZDs:** Improve insulin sensitivity.
Benefits of combo:	The combination of liraglutide, metformin, and rosiglitazone significantly lowered haemoglobin A1c (HbA1c) level after 26 weeks of therapy without major hypoglycemia.
Downsides of this combo:	• Warning with use of TZDs in patients with heart failure. • Potential for side effects (e.g., weight gain, fluid retention) with the TZDs.

Combo5:	(GLP-1)-RA plus sodium-glucose co-transporter 2 (SGLT2) inhibitors or "Flozins"
Rationale for combo:	• **(GLP-1)-RA:** Glucose-dependent increase in insulin secretion. • **Flozins:** Increase glycosuria and block reabsorption of glucose in the kidney.
Benefits of combo:	• (GLP-1)-RA agonists have been studied as add-on therapy to patients taking flozins and combined treatment with a flozin leading to improved glucose control, weight loss, potential for additive CV benefits & small reductions in systolic blood pressure without significant hypoglycemia. • Additional studies are needed to determine the best way to combine these meds (e.g., simultaneous or sequential).
When to consider:	Use a (GLP-1)-RA and flozins with proven cardiovascular benefits (e.g., liraglutide, empagliflozin, respectively) in patients with CV disease or at high CV risk.

Combo 6:	(GLP-1)-RA plus dipeptidyl peptidase-4 (DPP-4) inhibitors or
Rationale for combo:	• **(GLP-1)-RA:**Incretin mimetic (mimic incretin hormones action) and cause a glucose-dependent increase in insulin secretion. • **Gliptins:** Incretin enhancer (prevent the breakdown of endogenous incretins) and cause a glucose-dependent increase in insulin secretion and a decrease in glucagon
Downside of this combo:	• Avoid combining (GLP-1)-RA and gliptins. ***(Evidence level C: Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints).*** • Limited data suggest only an additional 0.3% reduction of HbA1c when exenatide was added to patients already receiving metformin and sitagliptin. • Though incidence is rare, pancreatitis has been seen with both (GLP-1)-RA and gliptins.

References:

- ***Combination Therapy with a GLP-1 Agonists: https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2018/Jul/Combination-Therapy-with-a-GLP-1-Agonist-12436. Accessed in April, 2019.***
- ***Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2018: http://www.clinicalkey.com. Accessed in April, 2019.***

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