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A REVIEW ON LATEST ANTIDIABETIC DRUG OF DAPAGLIFLOZIN

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Abstract:
*The C-aryl glucoside **6** (dapagliflozin) was identified as a potent and selective hSGLT2 inhibitor which reduced blood glucose levels in a dose-dependent manner by as much as 55% in hyperglycemic streptozotocin (STZ) rats. These findings, combined with a favorable ADME profile, have prompted clinical evaluation of dapagliflozin for the treatment of type 2 diabetes. Dapagliflozin is used along with diet and exercise, and sometimes with other medications, to lower blood sugar levels in adults with type 2 diabetes (condition in which blood sugar is too high because the body does not produce or use insulin normally). Dapagliflozin is also used to reduce the risk of needing to be hospitalized for heart failure in adults who have type 2 diabetes along with heart and blood vessel disease or who have multiple risk factors for developing heart and blood vessel disease. Dapagliflozin is also used in adults with heart failure to reduce the risk of needing to be hospitalized and death due to heart and blood vessel disease. Dapagliflozin is in a class of medications called sodium-glucose co-transporter 2 (SGLT2) inhibitors. It lowers blood sugar by causing the kidneys to get rid of more glucose in the urine. Dapagliflozin is not used to treat type 1 diabetes (condition in which the body does not produce insulin and, therefore, cannot control the amount of sugar in the blood) or diabetic ketoacidosis (a serious condition that may develop if high blood sugar is not treated).*

Key words: *dapagliflozin, anti-diabetic*

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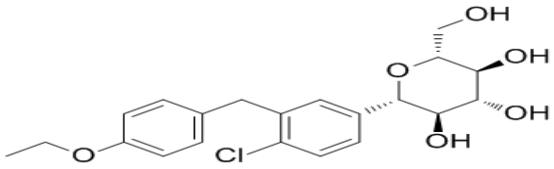
INTRODUCTION:

Obesity is the result of a positive imbalance between energy intake and energy expenditure, where the magnitude of the imbalance can be less than 100 kcal/day. Therefore, an induced negative balance of the same magnitude would be required to prevent obesity and a larger negative imbalance would be required to reverse it. The first law of thermodynamics suggests that there are only two ways to induce a negative energy balance: reduce energy intake or increase energy expenditure. Although exercise can increase energy expenditure, the data on exercise as a method to produce significant weight loss is equivocal with multiple reports showing minimal to no efficacy in women and modest efficacy in men. In contrast to the energy expenditure portion of the equation, energy intake is relatively voluntary, and therefore, susceptible to manipulation. Not surprisingly, diet restriction provides excellent efficacy on a short-term basis. Unfortunately, it has not been shown to be effective on a long-term basis, due presumably to behavioral and metabolic compensatory responses.

An alternative method of reducing energy intake is to reduce caloric absorption. This can be accomplished by reducing nutrient absorption in the intestine, but has side effects such as diarrhea or at the very least tolerability issues such as the fecal leakage observed with pancreatic lipase inhibitors. The kidney is also a site for significant caloric "absorption", reabsorbing (in humans) ~180 g/day of glucose through transporter proteins localized in the proximal tubules. Although there are several proteins which mediate glucose transport in the proximal tubule, the protein responsible for the majority of glucose reabsorption in the kidney is the sodium glucose cotransporter-2 (SGLT2). It is expressed on the luminal surface of cells in the S1 segment of the proximal tubule and is localized specifically to kidney. In addition, there are other SGLTs expressed in kidney which cotransport monosaccharides along with sodium (SGLT1, sodium/myo-inositol cotransporter (SMIT), SGLT4, SGLT5, and potentially SGLT6). SGLT2 is a low affinity, high-capacity cotransporter with a 1:1 sodium to glucose molecule cotransport ratio.

Over time, people who have diabetes and high blood sugar can develop serious or life-threatening complications, including heart disease, stroke, kidney problems, nerve damage, and eye problems. Taking dapagliflozin, making lifestyle changes (e.g., diet, exercise, quitting smoking), and regularly checking your blood sugar may help to manage your diabetes and improve your health. This therapy may also decrease your chances of having a heart attack, stroke, or other diabetes-related complications such as kidney failure, nerve damage (numb, cold legs or feet; decreased sexual ability in men and women), eye problems, including changes or loss of vision, or gum disease. Your doctor and other healthcare providers will talk to you about the best way to manage your diabetes.

CHEMISTRY OF DAPAGLIFLOZIN



MOLECULAR FORMULA - $C_{21}H_{25}ClO_6$
MOLECULAR WEIGHT - 408.9g/mol

BRAND NAMES:
DAJIO
DAPAGLYN
DAPONE
DAPAVEL
GLUCRETA
GLUXIT
OXRA
GLEDEPA
FORXIGA
UDAPA

Preparation:

Methylamine (40% in water; 0.75 mL) was added to a solution of (lC)-2,3,4,6- tetra-0-acetyl-l,5-anhydro-l-[4-chloro-3-(4-ethoxybenzyl) phenyl]-D-glucitol (1 g) in methanol (20 mL) at 25°C. The reaction mixture was stirred for about 5 hours at 20°C to 25 °C. After completion of the reaction, the reaction mixture was concentrated under vacuum at 25°C to 30°C. The pH of the reaction mixture was adjusted to 6-7 using hydrochloric acid (35% in water; -0.5 mL). Ethyl acetate (20 mL) was added to the reaction mixture and the mixture was stirred for about 10 minutes. The organic layer was separated, washed with water (10 mL), and dried using sodium sulphate (0.5 g). The organic layer was concentrated under vacuum at 40°C to 45 °C to obtain a residue. The residue was dissolved in methyltertiarybutyl ether (MTBE; 5 mL) to obtain a solution. The solution was added to hexanes (10 mL) at 5°C to 7°C and stirred for 60 minutes to obtain a solid residue. The solid residue

was filtered under nitrogen atmosphere and dried under vacuum at 25°C to 30°C to obtain dapagliflozin.

HISTORY:

Dapagliflozin was found effective in several studies in participants with type 2 and type 1 diabetes. The main measure of effectiveness was the level of glycosylated haemoglobin (HbA1c), which gives an indication of how well blood glucose is controlled.In two studies involving 840 participants with type 2 diabetes, dapagliflozin when used alone decreased HbA1c levels by 0.66 percentage points more than placebo (a dummy treatment) after 24 weeks.In four other studies involving 2,370 participants, adding dapagliflozin to other diabetes medicines decreased HbA1c levels by 0.54-0.68 percentage points more than adding placebo after 24 weeks.In a study involving 814 participants with type 2 diabetes, dapagliflozin used in combination with metformin was at least as effective as a sulphonylurea (another type of diabetes medicines) used with metformin.Both combinations reduced HbA1c levels by 0.52 percentage points after 52 weeks.

A long-term study, involving over 17,000 participants with type 2 diabetes, looked at the effects of dapagliflozin on cardiovascular (heart and circulation) disease.The study indicated that dapagliflozin's effects were in line with those of other diabetes medicines that also work by blocking SGLT2.

In two studies involving 1,648 participants with type 1 diabetes whose blood sugar was not controlled well enough on insulin alone, adding dapagliflozin 5 mg decreased HbA1c levels after 24 hours by 0.37% and by 0.42% more than adding placebo.

Dapagliflozin was approved for medical use in the European Union in November 2012.It is marketed in a number of European countries.

Dapagliflozin was approved for medical use in the United States in January 2014.

In 2020, the U.S. Food and Drug Adminisration (FDA) expanded the indications for dapagliflozin to include treatment for adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure. It is the first in this particular drug class, sodium-glucose co-transporter 2 (SGLT2) inhibitors, to be approved to treat adults with New York Heart Association's functional class II-IV heart failure with reduced ejection fraction.

Dapagliflozin was shown in a clinical trial to improve survival and reduce the need for hospitalization in adults with heart failure with reduced ejection fraction. The safety and effectiveness of dapagliflozin were evaluated in a randomized, double-blind, placebo-controlled study of 4,744 participants.The average age of participants was 66 years and more participants were male (77%) than female. To determine the drug's effectiveness, investigators examined the occurrence of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits. Participants were randomly assigned to receive a once-daily dose of either 10 milligrams of dapagliflozin or a placebo (inactive treatment).After about 18 months, people who received dapagliflozin had fewer cardiovascular deaths, hospitalizations for heart failure, and urgent heart failure visits than those receiving the placebo.

In July 2020, the FDA granted AstraZeneca a Fast Track Designation in the US for the development of dapagliflozin to reduce the risk of hospitalisation forheart failure or cardiovascular death in adults following a heart attack.

In August 2020, it was reported that detailed results from the Phase III DAPA-CKD trial showed that AstraZeneca's FARXIGA® (dapagliflozin) on top of standard of care reduced the composite measure of worsening of renal function or risk of cardiovascular (CV) or renal death by 39% compared to placebo ($p<0.0001$) in patients with chronic kidney disease (CKD) Stages 2-4 and elevated urinary albumin excretion. The results were consistent in patients both with and without type 2 diabetes (T2D)

PRECAUTION:

- tell your doctor and pharmacist if you are allergic to dapagliflozin, any other medications, or any of the ingredients in dapagliflozin tablets. Ask your pharmacist or check the Medication Guide for a list of the ingredients.
- tell your doctor and pharmacist what other prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products you are taking or plan to take. Be sure to mention any of the following: angiotensin-converting enzyme (ACE) inhibitors such as benazepril (Lotensin, in Lotrel), captopril, enalapril (Vasotec, in Vaseretic), fosinopril, lisinopril (in Zestoretic), moexipril (Univasc, in Uniretic), perindopril (Aceon, in Prestalia), ramipril (Altace), and trandolapril (Mavik, in Tarka); angiotensin receptor blockers (ARB) such as azilsartan (Edarbi, in Edarbyclor), candesartan (Atacand, in Atacand HCT), eprosartan (Teveten), irbesartan (Avapro, in Avalide), losartan (Cozaar, in Hyzaar), olmesartan (Benicar, in Azor, in Benicar HCT, in

Tribenzor), telmisartan (Micardis, in Micardis HCT, in Twynsta); aspirin and other nonsteroidal anti-inflammatory medications (NSAIDS) such as ibuprofen (Advil, Motrin) and naproxen (Aleve, Naprosyn); diabetes medications such as glimepiride (Amaryl, in Duetact), glipizide (Glucotrol), glyburide (DiaBeta, Glynase), repaglinide (Prandin, in Prandimet), and tolbutamide; diuretics ('water pills'); and insulin.

- tell your doctor if you are on dialysis and if you have or have ever had kidney disease. Your doctor may tell you not to take dapagliflozin.
- tell your doctor if you regularly drink alcohol or sometimes drink large amounts of alcohol in a short time (binge drinking) or if you are on a low sodium diet. Also tell your doctor if you have or have ever had heart failure, pancreatic disease including pancreatitis (swelling of the pancreas) or have had surgery on your pancreas, urinary tract infections or problems urinating, low blood pressure, yeast infections in the genital area, kidney or liver disease. If you are male, tell your doctor if you have never been circumcised. Also tell your doctor, if you are eating less due to illness, surgery or a change in your diet, or have recently had diarrhea, vomiting, not been drinking enough fluids, been in the sun too long, or have been sweating a lot, which may cause dehydration (loss of a large amount of body fluids).
- tell your doctor if you are pregnant, plan to become pregnant, or are breastfeeding. Do not breastfeed while you are taking dapagliflozin. If you become pregnant while taking dapagliflozin, call your doctor.
- if you are having surgery, including dental surgery, tell the doctor or dentist that you are taking dapagliflozin. Your doctor will probably tell you to stop taking dapagliflozin at least 3 days before a surgery.
- alcohol may cause a change in blood sugar. Ask your doctor about the safe use of alcoholic beverages while you are taking dapagliflozin.
- you should know that dapagliflozin may cause dizziness, lightheadedness, and fainting when you get up too quickly from a lying position. If you have this problem, call your doctor. This problem is more common when you first start taking dapagliflozin. To avoid this problem, get out of bed slowly, resting your feet on the floor for a few minutes before standing up.
- ask your doctor what to do if you get sick, develop an infection or fever, experience unusual stress, or are injured. These conditions can affect your blood sugar and the amount of dapagliflozin you may need.

ADERVERSE EFFECT:

- urinating a lot, including at night
- increased thirst
- frequent, urgent, burning, or painful urination
- urine that is cloudy, red, pink, or brown
- strong smelling urine
- decrease in amount of urine
- pelvic or rectal pain
- (in women) vaginal odor, white or yellowish vaginal discharge (may be lumpy or look like cottage cheese), or vaginal itching
- (in men) redness, itching, or swelling of the penis; rash on the penis; foul smelling discharge from the penis; or pain in the skin around the penis
- feeling tired, weak, or uncomfortable; along with a fever and pain, tenderness, redness, and swelling of the genitals or the area between the genitals and the rectum
- swelling of the legs or feet

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CONCLUSIONS:

These data suggest that dapagliflozin has the potential to be an efficacious treatment for type 2 diabetes. Since SGLT2 accounts for a significant proportion of glucose reabsorption in the kidney, inhibition of this transporter is being investigated as a strategy to reduce blood glucose in type 2 diabetes. Dapagliflozin is a potent and selective SGLT2 inhibitor, which has been shown to induce glucose excretion by 20–85 g/day in humans and 0.5–1.9 g/day in 200 g rats, which would be roughly equivalent to a caloric deficit of 80–340 kcal/day in humans and 2–7.6 kcal/day in a 200 g rodent. Assuming 6.16 kcal/g body fat for rodents and 3,500 kcal/lb body fat for humans, these caloric deficits would predict weight loss of 0.32–1.2 g/day in a rat and 0.022–0.097 lb/day in a human. Zhang reported an average weight loss of 2.5 kg in early-stage diabetic patients where average urinary glucose excretion was 71.2 g/24 h, which is 20% less than the

3.05 kg which would have been predicted from the glucose excretion values. Weight loss values reported in other studies have also appeared somewhat less than predictions based upon the glucose excretion data discussed above. It is not possible to know whether compensatory hyperphagia could explain these small discrepancies, since food intake was not directly measured in these clinical studies. If compensatory hyperphagia does occur in response to glucose excretion, it might be possible to enhance dapagliflozin-induced weight loss by preventing overeating. Since food intake is commonly measured in rodents, we queried whether compensatory hyperphagia would occur in response to dapagliflozin treatment, and if so, whether prevention of hyperphagia would enhance dapagliflozin-induced weight loss in the diet-induced obese (DIO) Sprague-Dawley rat.

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