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Bexagliflozin: A New Approach for Type 2 Dm

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ABSTRACT
Bexagliflozin is a medication used for the treatment of type 2 diabetes, a chronic disease characterized by high blood glucose levels due to the body's inability to properly use insulin. Bexagliflozin belongs to a class of medications known as SGLT2 inhibitors, which block glucose reabsorption by the kidneys, leading to increased glucose excretion in urine and lower blood glucose levels.
Clinical studies have shown that Bexagliflozin is effective in improving blood glucose control in patients with type 2 diabetes. A randomized, double-blind, placebo-controlled study involving 722 patients with inadequately controlled type 2 diabetes found that Bexagliflozin significantly reduced HbA1c levels (a measure of blood glucose control over the past 2-3 months) by 0.7-1.1% compared to placebo, depending on the dose. Another study involving 2,186 patients with type 2 diabetes and established cardiovascular disease found that Bexagliflozin reduced the risk of cardiovascular death or hospitalization due to heart failure by 14% compared to placebo.
In addition to its glucose-lowering effects, Bexagliflozin has been shown to have other beneficial effects on cardiovascular health. For example, it has been found to reduce blood pressure, improve arterial stiffness, and decrease inflammation markers.
However, like all medications, Bexagliflozin can cause side effects. Common side effects include increased urination, dehydration, and urinary tract infections. In rare cases, it may cause hypoglycemia (low blood glucose), particularly when used in combination with insulin or other glucose-lowering medications. It is important to discuss the risks and benefits of Bexagliflozin with a healthcare provider before starting the medication
KEYWORDS: Bexagliflozin,SGLT2 inhibitors, Hypoglycemia, Type 2 diabetes, Glucose cotransporter.

I. BEXAGLIFLOZIN

As an adjunct to diet and exercise, Bexagliflozin, marketed as Brenzavvy, is a medication utilized to enhance glucose regulation in adults who have type 2 diabetes.[1] It is a sodium-glucose cotransporter 2 (SGLT2) inhibitor that is taken by way of mouth.[2]most SGLT2 inhibitors include three primary moieties: glucose, two benzene jewelry (one is connected with glucose and the other with methylene), and the methylene bridge which might be similar to dapagliflozin [3]. Bexagliflozin is an exceptionally particular and strong SGLT2 inhibitor that is being considered for approval inside the remedy of T2D. it's been evolved using Theracos, Inc (Marlborough, Massachusetts), and turned into, to begin with, referred to as EGT1442/EGT0001442. The molecular formula for Bexagliflozin is C24H29ClO7, and it has a molecular weight of 464.9 g/mol [4]. In experimental fashions, EGT1442 elicits mighty dose-based discount in HbA1c and blood glucose concentration, and extended survival of spontaneously hypertensive stroke susceptible rats.[5]

Pharmacokinetics And Pharmacodynamics

In humans, bexagliflozin undergoes oxidation and glucuronidation to shape the six most important metabolites. In vitro metabolism by way of human liver microsomes is in most cases mediated via Cytochrome P450 3A4 and Uridine 5-diphosphoglucuronosyl transferase. three predominant oxidation products and three essential glucuronides have been diagnosed in vivo. The make contributions to be <1%.[6]

A phase 1 observation assessing the safety and efficacy of Bexagliflozin in sufferers with slight hepatic impairment (Child-Pugh total rating 7 to 9, i.e. magnificence B) showed comparable pharmacokinetic and pharmacodynamic traits to healthful, matched controls. [NCT03557658] this is consistent with the findings and consequent

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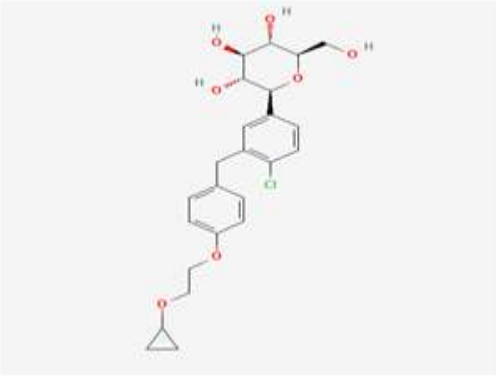
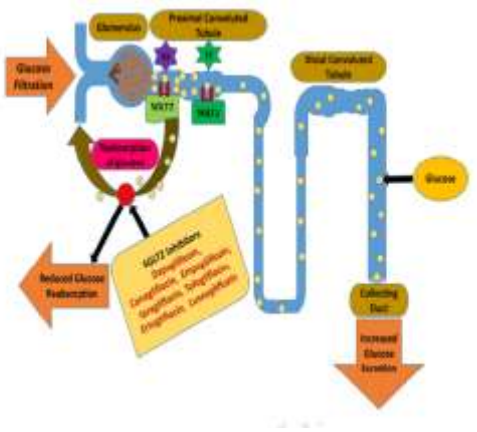
suggestions for other SGLT2 inhibitors in sufferers with moderate-mild hepatic impairment. A single oral dose of Bexagliflozin (20 mg) is hastily absorbed, achieving most plasma awareness at a median of two hours (variety 2 to a few.05 hours). extra these days, a phase 1 have a look at that tested the drug–drug interplay between bexagliflozin and three normally prescribed medicines, probenecid, verapamil, or rifampin showed no clinically relevant effect on bexagliflozin publicity. [NCT03296800] table 2 compares the pharmacological characteristics of Bexagliflozin with those of FDA-approved SGLT2 inhibitors. characteristics of FDA-permitted marketers are adapted from Kuchayet al.[7]

Chemistry And Mechanism Of Action



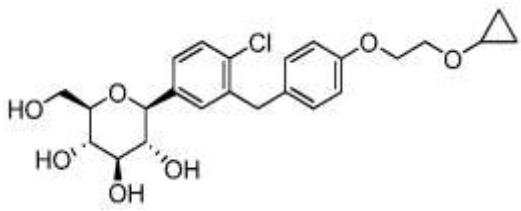
Bexagliflozin [**(2S,3R,4R,5S,6R)-2-[4-chloro-3- ({4-[2-(cyclopropyloxy) ethoxy] phenyl} methyl)phenyl]-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol**] is an orally administered drug for the treatment of Type 2 Diabetes Mellitus (T2DM) and is classified as a Sodium Glucose co-Transporter 2 (SGLT2) Inhibitor. It is in the Phase 2b study to evaluate the effect of bexagliflozin tablets in subjects with type 2 diabetes mellitus.

One promising target for therapeutic intervention in diabetes and related disorders is the glucose transport system of the kidneys. Cellular glucose transport is conducted by either facilitative ("passive") glucose transporters (GLUTs) or sodium-dependent ("active") glucose cotransporters (SGLTs). SGLTl is found predominantly in the intestinal brush border, while SGLT2 is localized in the renal proximal tubule and is reportedly responsible for the majority of glucose reuptake by the kidneys.



Recent studies suggest that inhibition of renal SGLT may be a useful approach to treating hyperglycemia by increasing the amount of glucose excreted in the urine.The capacity of this therapeutic method is further supported using current findings that mutations within the SGL T2 gene arise in cases of familial renal glucosuria, a reputedly benign syndrome characterized through urinary glucose excretion within the presence of ordinary serum glucose degrees and the absence of standard renal disorder or a different disorder. Consequently, compounds that inhibit SGLT, in particular SGL T2, are promising applicants for use as antidiabetic capsules.[8]

STRUCTURAL SIGHTS OF SGLT2



SGLT2 is a 14 transmembrane helical protein situated at the junction among S1 and S2 segments inside the proximal convoluted tubule of the kidney. The helical protein accommodates TM1 to TM14 segments with inverted repeat topology: TM2 to TM6 and TM7 to TM11 are related via nearly approximately 153° rotation parallel to the aircraft of the membrane [9]. Nakka and Guruprasad have defined that the active site of SGLT2 is made up of polar and non-polar amino acid residues. The polar residues are Ser74, Asn75, His80, Glu99, Lys154, Ser287, Lys321, Ser393, Ser396, Gln457 and non-polar residues are Phe98, Ala102, Val286, Trp289, Tyr290, Trp291, Ile397, Phe453, Ile456. The polar amino acid residues may be beneficial for H-bond formation with the

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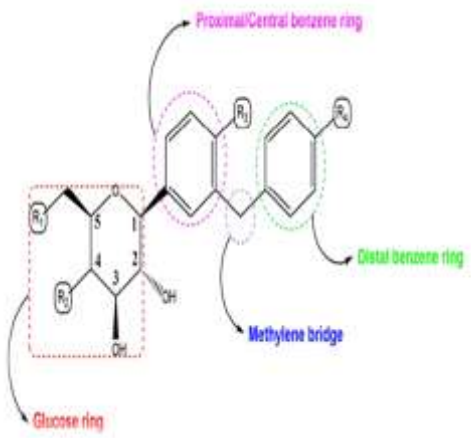
hydroxyl organization of the inhibitors and the non-polar residues can form bonds with the hydrophobic ring device gift within the inhibitor molecule.[10]

Structureactivity Relationship (Sar) Of Gliflozins



Modifications/substitutions in glucose moiety

Only C4 and C6 positions are available for substitution with different groups.

Substitution of the oxime group by replacing hydroxyl at the C6 position of the glucose may potentiate SGLT2 inhibitory activity.

A strong electronegative halogen group (fluoro) substitution at the C4 position in place of the OH group in the sugar nucleus may enhance the SGLT2 inhibitory activity.

Changing the hexose ring with pentose sugar may decrease the activity.

Modifications/substitution in the proximal benzene ring

Benzene ring is essential for SGLT2 inhibitory activity.

Substituting benzene with other aryl or heteroaryl groups may decrease the activity.

Ortho and para positions of the benzene ring are more prone to substitutions.

Ether substitution at the ortho position may potentiate the inhibitory activity while the chlorine group is most favorable at para substitution.

Modification of methylene bridge/linker

This linker is essential for SGLT2 inhibitory activity. Elongation of the methylene bridge into ethylene or propylene may decrease the activity.

Modification of distal benzene ring

The distal benzene ring is not essential for activity and can be replaced by other aryl or heteroaryl ring systems for better inhibitory activity.

Only the para position of the ring system was found to be favorable for substitution, the small alkoxy group can potentiate the inhibitory activity.

SAFETY DATA

Across the aforementioned research, the terrific protection and tolerability of Bexagliflozin became proven. the general detrimental event charges had been commonly balanced between Bexagliflozin and active or placebo comparator treatment fingers. Uncommonly, withdrawal from study participation due to intolerance or remedy-related unfavorable activities passed off. in one study, an affected person within the Bexagliflozin arm advanced an intense urinary tract infection necessitating health center admission.[9] In any other have a look at, a Bexagliflozin recipient evolved a rash that became assessed to be treatment-related by withdrawal and rechallenge.[12]

As predicted with this elegance of GLDs, polyuria, and pollakiuria have been constantly more often found in Bexagliflozin recipients. In all however, in the 96-week trial,[12] genital mycotic infections have been rather greater not unusual in sufferers randomized to Bexagliflozin, which mirrors the aspect effect profile from trials of different members of the magnificence[11,13,14] Hypoglycemia fees and severity have been commonly balanced across the research. The take a look through Allegretti et al. demonstrated Bexagliflozin's safety in sufferers with CKD level 3b. there was a slight growth in serum creatinine and the corresponding decrease in eGFR in contributors assigned to Bexagliflozin, with a rebound to near-baseline values after giving up the treatment length.[14]

II. CONCLUSION

Bexagliflozin belongs to a class of medications called SGLT2 inhibitors, which work by blocking the reabsorption of glucose by the kidneys, leading to increased glucose excretion in urine and lowering blood glucose levels.

According to clinical studies, Bexagliflozin is effective in reducing HbA1c levels (a measure of blood glucose control over the past 2-3 months) in patients with type 2 diabetes, as well as improving other markers of cardiovascular health.

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However, as with any medication, Bexagliflozin may cause side effects, such as increased urination, dehydration, urinary tract infections, and hypoglycemia (low blood glucose). It is important to discuss the risks and benefits of Bexagliflozin with a healthcare provider before starting the medication.

Ultimately, the suitability of Bexagliflozin as a treatment option for type 2 diabetes will depend on individual factors, such as medical history, current medications, and lifestyle.

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