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A Review On Remogliflozin Etabonate

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➢ Abstract:-

A recent addition to the class of SGLT-2 (sodium glucose cotransporter-2) inhibitors made available in India is remogliflozin. In comparison to other gliflozins, the medicine is introduced and sold at a cheaper price range. Because remogliflozin is less expensive than other gliflozins, it is anticipated to become more popular. Still, the It is still unclear if remogliflozin has any practical effect in establishing and preserving blood glucose control. The purpose of this study was to determine whether remogliflozin, as opposed to other gliflozin, is effective in helping individuals with type 2 diabetes maintain glycaemic control. A recent addition to the class of SGLT-2 (sodium glucose cotransporter-2) inhibitors made available in India is remogliflozin. In comparison to other gliflozins, the medicine is introduced and sold at a cheaper price range. Remogliflozin should increase in value. RE is a potent and selective inhibitor of SGLT2 with the unique distinction of being administered as a prodrug, existence of active metabolites, and short half-life necessitating twice-daily dosing. The Phase III study of RE demonstrated it to be an efficacious and safe agent and non-inferior to the currently available SGLT2 inhibitors. This paper reviews not only the pharmacokinetics, pharmacodynamics, clinical efficacy, and safety profile of RE but also its molecular and clinical development program This review has taken into consideration all available published as well as unpublished literature on RE and discusses the individual studies performed during its development for characterization of pharmacological profile.

➢ Introduction

Remogliflozin Etabonate, a sodium-glucose cotransporter subtype 2 (SGLT2) selective inhibitor, is to be supplied as Remogliflozin Etabonate (Remo™, Remozen™), the prodrug for Remogliflozin, and is being developed for the treatment of type 2 diabetes mellitus (T2DM) The preferential expression of SGLT2 in the kidneys causes higher glucose excretion in urine, which lowers blood glucose levels and has been shown to be therapeutically beneficial in type 2 diabetes. Remogliflozin etabonate may also be useful in the management of NASH, according to preliminary studies. Approved to treat type 2 diabetes, Glenmark Pharmaceuticals is now able to sell remogliflozin etabonate in India. The suggested dosage of In India, 100 mg of remogliflozin etabonate is prescribed twice day to treat type 2 diabetes.[(1-4)]

Remogliflozin Etabonate is Effective drug against type 2 diabetes. Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by deteriorating glycaemic control and an associated risk of complications. Evidence from controlled clinical trials suggests that improving glycaemic control can substantially reduce the long-term microvascular complications of diabetes.(4-6) Current guidelines recommend that T2DM patients should be initially managed with diet and exercise followed by pharmacological treatment with metformin as the preferred step 1 agent unless there are contraindications to metformin use. When glycaemic goals are not achieved, the dose of metformin is increased or a second agent is added In this treatment algorithm, suitability for combination with metformin becomes a critical concern in developing new antidiabetic agents. **(7-9)**

❖ Scientific Summary

➢ Pharmacodynamics-

Remogliflozin is a selective inhibitor of SLGT2 with Ki values of 4520 and 12.4 nM for human SLGT1 and 2 respectively in vitro] In vivo, administration of a single oral dose of remogliflozin etabonate to normal mice and rats was associated with a dose-dependent increase in urinary glucose excretion and decreased plasma insulin levels. Administration of a single oral dose dose-dependently inhibited the increase in plasma glucose levels seen after glucose loading in normal and streptozotocin-induced diabetic rats, with a markedly enhanced effect observed in the latter Administration of a single oral dose of remogliflozin etabonate to db/db mice decreased blood glucose and dose-dependently reduced blood glucose AUC6h. Also in db/db mice, oral administration of remogliflozin etabonate daily for 6 weeks was associated with reduced fasting plasma glucose and glycated haemoglobin (HbA1c), and reduced urinary glucose excretion. In high-fat diet-fed Goto-Kakizaki rats, oral remogliflozin etabonate administered for 8 weeks was associated with improvements in hyperglycaemia, hyperinsulinaemia, hypertriglyceridemia, and insulin resistance **(10)** Associated with reduced fasting plasma glucose and glycated haemoglobin (HbA1c), and reduced urinary glucose excretion. In high-fat diet-fed Goto-Kakizaki rats, oral remogliflozin etabonate administered for 8 weeks was associated with improvements in hyperglycaemia, hyperinsulinaemia, hypertriglyceridemia, and insulin resistance.(8) In a murine model of non-alcoholic fatty liver disease (NAFLD), oral administration of remogliflozin etabonate was associated with 76 and 48% reductions in plasma alanine aminotransferase and aspartate aminotransferase levels, respectively, and reduced liver weight by 42% and hepatic triglyceride content by 40%.(9) Administration of remogliflozin etabonate to volunteers (50–1000 mg) and patients with T2DM (50 and 500 mg) was associated with a dose-dependent increase in total urine glucose excretion from 0 to 24 h in a phase I study. The increase in urine glucose excretion was less than proportional with increasing doses, however, indicating a plateau of effect. Urinary glucose excretion was higher in patients with T2DM than in volunteers because of higher plasma glucose concentrations in the former. When urine glucose excretion was corrected according to circulating plasma glucose concentrations and creatinine clearance (to provide an estimate of percentage filtered glucose load), the percentage filtered glucose load was similar in both groups **(10-11)**

➢ Pharmacokinetics-

Following oral administration, remogliflozin etabonate (an ester prodrug) is rapidly absorbed and then extensively de-esterifed in the gastrointestinal mucosa to the active moiety remogliflozin, which appears maximally in plasma. Remogliflozin is metabolised to GSK 279782 (the active metabolite) and GSK 333081, predominantly by cytochrome P450 (CYP) 3A4, before undergoing glucuronidation to form inactive glucuronide conjugates. A single dose mass balance study in healthy volunteers indicated >93% of **(14)** remogliflozin etabonate was absorbed and was predominantly excreted in urine as inactive glucuronide conjugates. Both remogliflozin etabonate and remogliflozin are P-glycoprotein (P-gp) substrates but do not inhibit P-gp. However, as remogliflozin etabonate is almost completely absorbed, P-gp inhibitors are not expected to impact the pharmacokinetic profile of remogliflozin etabonate·**(12)** was 0.4–0.69 h, 1.5–1.9 h and 2.3–3.8 h, respectively [10]. In Indian patients with T2DM, geometric mean remogliflozin Cmax and AUCτ at steady state were ≈559 ng/mL and ≈1861 ng·h/mL, respectively, at 100 mg and ≈1370 ng/mL and ≈4632 ng·h/mL, respectively at 250 mg . Remogliflozin was ≈65% bound to plasma protein. Neither

remogliflozin etabonate nor remogliflozin are preferentially distributed to blood cells and no selective association of remogliflozin etabonate or its metabolites with melanin containing tissues was observed Remogliflozin etabonate is extensively metabolized by CYP3A4 and to a lesser extent by CYP2C19. Co-administration with the potent CYP3A4 inhibitor ketoconazole was associated with only 1.75-fold increase in remogliflozin exposure, indicating a low risk of drug interactions with CYP inhibitors **(12-13)**

The pharmacokinetic profile of remogliflozin etabonate were similar in patients with normal or mild to moderately impaired renal function (creatinine clearance 30–80 mL/min) indicating dose alterations are not required in patients with renal impairment Coadministration of remogliflozin etabonate 500 mg twice daily had no effect on the steady-state pharmacokinetic profile of metformin 500 mg twice daily in a repeat dose study in patients with T2DM (14-15)

For each analyte (metformin, remogliflozin etabonate, remogliflozin, and GSK279782), PK studies of plasma concentration–time data were carried out utilizing the WinNonlin Professional Edition version 4.1 noncompartmental Model 200 (for extravascular administration) (Pharsight Corporation, Mountain View, CA, USA).

Each unique plasma PK parameter was estimated using the actual amount of time that had passed since the dosage. Values for the subsequent PK parameters were determined for each analyte, as suitable, after three days of metformin, remogliflozin etabonate, or both were administered.

- **Therapeutic Trials-**

Type 2 Diabetes Mellitus

A phase III trial that was carried out in India compared the efficacy of dapagliflozin with remogliflozin etabonate. The study was double blind and double dummy. in individuals with T2DM not sufficiently managed by metformin (CTRI2017-07-009121). Patients were randomised to 24 weeks' treatment with remogliflozin etabonate 100 (n = 224) or 250 mg (n = 241) twice daily, or dapagliflozin 10 mg once daily (n = 146). In the per protocol population (163 and 166 remogliflozin etabonate 100 and 250 mg twice daily recipients, respectively, and 101 dapagliflozin recipients), HbA1c levels were reduced by 0.72 and 0.77% from baseline to 24 weeks in the two remogliflozin etabonate groups compared to 0.58% in the dapagliflozin group (non inferiority p 0.05 for all comparisons). Post-prandial plasma glucose were reduced by 39.2 and 41.5 mg/dL in the remogliflozin etabonate 100 and 250 mg twice daily groups, respectively, and 32.4 mg/dL in the dapagliflozin group (p > 0.05 for all comparisons). There was also no significant difference between the three treatment groups in the proportion of patients achieving glycaemic control (HbA1c) (16,12) Phase II The double blind, phase II, dose-ranging, Biphasic Remogliflozin etabonate In Diabetic subjects (BRID) study (NCT02537470) investigated the efficacy of remogliflozin etabonate as a treatment for T2DM. 191 patients were randomized to 12 weeks' treatment with once daily biphasic remogliflozin etabonate or placebo. Placebo adjusted HbA1c levels were reduced 0.44–0.6% in patients treated with remogliflozin etabonate Reductions in body weight and fasting plasma glucose were also observed **(17)**

- **Effect on plasma glucose levels-**

In one pilot study of patients with type 2 diabetes, the effect of RE on lowering plasma glucose was evident early after the first dose and with repeated dosing . In general, the drug efficacy seems greater with b.i.d. compared with q.d. regimen despite higher total daily dose in the q.d. regimen. For instance, compared with placebo, the reduction in fasting plasma glucose levels after 12 days of therapy was 1.3 mmol (23 mg/dl) with RE 100 mg b.i.d. and 2.3 mmol (41 mg/dl) with 1000 mg b.i.d., whereas the reduction was only 0.3 mmol (5 mg/dl), and not statistically significant from placebo, with RE 1000 mg given q.d. . Paradoxically, in the same study, urine glucose excretion and the reduction in systolic blood pressure were greatest in the group that received q.d. dose of RE 1000 mg. (18)

Effect on hemoglobin A1c levels

Results of the two trials that reported the effects of RE on HbA1c levels in drug-naive patients with type 2 diabetes suggest the following conclusions. First, overall the decrease in HbA1c levels in patients randomized to RE compared to placebo ranged from 0.5 to 1.0% after 12 weeks . Second, as in the case of fasting glucose values, RE seemed more effective in decreasing HbA1c levels when given as b.i.d. compared with q.d. administration. Thus, the reduction in HbA1c in patients receiving RE 500 mg given q.d. was only 0.34% (not statistically significant from placebo), whereas the corresponding reduction was 0.59% in the group receiving RE 250 mg b.i.d. This observation is most likely due to the short half-life of RE as mentioned earlier. Third, regarding the dose--response relationship, no increase in efficacy was noticed from RE doses ranging from 50 mg b.i.d. up to 250 mg b.i.d. . However, with greater doses of the drug, efficacy increased non-proportionally with maximum reduction in HbA1c levels of ~ 1% point recorded with the use of RE 1000 mg b.i.d. [19-20]

- **Advantages**

1.Acceptable efficacy with average HbA1c reduction of 0.5 -- 1.0%
2.Mild weight loss
3. Low-risk of hypoglycemia
4.Low potential for the interaction with drugs that inhibit the P450 enzyme system Overall, well-tolerate

- **Limitation-**

1.Twice-daily dosing may be necessary to achieve maximum efficacy
2.Common adverse effects (3 -- 12% versus 0% placebo)
3. genital mycotic infections
4.urinary tract infections
5.dizziness
6.Needs to be evaluated as add-on therapy, in the elderly, and in patients with chronic kidney disease Lack of long-term safety and efficacy data

- **Effects of RE on blood pressure**

The use of approved SGLT2 inhibitors was associated with mean reduction of systolic and diastolic blood pressure of 4.0 mmHg and 1.6 mmHg, respectively, compared with baseline . The decrease in blood pressure is most likely due to osmotic diuresis, but mild weight loss may be another contributing factor. Unfortunately, the effect of RE on blood pressure is not well studied. In one study, there was a mean significant reduction of 9 mmHg in systolic blood pressure in a small group of nine patients with type 2 diabetes randomized to RE 1000 mg q.d. after 12 day of therapy, but no significant decrease in blood pressure was observed in other groups receiving 100 and 1000 mg b.i.d. [20-21]

- **Effects of RE on plasma lipid**

For unclear reasons, the use of approved SGLT2 inhibitors was associated with dose-related increases in plasma concentrations of low-density lipoprotein-cholesterol (LDL-C) . In the case of RE, no significant changes were recorded in plasma levels of LDL-C, high-density lipoprotein-cholesterol, total cholesterol, and triglycerides with q.d. dosing after 12 weeks of therapy . Meanwhile, with the b.i.d. administration, significant increases from baseline in LDL-C levels of 13.2% with RE 250 mg b.i.d. and 11.9% with RE 500 mg b.i.d. were noted [9]. The increase in LDL-C levels with the b.i.d. regimen was accompanied by significant increases in high-density lipoprotein-cholesterol concentrations of 5.8 -- 13.6% relative to baseline and decreases in triglycerides of ~ 5 -- 10% . Clearly, the increase in plasma levels of LDL-C associated with various SGLT2 inhibitors is concerning, and its impact on cardiovascular events needs to be carefully examined. [22-23]

➢ **Adverse Events-**

The most commonly reported adverse reactions occurring in patients treated with remogliflozin etabonate in the phase III trial described above (CTRI2017-07-009121) included urinary tract infection (4.9%), pyrexia (2.7%), headache (2.5%), bacteriuria (2.3%), constipation (1.7%), diarrhoea (1.7%), decreased glomerular filtration rate (1.7%), ketonuria (1.7%), cough (1.5%), dyslipidaemia (1.5%), asthenia (1.0%), viral upper respiratory tract infection (RTI) (1.0%), hypoglycaemia (1.0%) and orthostatic hypotension (1.0%)Hypoglycaemia was reported in similar proportions of patients receiving remogliflozin or dapagliflozin as add-on treatment to metformin in the phase III trial Vulvovaginitis, balanitis and related genital infections, all of which were mild to moderate in severity and responded to an initial course of standard treatment, were reported in 1.8% and 1.2% of remogliflozin etabonate 100 and 250 mg recipients and in 2.7% of dapagliflozin recipients. Urinary tract infections were reported in 3.1% and 6.6% remogliflozin etabonate 100 and 250 mg recipients and in 2.1% of dapagliflozin recipients. Dehydration or hypovolaemia was not reported in remogliflozin or dapagliflozin recipient **(24)**

➢ **Current Status**

Remogliflozin etabonate received its first global approval on 30 April 2019 for the treatment of adults with T2DM in India **(25)**

➢ **Expert opinion-**

No doubt, the introduction of the new class of SGLT2 inhibitors was a welcome addition to the treatment of type 2 diabetes. As result of their unique mechanism of action, they can be used as monotherapy or add-on therapy to other diabetes medication while maintaining their efficacy [15,16]. Other advantages of SGLT2 inhibitors include low risk of hypoglycemia, mild weight loss, and decrease in blood pressure. Moreover, accumulating data suggest that SGLT2 inhibitors may be effective in type 1 diabetes. In general, available information suggests that RE shares the currently available SGLT2 the same advantages. However, the relatively short half-life of RE may make it slightly more effective when given b.i.d., a feature that may compromise compliance in some patients. Meanwhile, this limitation can be overcome if RE can be delivered in the future in fixed combination with metformin in a single tablet administered b.i.d. Available limited data suggest that RE is generally well-tolerated. Its safety profile is overall similar to other SGLT2 inhibitors. Thus, genital mycotic infections, UTI, and dizziness were the three most common adverse effects. However, the reassuring safety data of RE should be interpreted with caution because of exclusion of vulnerable patient populations from clinical trials, such as the elderly and those with any degree of renal dysfunction. Indeed, the efficacy of SGLT2 inhibitors decreases with worsening renal function, in large part due to decreased urine output [15,16]. In addition, the use of approved SGLT2 inhibitors is not recommended in the presence of various degrees of chronic kidney disease (CKD) because of concern about worsening renal function . Indeed, the longest-term available data showed significant mean reduction of 6.6% in estimated glomerular filtration rate in patients with Stage III CKD (defined as estimated glomerular filtration rate between 30 and 49 ml/min/1.73 m2) after 52 weeks of canagliflozin 300 mg/d versus placebo [22] Thus, RE use in patients with CKD should be studied thoroughly, particularly that renal excretion represents the major route of drug elimination [10]. In this respect, a recent Phase I study showed that administration of a single dose of RE 250 mg in patients with mild and moderate CKD was not associated with significant increase in plasma exposure to the drug [25]. However, there was 34 -- 51% increase in plasma exposure of the active metabolite GSK27982 and prolongation of time of its detection in plasma, up to 24 h in patients with moderate CKD compared with up to 16 h in subjects with normal kidney function or those with mild CKD [25] Therefore, further studies are needed to examine safety and possible accumulation of RE or its active metabolites in patients with CKD. Moreover, in order to better define the role of RE in diabetes management, ongoing and future studies should evaluate the use of RE in the following settings: as add-on therapy to other diabetes therapy, in the elderly, and in type 1 diabetes. More importantly, the long-term safety of RE and its impact on cardiovascular morbidity and mortality should be carefully examined. (26-28)

➢ **References-**

1) Kapur A, O'Connor-Semmes R, Hussey EK, et al. First human dose-escalation study with remogliflozin etabonate, a selective inhibitor of the sodium-glucose transporter 2 (SGLT2), in healthy subjects and in subjects with type 2 diabetes mellitus. BMC Pharmacol Toxicol. 2013;14(26):1–11.

2) Glenmark Pharmaceuticals. Glenmark launches novel, globallyresearched anti-diabetes drug remogliflozin in India [media release]. 30 Apr 2019. https://www.prnewswire.com/in/news-releases/glenmark-launches-novel-globally-researched-anti-diabetesdrug-remoglifozin-in-india-806614073.html.

3) Wilkison B, Cheatham B, Walker S. Remogliflozin etabonate reduces FIB-4 and NAFLD fbrosis scores in type 2 diabetic subjects [abstract no. 1087]. Hepatology. 2016;64(1 Suppl.):548A.

4) Glenmark Pharmaceuticals. Remogliflozin etabonate 100 mg tablets: proposed summary of product characteristics. 2019

5) DCCT Research Group: The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. Diabetes 1995, 44:968–983.

6) Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995, 28:103–117.

7) Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J 2000, 321:405–412

8) American Diabetes Association: Standards of medical care in diabetes. In PhD Thesis; 2007.

9) Nathan D, Buse J, Davidson M, Heine R, Holman R, Sherwin R, Zinman B: Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. Diabetologia 2006, 49:1711–1721.

10) Nakano S, Katsuno K, Isaji M, et al. Remogliflozin etabonate improves fatty liver disease in diet-induced obese male mice. J Clin Exp Hepatol. 2015;5(3):190–8.

11) Kapur A, O'Connor-Semmes R, Hussey EK, et al. First human dose-escalation study with remogliflozin etabonate, a selective inhibitor of the sodium-glucose transporter 2 (SGLT2), in healthy subjects and in subjects with type 2 diabetes mellitus. BMC Pharmacol Toxicol. 2013;14(26):1–11

12) Glenmark Pharmaceuticals. Remogliflozin etabonate 100 mg tablets: proposed summary of product characteristics. 2019

13) Glenmark Pharmaceuticals. Remogliflozin etabonate 100 mg tablets: proposed summary of product characteristics. 2019.

14) O'Connor-Semmes R, Walker S, Kapur A, et al. Pharmacokinetics and pharmacodynamics of the SGLT2 inhibitor remogliflozin etabonate in subjects with mild and moderate renal impairment. Drug Metab Dispos. 2015;43(7):1077–83

15) . Hussey EK, Kapur A, O'Connor-Semmes R, et al. Safety, pharmacokinetics and pharmacodynamics of remogliflozin etabonate, a novel SGLT2 inhibitor, and metformin when co-administered in subjects with type 2 diabetes mellitus. BMC Pharmacol Toxicol. 2013;14(25):1–11.

16) IND Committee. Minutes of IND committee meeting held on 15.03.2019 at ICMR (HQ). Agenda no. 3: application for marketing authorization of remogliflozin of M/s Glenmark Pharmaceuticals. 2019. https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadCommitteeFiles/IND15mar19.pdf. Accessed 3 May 2019.

17) Avolynt. Avolynt, Inc. announces positive topline data for phase 2b BRID study of SGLT2 remogliflozin [media release]. 19 Dec 2016. http://www.avolynt.com

18) Dobbins RL, O'Connor-Semmes R, Kapur A, et al. Remogliflozin etabonate, a selective inhibitor of the sodiumdependent transporter 2 reduces serum glucose in type 2 diabetes mellitus patients. Diabetes Obes Metab 2012;14:15-22

19) Sykes AP, Kemp GL, Dobbins R, et al. Randomized efficacy and safety trial of once-daily remogliflozin etabonate for the treatment of type 2 diabetes. Diabetes Obes Metab 2014;98-98:101

20) Dobbins RL, O'Connor-Semmes R, Kapur A, et al. Remogliflozin etabonate, a selective inhibitor of the sodiumdependent transporter 2 reduces serum glucose in type 2 diabetes mellitus patients. Diabetes Obes Metab 2012;14:15-22

21) Baker WL, Smyth LR, Riche DM, et al. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systemic review and meta-analysis.

22) Sykes AP, O'Connor-Semmes R, Dobbins R, et al. Randomized trial showing efficacy and safety of twice-daily remogliflozin etabonate for the treatment of type 2 diabetes. Diabetes Obes Metab 2015;17:94-7

23) Sykes AP, Kemp GL, Dobbins R, et al. Randomized efficacy and safety trial of once-daily remogliflozin etabonate for the treatment of type 2 diabetes. Diabetes Obes Metab 2014;98-98:101

24) Sykes AP, O'Connor-Semmes R, Dobbins R, et al. Randomized trial showing efficacy and safety of twice-daily remogliflozin etabonate for the treatment of type 2 diabetes. Diabetes Obes Metab 2015;17:94-7

25) Glenmark Pharmaceuticals. Glenmark launches novel, globallyresearched anti-diabetes drug remogliflozin in India [media release]. 30 Apr 2019. https://www.prnewswire.com/in/news-releases/glenmark-launches-novel-globally-researched-anti-diabetesdrug-remoglifozin-in-india-806614073.html

26) Mikhail N. Place of sodium-glucose type 2 co-transporters inhibitors in treatment of type 2 diabetes. World J Diab 2014;5(6):854-9

27) Mikhail N. Use of sodium-glucose cotransporter type 2 inhibitors in older adults with type 2 diabetes mellitus. South Med J 2015;108:1-6

28) O'Connor-Semmes R, Walker S, Kapur A, et al. Pharmacokinetics and pharmacodynamics of the SGLT2 inhibitor remogliflozin etabonate in subjects with mild to moderate renal impairment. Drug Metab Dispos 2015;43:1077-83