Remogliflozin: the new low cost SGLT-2 inhibitor for type 2 diabetes mellitus

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Abstract

SGLT-2 inhibitors have recently emerged as an important class of oral drugs for treatment of type 2 diabetes mellitus, especially in patients with cardiovascular or renal impairment, recommended in all recent treatment guidelines. They have additional advantages of weight and blood pressure reduction but also pose problems like genitourinary infections. These drugs generally have a high cost making affordability a major consideration in their prescription in developing countries like India. A new molecule remogliflozin has been approved in India in 2019 after a phase 3 trial proved its efficacy and safety in comparison to dapagliflozin. This drug has been priced substantially lower than other SGLT-2 inhibitors, and despite the disadvantage of twice daily administration, it potentially reduces treatment cost to less than half compared to other molecules of this class. With a good tolerability profile on the basis of available safety data till date, remogliflozin could be a useful alternative for providing SGLT-2 inhibitor therapy in a country like India where out of pocket expenses for drug acquisition matter significantly for the general population. However, long term safety and efficacy data especially on cardiovascular and renal outcomes are currently lacking for the drug.

Keywords Remogliflozin · SGLT-2 inhibitors · Type 2 diabetes mellitus · Cost

Introduction

Sodium glucose co-transporter 2 inhibitors (SGLT2 i's) are a prominent class of new generation oral drugs for type 2 diabetes mellitus (T2DM), which act by enhancing urinary glucose excretion to reduce blood glucose levels. Their peculiar insulin-independent mode of action provides benefit in patients with diminished pancreatic function or insulin resistance. They improve glycemic control, cause weight loss, decrease blood pressure, and are known to improve renal function and reduce cardiovascular risks. SGLT2 i's are especially effective in patients with hypertension and high risk of hypoglycemia [1].

SGLT2 i's are generally recommended as an important alternative or add on drug when metformin therapy fails in the management of T2DM by the American Diabetes Association (ADA) 2020 and the European Association for the Study of Diabetes (EASD) guidelines 2019, and hold a similar place in therapeutic recommendations in the recently released Indian guidelines for T2DM [1–3]. Atherosclerotic Cardiovascular Disease (ASCVD), Heart Failure (HF) and Chronic Kidney Disease (CKD) have been estimated to affect 15–25% of the T2DM population. SGLT-2 i's with proven benefits (empagliflozin > canagliflozin) are now recommended to be included as first choice drugs beyond metformin in the treatment regimens of T2DM individuals with established ASCVD and/or HF and/or CKD if estimated glomerular filtration rate (eGFR) is adequate (≥ 45 ml/min/1.73m²) [4]. In such individuals, reduction of CVD events, HF and CKD progression has been demonstrated with these agents. Without established ASCVD and CKD, SGLT2 i's are also recommended beyond metformin when considerations of minimizing hypoglycemia and promoting weight loss are there [1–3]. The three SGLT-2 i's commonly used worldwide—canagliflozin (100 mg, 300 mg), dapagliflozin (5 mg, 10 mg) and empagliflozin (10 mg, 25 mg) were

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approved in Nov 2014, Feb and May 2015 respectively in India [5, 6]. Remogliflozin is a novel SGLT-2 inhibitor to get approval exclusively in India in April 2019 and this review elucidates the clinical profile of this drug with a focus on its therapeutic potential in light of its significantly lower price.

Search strategy

To find evidence and data for reviewing the potential clinical utility of remogliflozin in light of its recent market launch, publications on clinical efficacy and safety, and costing of drugs for diabetes in India, a search was carried out using PubMed (Medline), Cochrane Library, Google Scholar search engines from 2010–2020. The search terms identified and used were “remogliflozin”, “SGLT-2 inhibitor”, “diabetes”, “cost” as the key terms extracted from the titles and abstracts of the relevant studies for different sections of the review. While Searching with Pubmed search engine, Medical subject headings (MeSH terms), subheadings and “All Fields” were combined with Key Boolean operators “AND”, “OR”, and “NOT” to get the relevant studies and exclude studies which do not match the requirements. Additionally hand/bibliography searching were performed along with accessing related data from commercial drug directories (for cost) and web resources as well as published treatment guidelines. Research articles, review articles, editorials were identified and reviewed. Both abstracts and full text articles in English language were included.

Remogliflozin: approval

Remogliflozin was initially discovered by a Japanese company Kissei Pharmaceutical, and was later developed by GlaxoSmithKline and Glenmark collaborator BHV Pharma [7]. Globally twenty six reported trials have been conducted for remogliflozin including 2500 patients from various ethnicities [8]. Three clinical trials, a phase 3 study and two pharmacokinetic (PK) studies, were conducted in India (CTRI/2017/06/0088887, CTRI/2017/07/009121 and CTRI/2017/10/010043) for this drug [9–11]. After completing the phase-3 clinical trial in which remogliflozin etabonate proved its efficacy and safety in comparison with dapagliflozin, Glenmark pharmaceuticals received regulatory approval for 100 mg tablets to be given twice daily for T2DM in April 2019 [12, 13]. Subsequently, Glenmark commercially launched remogliflozin in India, for which marketing was then taken up by an Indian firm Torrent pharmaceuticals through a sub-licensing agreement [14, 15]. In August 2019, regulatory approval was also received to market fixed dose combination tablets of remogliflozin etabonate and metformin hydrochloride in India in strengths of 500 mg or 1000 mg of metformin with 100 mg of remogliflozin

[16]. A prospective active post marketing surveillance study to assess safety and effectiveness of remogliflozin and remogliflozin-metformin combination in management of T2DM in real world setting (REFORM INDIA trial—CTRI/2019/11/022062) has been initiated in November 2019 [17, 18]. Besides these Indian studies, currently a phase II trial for Non Alcoholic Steato Hepatitis—remogliflozin etabonate In NASH patients (REIN) study is underway in US. In May 2019, a phase-I trial of remogliflozin for obesity was discontinued in US along with a phase-I trial for type 1 diabetes mellitus for undisclosed reasons [7].

Pharmacological profile

Remogliflozin Etabonate (RE) is a prodrug of the active moiety remogliflozin, indicated in treatment of T2DM. Remogliflozin is administered as a prodrug to prevent its hydrolytic degradation [19]. It is a potent and selective O-glycoside inhibitor of SGLT-2 as identified initially by studying COS-7 cells transiently expressing either high-affinity sodium glucose cotransporter (SGLT)—1 or 2 ($K_{is} = 12.4$ nM for humans) [20]. Its active moiety has a shorter half-life of 1.39 h compared to other SGLT2 i's, necessitating twice daily administration [Sykes]. Remogliflozin is metabolized to GSK 279782 (active metabolite) and GSK 333081 predominantly by CYP3A4. Other inactive metabolites include GSK355993, GSK1997711 and GSK19997714. RE metabolites are eliminated primarily via the renal route, and more than 90% of the dose is recovered in the urine [21]. CYP3A4 contributes less than 50% to remogliflozin metabolism, and other enzyme pathways like other CYP enzymes, UDP-glucuronosyl transferases, and glucosidases are also significant [22]. Dose-dependent increase in 24-h urinary glucose excretion has been seen which plateaus at doses ≥ 150 mg [23].

Clinical evidence available

Prior to the conduct of clinical studies in India which led to the approval of remogliflozin, a series of studies have been conducted in US showing the preliminary safety and efficacy of the drug. The first study on assessment of safety, tolerability along with pharmacokinetics/pharmacodynamics of RE, published in 2011, was conducted on 35 subjects with T2DM. It showed that the drug was well tolerated, and resulted in clinically significant reduction in plasma glucose at doses of 100 and 1000 mg BID along with improved body weight and blood pressure [24]. RE was evaluated in type 1 diabetes in 10 subjects at a dose range of 50–500 mg as an add on to basal insulin and showed significant increase in glucose excretion

and decrease in blood glucose compared to placebo [25]. Further a dose escalation, crossover, double blinded RCT was conducted on 10 healthy and 6 T2DM subjects at a dose range of 20–1000 mg of RE in 4:1 and 2:1 active to placebo ratio per treatment period. This study showed that the drug was well-tolerated with no serious adverse events. In all subjects, there was rapid absorption with the time to maximum plasma concentration [C_{max} ; T_{max}] being approximately ~ 1 h, and rapid elimination. There was dose-dependent increase in urinary glucose excretion. In T2DM subjects, there was reduction in plasma glucose following OGTT, and no effects on electrolyte levels [23].

To assess efficacy of RE, first an investigation of once daily dosing for T2DM was done in a 12 week double blind RCT in 252 newly diagnosed patients in a dose range of 100–1000 mg versus placebo and pioglitazone. There was a dose dependent response in the primary outcome parameters of HbA1c reduction from the baseline ($p=0.047$), with good tolerability among the subjects [26]. RE was then evaluated in a twice daily dosing regimen in the same dose range in a similar study design in 336 treatment naïve T2DM patients. A dose ordered response in HbA1c reduction and body weight versus placebo was seen [27].

In India, an open label, single treatment, single period, single oral dose Pharmacokinetic (PK) study of remogliflozin etabonate 250 mg tablet in normal, healthy, adult male subjects under fasting condition was first carried out carried out in June 2017 [11]. Another open label, single-treatment study to assess the PK and safety of remogliflozin etabonate 100 mg and 250 mg in 65 healthy adult male subjects under fasting and/or fed condition, was conducted in October 2017 [10].

Subsequently, a 24-week, randomized, double blind, double-dummy parallel group, multi-centre, active-controlled phase 3 trial was started in July 2017 to evaluate efficacy and safety of remogliflozin etabonate versus dapagliflozin in subjects with T2DM having inadequate glycemic control on a stable dose of metformin (≥ 1500 mg) [9]. In this study, conducted on 612 subjects, the change in HbA1c from baseline to 24 weeks was -0.58 , -0.72 and -0.77% respectively with dapagliflozin 10 mg, remogliflozin 100 mg and remogliflozin 250 mg establishing the non-inferiority of remogliflozin with dapagliflozin ($p<0.001$). Proportion of subjects achieving glycemic control, defined as HbA1c $<7\%$ at 24 weeks, was more with both the remogliflozin groups (36.4% and 37.1%) compared with dapagliflozin (30.3%); but the difference was not statistically significant. The change from baseline in fasting plasma glucose (FPG) at week 24 for dapagliflozin, remogliflozin 100 mg and remogliflozin 250 mg was -20.45 mg/dL, -17.54 mg/dL and -20.51 mg/dL respectively and the postprandial plasma glucose (PPG) reduction was -31.1 mg/dL, -37.2 mg/dL and -39.0 mg/dL respectively. There was no statistical

difference ($p>0.05$) between the 2 doses of remogliflozin versus dapagliflozin in FPG and PPG reduction [13, 28].

Outside of India, the topline results of a twelve-week double blinded phase 2b clinical trial—the Biphasic Remogliflozin Etabonate In Diabetic subjects (BRID) study, which was conducted at twenty sites across the United States from 2015 to 2016, have been declared. In this dose ranging study, three doses of remogliflozin, plus placebo, were administered to 191 randomized individuals with T2DM. Significant reductions in placebo-adjusted HbA1c ranging from 0.44 to 0.6%, in body weight, FPG, and systolic (-2.4 to -5.6 mmHg) and diastolic (-1.7 to -3.7 mmHg) blood pressure were seen with remogliflozin [29].

Safety

Studies with remogliflozin, while showing an average HbA1c reduction of 0.5–1%, weight loss and low risk of hypoglycemia, have also demonstrated good tolerability, and a low potential of interaction with drugs that inhibit cytochrome P450 enzymes because of the involvement of multiple biotransformation pathways [30]. Alternative contraceptive methods are advised while taking this drug, since absorption of oral contraceptives has been shown to be affected [13]. Approximately 0–11% and 0–4% cases reported genital fungal infections and urinary tract infections respectively in various studies [13, 30, 31]. Headache, diarrhea and constipation are the other adverse events reported in the completed trials [23, 27]. In one of the studies, isolated events of hyperhidrosis, flatulence, dysuria and genital pruritus were reported for 100 mg BD dose given in 9 individuals with T2DM [24]. In another study, the rate of adverse events reported was higher at a higher dose of 250 mg (31–59% in the once-daily and 56% in the twice-daily treatment groups) than pioglitazone (34%) and placebo groups (22%) [26]. Single and multiple dose treatment at doses up to 1000 mg BID and 4000 mg QD have also been well tolerated [13].

It is pertinent to note that some major concerns have been raised for the other available SGLT-2 i's like risk of amputation (canagliflozin), diabetes ketoacidosis (rare in type2 diabetes), genitourinary infection, volume depletion, hypotension, increased LDL cholesterol, risk of acute kidney injury, increased risk of fractures, and more recently the risk of Fournier's gangrene [30, 31]. In August 2018, the US FDA raised a black box warning for serious infections of pancreas and genitals with SGLT-2 i's. In March 2019, the Indian drug regulator (DCGI) made provisions for gathering information on adverse drug reactions or any signals on SGLT-2 i's emphasizing the potential risk of acute pancreatitis and Fournier's gangrene in Indian patients. Subsequently, a safety warning was instructed to be printed on the

label of SGLT-2 i's by its manufacturers in India for cases of necrotizing fasciitis of perineum or Fournier's gangrene [32, 33].

Whether the above serious concerns are a class effect, thereby expected to also be seen with remogliflozin, is not known yet. Safety data from clinical trials in vulnerable patient populations such as elderly patients, pregnant women is not available for this drug. No dose adjustment of remogliflozin is indicated in patients with mild and moderate renal impairment, similar to other SGLT2 i's [21]. No data is available yet on remogliflozin in moderate to severe renal impairment where other SGLT-2 i's require monitoring, and are contraindicated in severe renal impairment [4]. Long term safety data from cardiovascular outcome trials (CVOTs) are missing as of now for remogliflozin, which is available for other SGLT2 i's through trials such as EMPAREG OUTCOME, CANVAS, DECLARE-TIMI [34–36]. There are limited number of efficacy trials which have been conducted, primarily in the Indian population. No multicentric trials have been done in US or Europe yet.

Pharmacoeconomic consideration: the price picture

Diabetes care is expensive because of the chronic nature and complications of the condition. The ADA estimated that total costs of diabetes management have increased from \$245 billion to \$327 billion in 5 years (2012–2017) in USA. The growing burden of diabetes is posing an even more serious challenge to the under resourced health care systems in countries like India. A significant proportion of

the world's diabetes burden, second highest in the world, is represented by India with an estimated 77 million cases in 2019, this is expected to almost double to 134 million by 2045 [37]. As per definition of the world bank, more than 30% of the Indian population lives below poverty line defined as monthly income of less than approximately INR 2208 (~USD 29) [38]. Estimates have shown that in India, approximately 33% and 10% of individuals with diabetes spend 5% and 20% of their family income respectively on their treatment [39]. In recent studies, and in diabetes prescription audit at our own tertiary care center, the mean cost of diabetes management has been estimated to range approximately from INR 400–900 (~USD 5–12) per month [40, 41].

These statistics clearly show that diabetes imposes a significant economic burden on individuals and their families in terms of higher out-of pocket health care payments, and loss of financial gain related to incapacity and premature loss of life. India's SGLT2 i's market size was estimated at INR 5740 million (~USD 73 million) in March 2019 [14]. Treatment with SGLT2 i's is particularly expensive because of the high retail costs of the available formulations as evident from Table 1. Among these drugs, the leader is empagliflozin, which recorded 28% sales growth [42]. The table below gives a comparative estimate of the prices of various SGLT-2 i's and their brands in India vis a vis the newly launched remogliflozin (Table 1).

The prices of currently available SGLT2 i's range somewhere between INR 45–60 (~USD 0.6–0.85) per tablet leading to a monthly expense of approximately INR 1500 (~USD 20) whereas remogliflozin is priced at almost one fourth of these drugs at INR 12.5 per tablet, ~USD 0.17

Table 1 Comparative costs of SGLT-2 inhibitors available in Indian market

Drug	Manufacturer	Brand name	Dose (in mg)	Price per tablet (in INR)
Remogliflozin	Glenmark pharmaceuticals	Remo	100	12.5 (\$ 0.17)
		Remo-Zen	100	12.5 (\$ 0.17)
	Mankind Pharma Ltd	Sgltr	100	12.6 (\$ 0.17)
		Torrent Pharmaceuticals Ltd	Zucator 100	12.6 (\$ 0.17)
Empagliflozin	Lupin Pharmaceuticals, Inc	Gibtulio	25	57 (\$ 0.76)
			10	47 (\$ 0.63)
	Boehringer Ingelheim	Jardiance	25	57 (\$ 0.76)
			10	47 (\$ 0.63)
Dapagliflozin	Sun Pharmaceutical Industries Ltd	Oxra	10	52 (\$ 0.69)
			5	50 (\$ 0.67)
	AstraZeneca plc	Forxigo	10	52 (\$ 0.69)
			5	50 (\$ 0.67)
	Abbott	Gledepa	10	52 (\$ 0.69)
			5	50 (\$ 0.67)
Canagliflozin	Johnson & Johnson Ltd	Invokana	100	54.5 (\$ 0.73)
	USV Ltd	Sulisent	100	55 (\$ 0.74)
	Janssen Pharmaceuticals	Motivyst	300	120 (\$ 1.6)

(INR 25, ~USD 0.35 per day with twice daily dosing) and thus would literally reduce the monthly expense to half in comparison [43]. Remogliflozin at this significantly cheaper price may emerge like teneligliptin, which disrupted its category with its reduced price and similar safety profile among the DPP IV inhibitors. In 2015, teneligliptin was launched in India at the lowest price in its drug class i.e. DPP4 inhibitors, at INR 19.90 (~USD 0.27) per day which was approximately one third or even lesser the price of the other drugs of its class [44]. It has since become one of the preferred treatment options for T2DM in the country especially at government health facilities because of its further reduced price and availability under the Indian government's generic drug scheme for the masses as at INR 4.95 (~USD 0.07) [45]. Similar to teneligliptin, vildagliptin is also now available at significantly cheaper price in the country since it has gone off patent recently (December 2019) and cheaper generic versions of this popular drug are available in the Indian market [46, 47].

A flipside for remogliflozin, however, is the requirement of twice daily dosing which may hamper adherence by increasing the daily pill burden for diabetes which is likely to be already high for individuals requiring SGLT-2 inhibitor therapy. Still, the affordability of therapy may positively enhance adherence and the clinical utility of this drug in diabetes therapeutics. For that, it needs to be backed by continued evidence of efficacy and safety in future studies including post marketing surveillance and planned CVOTs in future to address cardiac and/or renal safety and benefits.

Conclusion

There are many established and inexpensive or relatively affordable drug options available for T2DM beyond metformin like sulfonylureas, teneligliptin, vildagliptin, pioglitazone. So a molecule like remogliflozin is unlikely to become the first choice add-on therapy in terms of its cost effectiveness. But, being more than 50% cheaper than the existing drugs of the same class in the market, it may take up the mantle of the preferred SGLT-2 inhibitor primarily where affordability is the main consideration. With the diabetes epidemic reaching alarming proportions in a country like India, remogliflozin will significantly reduce the drug cost burden when SGLT-2 i's need to be included as part of the treatment regimen for T2DM for specific subsets of patients. The relative affordability of remogliflozin may change the perception regarding SGLT-2 i's, which are not frequently prescribed as of yet mainly due to high cost and safety concerns. It may prove to be a very promising drug for T2DM provided that future evidence maintains and confirms the effectiveness and safety profile of the drug.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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References

1. American Diabetes Association. 9 Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2020. *Diabetes Care*. 2020;43:S98–110.
2. Indian Council of Medical Research. ICMR Guidelines for Management of Type 2 Diabetes 2018. <https://medibulletin.com/wpcontent/uploads/2018/05/ICMR.diabetesGuidelines.2018.pdf>. Accessed 26 Nov 2019.
3. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the task force for Diabetes, pre diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2020;4:255–323.
4. Betonico CC, Titan SM, Correa-Giannella ML, et al. Management of diabetes mellitus in individuals with chronic kidney disease: therapeutic perspectives and glycemic control. *Clinics*. 2016;71:47–53.
5. Central Drugs Standards Control Organisation. Approval of dapagliflozin and empagliflozin. List of approved drugs from 01-01-2015 to 31-01-2015. <https://cspc.in/dic/pdf/Approved%20drugs%20In%20India%20Year%202015.pdf>. Accessed 20 Dec 2019.
6. Central Drugs Standards Control Organisation. Approval of canagliflozin. Drugs approved from 1st Jan 2014 to 31 december 2014. https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MzIyOA==. Accessed 20 Dec 2019.
7. Remogliflozin etabonate—Avolynt/Kissei-Pharmaceutica. <https://adisinsight.springer.com/drugs/800021813>. Accessed 26 Nov 2019.
8. Avolynt, Inc. Announces First Marketing Authorization and Commercial Launch of Novel SGLT2 Inhibitor Remogliflozin Etabonate for Type 2 Diabetes. https://13e7f770-4ade-43d5-8f6a-6c643672a9c0.filesusr.com/ugd/e4def4_76977eb2388d40afbcc14bf28561fe89.pdf. Accessed 28 Nov 2019.
9. Clinical trials registry-India. CTRI /2017/07/009121. <https://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=19549&EncHid=&userName=remogliflozin>. Accessed 26 Nov 2019.
10. Clinical trials registry-India. CTRI/2017/10/010043. <https://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=20565&EncHid=&userName=remogliflozin>. Accessed 26 Nov 2019.
11. Clinical trials registry-India. CTRI/2017/06/008887. <https://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=19284&EncHid=&userName=remogliflozin>. Accessed 26th Nov 2019.
12. Central Drugs Standards Control Organisation. List of new drugs approved in the year 2019 till date. <https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadApprovalNewDrugs/newdruaaopvalariol.pdf>. Accessed 26 Nov 2019.

13. 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 26 Nov 2019.
14. Glenmark Pharma launches anti-diabetes drug Remogliflozin in India. <https://economictimes.indiatimes.com/markets/stocks/news/glenmark-pharma-launches-anti-diabetes-drug-remogliflozin-in-india/articleshow/69109769.cms?from=mdr>. Accessed 10 Dec 2019.
15. Press Release. Glenmark & Torrent sign licensing agreement for co-marketing of Remogliflozin Etabonate in India. <https://www.glenmarkpharma.com/sites/default/files/Glenmark-%26-Torrent-sign-licensing-agreement-for-co-marketing-of-Remogliflozin-Etabonate-in-India.pdf>. Accessed 26 Nov 2019.
16. Press Release. Glenmark receives approval for combination of Remogliflozin Etabonate and Metformin Hydrochloride for adults with type 2 diabetes in India. <https://www.glenmarkpharma.com/sites/default/files/Glenmark-receives-approval-for-combination-of-Remogliflozin-Etabonate-an.pdf>. Accessed 26 Nov 2019.
17. Clinical trials registry-India. A post marketing study to evaluate safety and effectiveness of Remogliflozin and Remogliflozin-Metformin Combination in treatment of Diabetes patients. <https://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=36536&EncHid=&userName=remogliflozin>. Accessed 26 Nov 2019.
18. IND Committee. Minutes of IND committee meeting held on 10.06.2019 at ICMR (HQ). Agenda no. 4: Application for marketing authorization of Remogliflozin and Metformin of M/s Glenmark Pharmaceuticals. 2019. <https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadCommitteeFiles/INDCommitteeheldonjun19.pdf>. Accessed 28 Nov 2019.
19. Dash RP, Babu RJ, Srinivas NR. Comparative pharmacokinetics of three SGLT-2 inhibitors sergliflozin, remogliflozin and ertugliflozin: an overview. *Xenobiotica*. 2016;47:1015–26.
20. Fujimori Y, Katsuno K, Nakashima I, et al. Remogliflozin etabonate, in a novel category of selective low-affinity sodium glucose cotransporter (SGLT2) inhibitors, exhibits antidiabetic efficacy in rodent models. *J Pharmacol Exp Ther*. 2008;327:268–76.
21. 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.
22. Sigafos JF, Bowers GD, Castellino S, et al. Assessment of the drug interaction risk for remogliflozin etabonate, a sodium-dependent glucose cotransporter-2 inhibitor: evidence from in vitro, human mass balance, and ketoconazole interaction studies. *Drug Metab Dispos*. 2012;40:2090–101.
23. 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;14:1–11.
24. Dobbins RL, O'Connor-Semmes R, Kapur A, et al. Remogliflozin etabonate, a selective inhibitor of the sodium dependent transporter 2 reduces serum glucose in type 2 diabetes mellitus patients. *Diabetes ObesMetab*. 2012;14:15–22.
25. Mudaliar S, Armstrong DA, Maviani AA, et al. Remogliflozin etabonate, a selective inhibitor of the sodium-glucose transporter 2, improves serum glucose profiles in type 1 diabetes. *Diabetes Care*. 2012;35:2198–200.
26. 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. *DiabetesObesMetab*. 2014;98–98:101.
27. 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. *DiabetesObesMetab*. 2015;17:94–7.
28. Dharmalingam M, Aravind SR, Thacker H, et al. Efficacy and safety of remogliflozin etabonate, a new sodium glucose co-transporter-2 inhibitor, in patients with type 2 diabetes mellitus: a 24-week, randomized, double-blind, active-controlled trial. *Drugs*. 2020;80:587–600.
29. Avolynt, Inc. Announces Positive Topline Data for Phase 2b BRID Study of SGLT2 Remogliflozin. https://13e7f770-4ade-43d5-8f6a-6c643672a9c0.filesusr.com/ugd/e4def4_f13db80522d64501810463a93434bd81.pdf. Accessed 26 Nov 2019.
30. Mikhail N. Remogliflozin etabonate: a novel SGLT2 inhibitor for treatment of diabetes mellitus. *Expert OpinInvestig Drugs*. 2015;24:1–7.
31. Donnan JR, Grandy CA, Chibrikov E, et al. Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis. *BMJ Open*. 2019;9:e022577.
32. Drug Watch. SGLT2 Inhibitors Side Effects. <https://www.drugwatch.com/sgl2-inhibitors/side-effects/>. Accessed 26 Nov 2019.
33. Food and Drug Administration. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrences-serious-infection-genital-area-sgl2-inhibitors-diabetes>. Accessed 26 Nov 2019.
34. India: DCGI Asked Manufacturers To Write Safety Warning For SGLT2 Inhibitors. <https://www.mondaq.com/india/x/799006/Healthcare/DCGI+Asked+Manufacturers+To+Write+Safety+Warning+For+SGLT2+Inhibitors> Accessed 26 Nov 2019.
35. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:211728.
36. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–57.
37. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–57.
38. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. <https://www.diabetesatlas.org>. Accessed 28 Nov 2019.
39. Bhalla SS. India is middle income country now: raise the poverty line. <https://indianexpress.com/article/opinion/columns/india-is-middle-income-now-raise-the-poverty-line-5239269/>. Accessed 26 Nov 2019.
40. Thakur A, Ray TK, Goel MK. Expenditure pattern on diabetes care: a community based longitudinal study in resettlement colony of East Delhi. *Indian J Community Health*. 2017;29:209–12.
41. Fernandes SD, Fernandes SDA. Economic burden of diabetes mellitus and its socio-economic impact on household expenditure in an urban slum area. *Int J Res Med Sci*. 2017;5:1808–13.
42. Kumar A, Nagpal J, Bhartia A. Direct cost of ambulatory care of type 2 diabetes in the middle and high income group populace of Delhi. *J Assoc Physician India*. 2008;56:667–74.
43. Pharma may see a price war in good news for diabetics. <https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/pharma-may-see-a-price-war-in-good-news-for-diabetics/articleshow/69122707.cms?from=mdr>. Accessed 26 Nov 2019.
44. Glenmark brings new diabetes drug Remogliflozin to India. <https://www.thehindubusinessline.com/companies/glenmark-pharma-launches-anti-diabetes-drug-remogliflozin-in-india/article26990038.ece>. Accessed 26th Nov 2019.
45. Glenmark launches Tenueligliptin—an advanced Diabetes treatment at significantly affordable cost in India. <https://mdcurrent.in/press-releases/glenmark-launches-tenueligliptin-an-advanced-diabe>

- [tes-treatment-at-significantly-affordable-cost-in-india/](#). Accessed 26 Nov 2019.
46. Pradhan mantra bhartiya jan aushadhi yojana Kendra. <https://janau.shadhi.gov.in/Data/pmbjp-book.pdf>. Accessed 26 Nov 2019.
47. Sharma EK. Diabetes drug price to halve as patent expires; cheaper versions expected soon. <https://www.businesstoday.in/sectors/pharma/diabetes-drug-price-to-halve-as-patent-expires-cheaper-versions-expected-soon/story/391768.html>. Accessed 28 Mar 2020.

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