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SGLT2 Inhibitor and DPP4 Inhibitor Co-Administration In Type 2 Diabetes -Are We Near The "Promised Land"?

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Research Article

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ABSTRACT

Diabetes is progressive disease needing multiple drugs for achieving and maintaining good glycemic control. The drugs with different mechanisms of action are administered either alone or as fixed dose combinations. Usually the combined effect of each is less than the added effect except with Metformin DPP-4 inhibitor combination because they seldom complement/synergise each other's action. More of such effective drug combinations that provide glycemic control are needed. SGLT 2 inhibitor, when combined with DPP4 inhibitor has the potential to be that ideal combination. Both of these drugs address different pathophysiological mechanisms for hyperglycemia and when combined provide reductions in HbA1c level with no inherent risk of hypoglycaemia. Genitourinary infection, a major hindrance with SGLT 2 inhibitor use are potentially reduced when it is combined with DPP4 inhibitor, which also can counteract the increase in glucagon level produced by the former. Cost, differing applicability in patients with renal dysfunction and limited clinical experience restricts the universal application of this combination as first line agents.

INTRODUCTION

Diabetes is a chronic disease that affects a large percentage of population around the world and has assumed epidemic dimensions [1,2]. The majority of these cases, approximately 90%, are of type 2 diabetes. The estimated number of diabetic patients in the world was 171.2 million (2.8%) in the year 2000 and 382 million (8.3%) in the year 2013 predicted to be 366.2 million (4.4%) by the year 2030 [3]. Of this 61.3 million patients were in India in the year 2011, and this number is expected to become close to 101.2 million in the year 2030 [4]. The prevalence of type 2 diabetes is rapidly increasing, particularly among older, overweight persons who have concomitant cardiovascular (CV) risks [5].

Type 2 Diabetes is caused by insulin resistance as well as decrease in insulin secretion [6] though there are other contributors. As the disease progresses there is a gradual but relentless decline in the beta cell function [7] necessitating up gradation of the initially chosen drug with addition of more [8], eventually culminating in the use of insulin [9]. Co administration of drugs targeting different pathophysiological processes precedes the use of insulin and if these are in the form of fixed drug combinations there is better compliance of the patient who is taking many drugs addressing other components of the disease viz: hypertension, dyslipidemia etc.; While many drug combinations most containing Metformin are approved for use, each has its own limitations and some need multiple dosing.

SGLT 2 inhibitor (SGLT2i) is a novel agent which offers the advantage of action independent of insulin and has been approved for use in Type 2 diabetes mellitus at various stages of the disease even as first line [10,11]. The article explores the issues and advantages of its combination with DPP4 inhibitor (DPP4i).

SGLT2 INHIBITOR

SGLT inhibitors block the SGLT2 protein [10-12], which plays an important role in absorption of glucose from proximal convo-

luted tubule, resulting in increased renal glucose excretion and lower blood glucose levels. These agents also increase insulin sensitivity, decrease gluconeogenesis, and improve insulin release from pancreatic beta cells by improving glucotoxicity [13,14]. However these agents are known to increase Glucagon secretion, by a mechanism as yet unknown [15].

Different types of SGLT2 inhibitors are-

- Dapagliflozin
- Canagliflozin
- Ipragliflozin (ASP-1941), in Phase III clinical trialsTofogliflozin, in Phase III clinical trials
- Empagliflozin (BI-10773)
- Sergliflozin etabonate, discontinued after Phase II trials
- Remogliflozin etabonate, in Phase IIb trials
- Ertugliflozin (PF-04971729 / MK-8835), in Phase III clinical trials
- Luseogliflozin, in Phase III clinical trials
- Fogliflozin, in Phase III clinical trials

DPP4 INHIBITORS

Dipeptidyl-peptidase 4 (DPP-4) inhibitors block the action of DPP-4, an enzyme which inactivates the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).Incretins stimulate insulin secretion and suppress glucagon secretion in glucose dependent manner [16]. There are currently five marketed DPP-4 inhibitors (Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin and Alogliptin) approved in different regions of the world.

RATIONALE FOR COMBINING MULTIPLE MEDICATIONS

Type 2 diabetes is progressive disorder and as beta cell function decreases over time, patient needs multiple medications. For better glycemic control we have for long relied on combination of therapeutic agents that target both insulin resistance as well as defects in insulin secretion. With unraveling of additional contributors to hyperglycemia newer combinations have been added and the last one was that of Metformin and DPP-4 inhibitors. For better results the drug combination could possess one or more of the following attributes: [17- 21]

- Target different pathologic process
- Synergism
- Augmentation
- Improved tolerability by minimizing/counteracting the adverse effects of the individual component

When co administered the patient has the convenience of having to take less number of pills, with better compliance and reduced potential for dosing errors.

Combination of DPP4 inhibitor and SGLT2 inhibitor may reach this IDEALISTIC GOAL.

Advantages of combination of DPP4 inhibitor and SGLT2 inhibitor include

1. SGLT2 inhibitors increase glucagon levels, by an as yet to be understood mechanism [22] and it is hypothesized that this effect has compromised the efficacy of SGLT2 inhibitors. DPP-4 inhibitors by increasing incretin levels (GLP-1 and GIP) [23-25], inhibit glucagon release; there is thus synergy in action, a much desired characteristic in any combination [26-29].

2. The HbA1c lowering of SGLT2 inhibitors is approximately 0.5%-0.8% [30] and that of DPP4 inhibitors is 0.43%-1.17% [31]. In head to head trials SGLT2 inhibitors cause better lowering of HbA1c than DPP4 inhibitors A recent study compared the effect of add-on Dapagliflozin and Saxagliptin singly or in combination in patie

3. nts with background Metformin monotherapy failure. Patients on Saxagliptin alone had a HbA1c reduction of 0.9%, Dapagliflozin a reduction of 1.2% and those with the combination had a reduction of 1.5% [22,23,29-31].

As expected the impact is more when the baseline HbA1c is >8.5%.

4. This combination has another desirable trait, that of improving tolerability. The most common adverse effect of SGLT2 inhibitors is increased propensity to genital infection, which is about four times more than that occurring in the placebo group. In a study subjects receiving the combination of Saxagliptin and Dapagliflozin drugs showed no evidence of genital infection [31], this finding need to be studied further as the same was not seen when Empagliflozin was combined with Linagliptin [32].

5. There is a potential of Reno protective effect with these drugs. Several studies have shown a reduction in micro albuminuria with DPP4 inhibitors [33,34] and SGLT2 inhibitors [35-37].

6. These drugs also can be used as add-on to insulin therapy in patients with Type 1 Diabetes. DPP4 inhibitor through a possible immunomodulatory effect and the SGLT2 inhibitor through their renal action. This is being investigated, though with individual agents [38,39].

7. The other advantage is the dose does not need titrations, a bane in anti-diabetic therapy.

The other advantages offered by these medications are

1. Lack of hypoglycemia is an attribute of both the agents by virtue of their mechanism of action. SGLT2 inhibitors do not cause insulin release [40-43] and DPP-4 inhibitors release it in a glucose sensitive manner [44, 45].

2. Weight loss attributable to the SGLT2 inhibitors is approximately in the range of 1-5 kgs [46-53] which is initially due to osmotic diuresis [54] and later to caloric loss with predominant reduction of (visceral) fat mass [55,56]. DPP-4 inhibitors are weight neutral [57-60].

3. Blood pressure reduction–Effects of blood pressure control especially on the micro vascular complications have amply been demonstrated by the UKPDS, ADVANCE, and other studies. Decreases in systolic (4–7 mm of Hg) and diastolic blood pressure (1–3 mm of Hg) have been observed in patients treated with SGLT2 inhibitors [46,53,54,61,62]. These decreases in blood pressure may be related to SGLT2 inhibitor–induced diuresis [63] and body weight changes. There is a blood pressure lowering data with DPP-4i as well (SBP: 2–3 mm of Hg, DBP: 1.6-1.8 mm of Hg) [28]. This would be of benefit to patients with blood pressures slightly above target.

4. Decreased levels of plasma uric acid with SGLT2 inhibitors [64,65]. The high concentration of glucose in the tubule favors the exchange of glucose for urate, resulting in increased excretion of urate in the urine [66].

So far fixed dose combination of oral anti-diabetics have always included Metformin along with one or more of the other class of drugs viz. Sulfonylureas, Thiazolindiones, α-Glucosidase inhibitors, DPP 4 inhibitors, SGLT2 inhibitors . With discovery of additional mechanisms causing hyperglycemia, there is a scope for more combination.

A combination of a SGLT2 inhibitor and a DPP4 inhibitor fulfils the criteria listed earlier. These drugs have different mechanism of action, target different pathways in the pathological process. They neither interact with each other, nor do they alter each other's pharmacokinetic and pharmacodynamic profile [30]. While the SGLT2 inhibitors cause weight loss, the DPP4-inhibitors cause glucagon suppression overcoming the theoretical disadvantage conferred by its elevation with the use of SGLT2 inhibitors. Both intrinsically do not cause hypoglycemia and have blood pressure lowering capabilities and the risk of genital infections caused by SGLT2 inhibitors is substantially reduced when they are combined. Combinations of both these agents have synergistic effect and lead to better glycemic control.

LIMITATIONS

Both the agents have modest HbA1c lowering capabilities and would not be as potent as the Metformin - Sulphonylurea or Metformin and DPP-4i which are cheaper and/or available for a longer time. However since the combined HbA1c lowering capability is in the neighborhood of 1.5%, their addition after Metformin failure is likely to cover a vast majority of subjects without the risk of hypoglycemia.

The combination is not possible with Vildagliptin which needs to be dosed twice daily whereas the SGLT2i need a single daily dosing. Further the SGLT-2 inhibitors cannot be used across all degrees of renal insufficiency while DPP-4 inhibitors can be though some require dose modification. Combination of Linagliptin and SGLT-2 inhibitor is theoretically ideal and can be used till the GFR of 30 ml/min/1.73 m^2 with Canagliflozin [67] and 60 ml/min/1.73 m^2 with Dapagliflozin and Empagliflozin. The combination of Dapagliflozin and Saxagliptin [68] for instance can be used till GFR of 60 ml/min/1.73 m^2 and not beyond and while these could still be administered individually to get the best for the patient the other advantages of a fixed dose combination would be lost.

The compulsions of the manufacturer to stick to the molecules discovered/developed by them may limit the formation of the ideal formulation and the cost would be another limiting factor restricting its use. The combinations currently undergoing clinical trials include Linagliptin+Empagliflozin, Saxagliptin+Dapagliflozin, Sitagliptin+Ertugliflozin and Linagliptin+BI 38335. This only underscores the fact that the manufacturers should be willing to join hands and not tether themselves to their own molecules.

CONCLUSION

A fixed dose combination of DPP4 inhibitor and SGLT2 inhibitor could be novel addition to our armamentarium against diabetes. The combination of SGLT2 inhibition and DPP4 inhibitor is likely to emerge as an ideal combination approach for type 2 diabetes. This will offer excellent glycemic lowering efficacy with the added benefit of weight loss and low risk of hypoglycemia, with each agent targeting a different part of the pathophysiology of type 2diabetes. It would provide the best of both drugs while minimizing the adverse effects of each. Further research will help establish the role of such therapy in the future management of type 2 diabetes.

REFERENCES

1. Dunstan DW, et al. The rising prevalence of diabetes and impaired glucose tolerance: The Australian diabetes, obesity, and lifestyle study. Diabetes Care. 2002;25:829-834.
2. Rizvi AA. Type 2 diabetes: epidemiologic trends, evolving pathogenic concepts, and recent changes in therapeutic approach. South Med J. 2004;97:1027-1008.
3. Wild S, et al. Global prevalence of diabetes, estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27:1047-1053.
4. International diabetes Federation 2012. (5thedn). The Global burden.
5. Carver C. Insulin treatment and the problem of weight gain in type 2 diabetes. Diabetes Educ. 2006;32:910–917.
6. Cavaghan MK, et al. Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. J Clin Invest. 2000;106:329–333.
7. UK Prospective Diabetes Study Group. Overview of 6 years' therapy of Type II diabetes: a progressive disease. Diabetes. 1995;44:1249–1258.
8. Turner RC, et al. Glycaemic control with diet, sulfonylurea, metformin, or insulin in patients with Type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA. 1999;281:2005–2012.
9. Nathan DM, et al. Medical management of hyperglycemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2009;52:17–30.
10. Silvio E Inzucchi, et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach: Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care January. 2015;38:140-149.
11. Alan J Garber, et al. American Association of Clinical Endocrinologists' Comprehensive Diabetes Management Algorithm. Endocr Pract. 2013;19:1-48.
12. Marsenic O. Glucose control by the kidney: an emerging target in diabetes. Am J Kidney Dis. 2009;53:875–883.
13. Rossetti L, et al. Effect of chronic hyperglycemia on in vivo insulin secretion in partially pancreatectomized rats. J Clin Invest. 1987;80:1037-1044.
14. Rossetti L, et al. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987;79:1510–1515.
15. Nair S, et al. From history to reality: sodium glucose co-transporter 2 inhibitors—a novel therapy for type 2 diabetes mellitus. Pract Diabetes Int. 2010;27:311–316.
16. Drucker DJ. Dipeptidyl peptidase-4 inhibition and the treatment of Type 2 diabetes: preclinical biology and mechanisms of action. Diabetes Care. 2007;30:1335–1343.
17. Taylor AA. Combination drug treatment of hypertension: have we come full circle? Curr Cardiol Rep. 2004:6:421-426.
18. Orloff DG. Fixed combination drugs for cardiovascular disease risk reduction: regulatory approach. Am J Cardiol. 2005;96:28K-33K.
19. Frank J. Managing hypertension using combination therapy. Am Fam Physician. 2008;77:1279-1286.
20. Bell D. Current status of diabetes treatment. South med J. 2002;95. Medscape website. www.medscape.com/viewarticle/426918.
21. Bangalore S, et al. fixed dose combinations improve medication compliance: a metaanalysis. Am J Med. 2007;120:713-719.
22. Ahrén B, et al. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab. 2004;89:2078-2084.
23. McIntosh C, et al. "Dipeptidyl peptidase IV inhibitors: How do they work as new anti-diabetic agents?" Regulatory Peptides. 2005;128:159–165.
24. Behme. "Glucagon-like peptide 1 improved glycemic control in type 1 diabetes". BMC Endocrine Disorders. 2003:3:3.
25. Dupre J, et al. "Glucagon-like peptide I reduces postprandial glycemic excursions in IDDM". Diabetes. 1995;44:626–630.
26. Hansen L, et al. Postprandial dynamics of plasma glucose, insulin, and glucagon in patients with type 2 diabetes treated with saxagliptin plus dapagliflozin add-on to metformin therapy. Endocr Pract. 2014;20:1187-1197.
27. Mikhail N, et al. Place of sodium-glucose co-transporter type 2 inhibitors for treatment of type 2 diabetes. World J Diabetes. 2014;5:854-859.

28. Dror Dicker. DPP-4 Inhibitors Impact on glycemic control and cardiovascular risk factors. Diabetes Care. 2011; 34:S276-S278.

29. Jabbour SA, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care. 2014;37:740-750.

30. Chen L, et al. Effects of Combining Linagliptin treatment with BI-38335, A Novel SGLT2 Inhibitor, on Pancreatic Islet Function and Inflammation in db/db Mice. Curr Mol Med. 2012;12:995-1004.

31. Rosenstock J, et al. Dual Add-on Therapy in Type 2 Diabetes Poorly Controlled With Metformin Monotherapy: A Randomized Double-Blind Trial of Saxagliptin Plus Dapagliflozin Addition Versus Single Addition of Saxagliptin or Dapagliflozin to Metformin. Diabetes Care. 2014;38:376-383.

32. Dr. R DeFronzo, et al: Fixed dose combinations of empagliflozin/linagliptin for 52 weeks as add-on to metformin in subjects with type 2 diabetes.Available at: http://www.easdvirtualmeeting.org/resources/16837. Accessed on 13 Jan 2015.

33. Hattori S. Sitagliptin reduces albuminuria in patients with type 2 diabetes. Endocr J. 2011;58:69–73.

34. Groop PH, et al. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care. 2013;36:3460–3468.

35. Yale JF, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;15:463–473.

36. Barnett AH, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2014;2:369–384.

37. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM336236.pdf

38. Henry RR, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. Diabetes Care. 2015;38:412-419.

39. Bruce A Perkins, et al. Odd-Erik Johansen Sodium-Glucose Cotransporter 2 Inhibition and Glycemic Control in Type 1 Diabetes. Diabetes Care. 2014;37:1480-1483.

40. McCrimmon RJ. AICAR and phlorizin reverse the hypoglycemia-specific defect in glucagon secretion in the diabetic BB rat. Am J Physiol Endocrinol Metab. 2002;283:E1076–E1083.

41. Han S, et al. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. Diabetes. 2008;57:1723–1729.

42. Rossetti L, et al. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest. 1987;79:1510–1515.

43. Rajesh R, et al. Sodium Glucose Co transporter 2 (SGLT2) Inhibitors: A New Sword for the Treatment of Type 2 Diabetes Mellitus. Int Jour Pharma Sci and Research (IJPSR). 2010;1:139-147.

44. Jabbour SA, Goldstein BJ. Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycemic control in patients with diabetes. Int J Clin Pract. 2008;62:1279–1284.

45. Boldys A and Okopien B. Inhibitors of type 2 sodium glucose co-transporters–a new strategy for diabetes treatment: Review. Pharmacol Rep. 2009;61:778–784.

46. Wilding JPH, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. Ann Intern Med. 2012;156:405–415.

47. Nauck MA, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care. 2011;34:2015–2022.

48. Inagaki N, et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2 (SGLT2) improves glycemic control and reduces body weight in Japanese type 2 diabetes mellitus (T2DM). Diabetes. 2011;60:A274.

49. Ferrannini E, et al. The potent and highly selective sodium-glucose co-transporter (SGLT-2) inhibitor BI10773 is safe and efficacious as monotherapy in patients with type 2 diabetes mellitus. Diabetologia. 2010;53:S351.

50. Bailey CJ, et al. Long-term efficacy of dapagliflozin as add-on to metformin (MET) in T2DM inadequately controlled with MET alone. Diabetes. 2011;60:A271.

51. Rosenstock J, et al. Efficacy and safety of BI 10773, a new sodium glucose cotransporter-2 (SGLT-2) inhibitor, in type 2 diabetes inadequately controlled on metformin. Diabetes. 2011;60:A271.

52. Kashiwagi A, et al. ASP1941, selective SGLT2 inhibitor, was effective and safe in Japanese healthy volunteers and patients with type 2 diabetes. Diabetes. 2010;59:75.

53. Ferrannini E, et al. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care. 2010;33:2217–2224.

54. Bailey CJ, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, double-blind, placebo-controlled trial. Lancet. 2010;375:2223–2233.

55. Bolinder J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012;97:1020–1031.

56. Wilson PW, et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med. 2002;162:1867–1872.

57. Scott R, et al. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract. 2007;61:171–180.

58. Hanefeld M, et al. Once-daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. Curr Med Res Opin. 2007;23:1329–1339.

59. Rosenstock J, et al. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. Diabetes Obes Metab. 2008;10:376–386.

60. Chacra AR, et al. Saxagliptin added to a submaximal dose of sulphonylurea improves glycaemic control compared with uptitration of sulphonylurea in patients with type 2 diabetes: a randomised controlled trial. Int J Clin Pract. 2009;63:1395–1406.

61. Strojek K, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2011;13: 928–938.

62. Amin NB, et al. The sodium glucose co-transporter-2 (SGLT2) inhibitor, PF04971729, yielded BP lowering in hypertensive patients with type 2 diabetes mellitus (T2DM). Diabetes. 2011;60:LB14.

63. List JF and Whaley JM. Glucose dynamics and mechanistic implications of SGLT-2 inhibitors in animals and humans. Kidney Int Suppl. 2011;120:S20–S27.

64. Musso G, et al. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med. 2012;44:375–393.

65. Chino Y, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria Biopharm Drug Dispos. 2014;35:391-404.

66. Cheeseman C. Solute carrier family 2, member 9 and uric acid homeostasis. Curr Opin Nephrol Hypertens. 2009;18:428–432.

67. Janssen-Cilag Pty Ltd. Invokana, Approved Product Information 2012. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf.

68. Bristol-Myer Squibb Australia Pty. Ltd. Dapagliflozin (Forxiga) Approved Product Information 2012. https://www.ebs.tga.gov.au/ebs/picmi/picmirepos itory.nsf/pdf