Type 2 Diabetes Mellitus: Glycemia Treatment

CHI Formulary Indication Review

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INDICATION UPDATE

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ADDENDUM to the CHI Original Diabetes Type 2 Clinical Guidance- Issued November 2019

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Abbreviations

ACT: Appropriate Comparator Therapy

ADA: American Diabetes Association

ASCVD: Atherosclerotic Cardiovascular Disease

BG: Blood Glucose

CADTH: Canadian Agency for Drugs and Technologies in Health

CDC: Centers for Disease Control and Prevention

CHI: Council of Health Insurance

CKD: Chronic Kidney Disease

CSII: Continuous Subcutaneous Insulin Infusion

CVD: Cardiovascular Disease

DM2: Diabetes Mellitus Type 2

DPP-4 Inhibitors: Dipeptidyl Peptidase-4 Inhibitors

GLP-1 Receptor Agonists: Glucagon-Like Peptide-1 Agonists

HAS: Haute Autorité de Santé

HF: Heart Failure

HHF: Hospitalization for Heart Failure

HTA: Health Technology Assessment

IDF: International Diabetes Federation

IQWIG: Institute for Quality and Efficiency in Health Care

MACE: Major Adverse Cardiovascular Events

MEN2: Multiple Endocrine Neoplasia Syndrome Type 2

MTC: Medullary Thyroid Carcinoma

NAFLD: Non-Alcoholic Fatty Liver Disease

NCD: Non-Communicable Disease

NICE: National Institute for Health and Care Excellence
PBAC: Pharmaceutical Benefits Advisory Committee

PG: Plasma Glucose

SGLT2 Inhibitors: Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

SNAC: Salcaprozate Sodium

TZD: Thiazolidinediones

WHO: World Health Organization

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Executive Summary

Diabetes Mellitus Type 2 (DM2), a non-communicable disease (NCD), is a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency. This results in elevated blood glucose levels, which can lead to a range of complications including cardiovascular disease, neuropathy, retinopathy, and renal disease. The impact of diabetes goes beyond individual health, placing a significant burden on healthcare systems and economies. The direct and indirect costs associated with diabetes management, including medical care, medications, and lost productivity, are substantial. These costs strain healthcare resources and pose challenges for individuals and societies worldwide.[1]

DM2 is a global health problem affecting millions of people worldwide. In 2021, the International Diabetes Federation (IDF) estimated that there were 537 million adults living with diabetes globally, and this number is projected to rise to 643 million by 2045.[2]

In Saudi Arabia, the prevalence of DM2 is particularly high, with an estimated 23.9% of the adult population affected. This is likely due to a combination of genetic and lifestyle factors, including a high prevalence of obesity and physical inactivity. The burden of diabetes in Saudi Arabia is expected to continue to rise, with projections suggesting that the prevalence of DM2 could reach 33.4% by 2030.[3]

Recognizing the urgency of addressing diabetes as a global health challenge, the World Health Organization (WHO) has prioritized diabetes prevention and control as part of its NCD agenda. The organization aims to promote healthy lifestyles, strengthen healthcare systems, improve access to essential medicines, and enhance diabetes management and care.[1]

The management of DM2 is based mainly on lifestyle modifications, drug therapy, and controlling risk factors. There are several classes of medications that can be used to lower blood glucose levels and reduce the risk of complications. These include metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and others. Treatment is typically individualized based on factors such as patient age, comorbidities, and glucose control. Combination therapy with multiple medications is often necessary to achieve optimal glycemic control. In addition to drug therapy, lifestyle modifications such as dietary changes, weight loss, and physical activity are also important for the management of DM2.

CHI issued Diabetes type 2 clinical guidance after thorough review of renowned international and national clinical guidelines in November 2019. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Diabetes Type 2 clinical guidance and seeks to offer guidance for the effective management of Diabetes Type 2. It provides an **update on the Diabetes Type 2 Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** the 2023 ADA Guidelines on pharmacologic approaches to glycemic treatment and 2022 Consensus Report of The ADA/EASD guidelines, the 2022 NICE Management of Type 2 Diabetes in Adults guidelines and the 2022 AACE Diabetes Mellitus Clinical Practice Guideline along with an algorithm (2023). Moreover, **new guidelines are added to the report** such as the Saudi Diabetes Clinical Practice Guidelines by the Saudi National Diabetes Center (SNDC) at the Saudi Health Council (2021), the Australian Evidence Based Clinical Guidelines for Diabetes (2021), and the Diabetes Canada Clinical Practice Guidelines Pharmacologic Glycemic Management of Type 2 Diabetes in Adults (2020).

Other triggers include **a new drug submission** for oral Semaglutide (Rybelsus), the **SFDA registration of new drugs** to treat DM2 such as Ertugliflozin, Semaglutide (SQ injection and oral tablet), Tirzepatide, Insulin/GLP-1 RAs fixed ration combinations (Degludec-Liraglutide and Glargine-Lixisenatide) and **the approval of non-SFDA registered drugs** as Bexagliflozin and newly introduced extended-release tablets consisting of a combination of empagliflozin, linagliptin, and metformin hydrochloride.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Type 2 Diabetes Mellitus therapeutic management.

Below is a table summarizing the major changes based on the different Type 2 Diabetes Mellitus guidelines used to issue this report:

Table 1: General Recommendations Regarding Type 2 Diabetes Mellitus Management

Management of Type 2 DM		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Metformin is the first-line medication for management of type 2 diabetes mellitus and has beneficial effects on A1C, weight, and cardiovascular mortality.	Grade A	Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023[4]
In patients with contraindications or intolerance of metformin, initial therapy should be based on patient factors; consider a drug from another class: sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitor, sodium glucose cotransporter 2 (SGLT2) inhibitor, GLP-1 receptor agonist (GLP1-RA), or basal insulin.	Grade A	Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023[4]
Consider initiating stepwise dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5-2.0% above their glycemic target.	Grade A	Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023[4]
The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (>300mg/dL [16.7mmol/L]) are very high.	Grade E	Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023[4]
If insulin is used, combination therapy with a GLP1-RA is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit.	Grade A	Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023[4]
Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk	Grade A	Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023[4]

reduction, independent of A1C and in consideration of person-specific factors. GLP-1 medications with ASCVD benefits: Dulaglutide, Liraqlutide, Semaglutide (SQ).		
If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved.	Strong Recommendation	NICE Type 2 Diabetes in Adults: Management (Published in 2015 – Last Updated in 2022)[5]
In adults with type2 diabetes, if metformin is contraindicated or not tolerated and if they don't have chronic heart failure, established ASCVD, or are at high risk of developing cardiovascular disease, consider initial drug treatment with: a DPP-4 inhibitor, pioglitazone, a sulfonylurea, or an SGLT2 inhibitor.	Strong Recommendation	NICE Type 2 Diabetes in Adults: Management (Published in 2015 – Last Updated in 2022)[5]
The addition of a DPP-4 inhibitor is suggested to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor or a GLP-1 receptor agonist due to either intolerance or contraindication.	Conditional Recommendation, High	Australian Evidence-Based Clinical Guidelines for Diabetes - Living Evidence for Diabetes Consortium[6]
For adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for further intervention intensification, consider either: Triple therapy by adding a DPP-4 inhibitor, pioglitazone or a sulfonylurea or an SGLT2 inhibitor **OR** starting insulin-based treatment	Strong Recommendation	NICE Type 2 Diabetes in Adults: Management (Published in 2015 – Last Updated in 2022)[5]
Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), Degludec (U100 or U200), or detemir are preferred.	Grade A	NICE Type 2 Diabetes in Adults: Management (Published in 2015 – Last Updated in 2022)[5]
When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins.	Grade A	NICE Type 2 Diabetes in Adults: Management (Published in 2015 – Last Updated in 2022)[5]

Ertugliflozin may be used as an adjunctive agent or alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or who cannot take metformin.	No stated level of evidence	SFDA Drug List[7], Lexicomp[8], CenterWatch[9]
Tirzepatide is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	No stated level of evidence	SFDA Drug List[7], Lexicomp[8], CenterWatch[9]
Semaglutide is recommended to be used as an adjunctive agent or alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or those who cannot take metformin. It is preferred in patients who have or are at risk for atherosclerotic cardiovascular disease, when weight loss is desired, and/or in patients with an HbA1c relatively far from goal and type 1 diabetes is not likely.	No stated level of evidence	SFDA Drug List[7], Lexicomp[8], CenterWatch[9]
The Degludec-Liraglutide combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).	No stated level of evidence	SFDA Drug List[7], Lexicomp[8], CenterWatch[9]
The Glargine-Lixisenatide combination is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	No stated level of evidence	SFDA Drug List[7], Lexicomp[8], CenterWatch[9]

The following table details the different HTA recommendations issued for each SFDA-registered new molecule.

Table 2. HTA Analysis for SFDA-Registered New Molecules

SFDA-Registered New Molecules	HTA Recommendations
Ertugliflozin	Positive Recommendation from NICE[10] and PBAC[11]. Negative Recommendation from CADTH[12], HAS[13] and IQWIG[14]. The negative recommendations are attributed to the lack of sufficient evidence.
Tirzepatide	HTA analysis is still underway by NICE[15] and CADTH[16].
Semaglutide	Positive Recommendation from CADTH[17], HAS[18] (For the SQ formulation) and PBAC[19].

	Negative Recommendation from IQWIG[20] and HAS[18] (For the oral formulation).
Degludec-Liraglutide	Positive Recommendation from CADTH[21] and HAS[22]. Negative Recommendation from IQWIG[23]. The negative recommendation is attributed to lack of sufficient evidence.
Glargine-Lixisenatide	Positive Recommendation from CADTH[24]. Negative Recommendation from HAS[25] and PBAC[26]. HAS: The negative recommendation is attributed to the lack of evidence and absence of conclusive new data. (Insufficient clinical benefit) PBAC: The negative recommendation is attributed to the absence of a strong clinical need for insulin glargine with Lixisenatide due to other PBS listed treatment options.

In section 2, the drug therapy is discussed, encompassing an examination of the aforementioned drugs regarding their regulatory status, safety profile, indications and utilization, along with a summary review of HTA bodies. The section concludes by presenting a conclusive statement regarding the appropriateness of the therapy's implementation.

At the end of the report, **a key recommendation synthesis section is added highlighting the use of each drug class in specific groups of patients.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts; one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Type 2 Diabetes Mellitus report, and the other part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

The following segment contains the updated versions of the guidelines mentioned in the November 2019 CHI Type 2 Diabetes Mellitus Report and the corresponding recommendations:

Table 3: Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 The American Diabetes Association (ADA) pharmacologic approaches to glycemic treatment: standard of medical care in diabetes-**[2019]** and Consensus Report of The American Diabetes Association (ADA) with the European Association for the Study of Diabetes (EASD) guidelines **[2018]**	American Diabetes Association (ADA) pharmacologic approaches to glycemic treatment: standards of care in diabetes – **[2023]** and Consensus Report of The American Diabetes Association (ADA) with the European Association for the Study of Diabetes (EASD) guidelines **[2022]**
1.2 NICE guidelines 2015 with last update 2019	NICE Type 2 Diabetes in Adults: Management (Published in 2015 – Last Updated in **[2022]**)
1.3 The American Association of Clinical Endocrinologists, the American College of Endocrinology guidelines **[2019]**	The American Association of Clinical Endocrinologists, the American College of Endocrinology guidelines **[2022]**

1.1.1 American Diabetes Association (ADA) pharmacologic approaches to glycemic treatment: standards of care in diabetes – **[2023]** and Consensus Report of The American Diabetes Association (ADA) with the European Association for the Study of Diabetes (EASD) guidelines **[2022]** *Please refer back to Section 1.1 of the CHI Type 2 Diabetes Mellitus Report Version 2.*

The 2023 ADA and 2022 EASD guidelines introduced a set of recommendations accompanied by a grading scheme, outlined as follows[27]:

Table 4. ADA Grading/Level of Evidence

ADA Evidence-Grading System for Standards of Care in Diabetes	
Level of Evidence	**Description**
A	Clear evidence from well-conducted,

	generalizable randomized controlled trials that are adequately powered, including • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., "all or none" rule developed by the Centre for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case-control study
C	• Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

The following recommendations were stated:

Lifestyle Modifications and Patient/Caregiver Education:

- Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes.

- Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals.

Pharmacological Treatment:

- Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals.

- Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.

- Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits.

- Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure.

- Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5-2.0% above their glycemic target. Use a stepwise addition of medications (one medication at a time) to metformin to maintain A1C at target.

- The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (>300mg/dL [16.7mmol/L]) are very high.

- As glucose toxicity resolves, simplifying the regimen and/or changing to noninsulin agents is often possible. However, there is evidence that people with uncontrolled hyperglycemia associated with type 2 diabetes can also be effectively treated with a sulfonylurea.

- If the individual is not already being treated with a GLP-1 RA, a GLP-1 RA (either in free combination or fixed-ratio combination) should be considered prior to prandial insulin.

- For individuals who advance to prandial insulin, a prandial insulin dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the greatest postprandial excursion is a safe estimate for initiating therapy. The prandial insulin regimen can then be intensified based on individual needs.

- When initiating combination injectable therapy, metformin therapy should be maintained, while sulfonylureas and DPP-4 inhibitors are typically weaned or discontinued.

Additional Risk Factors to Take Into Consideration:

- In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk.

- Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. GLP-1 medications with ASCVD benefits: Dulaglutide, Liraqlutide, Semaglutide (SQ).

1.1.2 NICE Type 2 Diabetes in Adults: Management (Published in 2015 – Last Updated in **[2022]**) *Please refer back to Section 1.2 of the CHI Type 2 Diabetes Mellitus Report Version 2.*

The following recommendations were stated[5]:

Rescue Therapy At Any Phase of Treatment:

- If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved.

First Line Drug Treatment:

- Gradually increase the dose of standard-release metformin over several weeks to minimize the risk of gastrointestinal side effects in adults with type 2 diabetes.

- Based on the cardiovascular risk assessment for the person with type 2 diabetes: If they have chronic heart failure or established atherosclerotic cardiovascular disease (ASCVD), offer an SGLT2 inhibitor with proven cardiovascular benefit in addition to metformin.

- If they are at high risk of developing cardiovascular disease, consider an SGLT2 inhibitor with proven cardiovascular benefit in addition to metformin.

- When starting an adult with type 2 diabetes on dual therapy with metformin and an SGLT2 inhibitor as first-line therapy, introduce the drugs sequentially, starting with metformin and checking tolerability. Start the SGLT2 inhibitor as soon as metformin tolerability is confirmed.

- In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and if they don't have chronic heart failure, established ASCVD, or are at high risk of developing cardiovascular disease, consider initial drug treatment with: a DPP-4 inhibitor, pioglitazone, a sulfonylurea, or an SGLT2 inhibitor for people who meet the criteria in NICE's technology appraisal guidance on canagliflozin, dapagliflozin and empagliflozin as monotherapies or ertugliflozin as monotherapy for treating type 2 diabetes. (Adults with type 2 diabetes when metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycemic control, ONLY if: A dipeptidyl peptidase 4 (DPP 4) inhibitor would otherwise be prescribed, and a sulfonylurea or pioglitazone is not appropriate.)

Treatment Options If Further Interventions Are Needed:

- Introduce drugs used in combination therapy in a stepwise manner, checking for tolerability and effectiveness of each drug.

- For adults with type 2 diabetes, if monotherapy has not continued to control HbA1c to below the person's individually agreed threshold for further intervention, consider adding: a DPP-4 inhibitor or pioglitazone or a sulfonylurea or an SGLT2 inhibitor for people who

meet the criteria in NICE's technology appraisal guidance on canagliflozin in combination therapy, ertugliflozin as monotherapy or with metformin, or dapagliflozin or empagliflozin in combination therapy.

- For adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for further intervention consider either:

  Triple therapy by adding a DPP-4 inhibitor, pioglitazone or a sulfonylurea or an SGLT2 inhibitor for people who meet the criteria in NICE's technology appraisal guidance on canagliflozin in combination therapy, dapagliflozin in triple therapy, empagliflozin in combination therapy, or ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor.

- In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and dual therapy with 2 oral drugs has not continued to control HbA1c to below the person's individually agreed threshold for intervention, consider insulin-based treatment.

Insulin-based treatments:

- When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.

- Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if:

  The patient needs help from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily.

  OR

  The person's lifestyle is restricted by recurrent symptomatic hypoglycemic episodes

OR

The person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.

- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if:

  The person prefers injecting insulin immediately before a meal

  OR

  Hypoglycemia is a problem

  OR

  Blood glucose levels rise markedly after meals

- Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes:

  Who do not reach their target HbA1c because of significant hypoglycemia.

  OR

  Who experience significant hypoglycemia on NPH insulin irrespective of the level of HbA1c reached.

  OR

  Who cannot use the device needed to inject NPH insulin but could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made.

  OR

  Who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections.

- When starting an insulin for which a biosimilar is available, use the product with the lowest acquisition cost.

- When people are already using an insulin for which a lower cost biosimilar is available, discuss the possibility of switching to the biosimilar. Make a shared decision with the person after discussing their preferences.

1.1.3 The American Association of Clinical Endocrinologists, the American College of Endocrinology guidelines **[2022]** *Please refer back to Section 1.3 of the CHI Type 2 Diabetes Mellitus Report Version 2.*

The American Association of Clinical Endocrinologists and the American College of Endocrinology guidelines introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 5. Revised Logical Ranking of Scientific Methodologies (Step I: Evidence Rating)

Numerical Descriptor[b]	Semantic Descriptor	Methodology Descriptor
STRONG EVIDENCE		
1 (1)	RCT	Randomized controlled trial[c]
1 (1)	MRCT	Meta-analysis of only randomized controlled trials
INTERMEDIATE EVIDENCE		
2 (2)	MNRCT	Meta-analysis including nonrandomized prospective or case-controlled trials
2 (new)	NMA	Network meta-analysis (44, 45)
2 (2)	NRCT	Nonrandomized controlled trial (or unconfirmed randomization)
2 (2)	PCS	Prospective cohort study (does not include open-label extension study)
2 (2)	RCCS	Retrospective case-control study
2 (new)	NCCS	Nested case-control study
2 (3; reassigned)	CSS	Cross-sectional study
2 (3; reassigned)	ES	Epidemiological study (hypothesis driven; includes survey, registry, data mining, with or without retrospective

		uni-multivariate analyses or propensity matching)
2 (new)	OLES	Open-label extension study (46)
2 (new)	PHAS	Post hoc analysis study (47)
WEAK EVIDENCE		
3 (new)	DS	Discovery science (explorative/inductive; includes -omics, "big data," network analysis, systems biology, Bayesian inference, modeling) (48)
3 (new)	ECON	Economic study (includes Markov models, pharmaco-economics) (49-53)
3 (3)	CCS	Consecutive case series (N > 1)
3 (3)	SCR	Single case report (N = 1)
3 (new)	PRECLIN	Preclinical study (e.g., feasibility, safety)
3 (new)	BR	Basic research (must be high impact and relevant)
NO EVIDENCE		
4 (4)	NE	No evidence (theory, opinion, consensus, review, position, policy, guideline)
4 (new)	O	Other (e.g., lower impact/relevant basic research; any highly flawed study)

Abbreviations: **EBM** = evidence-based methodology; **EL** = evidence level.
a Based-on principle that interventions, scientific control, generalizability, methodological flaws, and evidentiary details determine strength (54), consistent with other EBM systems (reviewed in Table 2 in reference (2)). Numerical and semantic descriptors of ELs provided in on-line supplementary material.
b The original numerical description from G4GAC 2004, 2010, and 2014 are provided in parentheses.

c The superiority of RCT over all other studies, and in particular MRCT, is discussed in reference (55). MRCTs are inferior to RCTs due to the bias introduced by being a retrospective analysis (56).

The following recommendations were stated [28]:

- Individualized pharmacotherapy for persons with T2D should be prescribed based on evidence for benefit that includes glucose lowering, avoidance of hypoglycemia and weight gain, and reduction of cardio-renal risk.
- Independent of glycemic control, targets, or treatment, if there is established or high risk for ASCVD, HF, and/or CKD, clinicians should prescribe a GLP-1 RA or an SGLT2i with proven efficacy for the specific condition(s) of the person with T2D being treated.
- Metformin is often the preferred initial therapy. Other agents may be appropriate as first line or in addition to metformin to reduce BG and/or to address specific comorbidities (such as ASCVD, HF, CKD, obesity, NAFLD), *independent of glucose-lowering effects*.
- For some recently diagnosed individuals with T2D and more severe hyperglycemia (A1C ≥7.5%), unlikely to attain the A1C target with a single agent, early combination pharmacotherapy should be considered, usually to include metformin plus another agent that does not cause hypoglycemia, especially a GLP-1 RA, SGLT2i, or dipeptidyl peptidase 4 (DPP-4) inhibitor.
- For newly diagnosed persons with T2D and an entry A1C>9.0% and/or 1.5% above target, one should initiate, along with lifestyle modifications, dual- or possibly triple-combination pharmacotherapy usually including metformin. Basal insulin along with noninsulin therapy is recommended if there are significant signs or symptoms of hyperglycemia, especially including catabolism (eg, weight loss) or a very high A1C >10% or BG levels (300 mg/dL).
- Persons with T2D who start on metformin should continue it unless intolerance or contraindications occur. When intensification of antihyperglycemic treatment is needed, other agents should be added to metformin.
- Most persons with T2D who require intensification of antihyperglycemic therapy with a GLP-1 RA or insulin should initially be prescribed a GLP-1 RA. If further intensification is required, one should prescribe a basal insulin or a switch to a fixed-ratio combination of a basal insulin and a GLP-1 RA (insulin glargine U100 + Lixisenatide [GlarLixi] or insulin Degludec + liraglutide [IdegLira]).
- Insulin should be prescribed for people with T2D when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a person has symptomatic hyperglycemia.

- Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), Degludec (U100 or U200), or detemir are preferred over intermediate-acting Neutral Protamine Hagedorn (NPH) insulin because analog insulins have demonstrated less hypoglycemia in some studies. Glargine U300 and Degludec can be associated with less hypoglycemia than glargine U100 or detemir.
- Many persons with T2D receiving basal insulin and not at goal A1C can have significantly improved glycemia by the addition of a GLP-1 RA or being switched to a fixed-ratio combination basal insulineGLP-1 RA (GlarLixi or IdegLira). One of these changes should be considered before adding a meal-time insulin for postprandial glycemic control.
- When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or the rapid-acting inhaled human insulin powder) over regular human insulin. The former have a more consistent and a more rapid onset and offset of action with less risk of hypoglycemia.
- Ultra-rapid-acting insulins (faster-acting insulin aspart, lispro aabc, and [human insulin] inhalation powder) may allow a decrease in the time between insulin administration and food intake and reduce the postprandial peak of PG as compared with rapid-acting insulins. The significance of this on long-term complications is unknown.
- Basal-bolus insulin regimens or continuous subcutaneous insulin infusion (CSII) (ie, insulin pump) allow for adjustment of insulin doses according to carbohydrate intake and activity levels and are recommended for intensive insulin therapy in persons with T2D.

  Premixed insulin formulations (fixed combinations of shorter- and longer-acting components) of human or analog insulin may be considered for persons with T2D who have consistent dietary and exercise patterns and in whom adherence to more intensive insulin regimens is problematic. However, these preparations have reduced dosage flexibility and may increase the risk of hypoglycemia compared with basal insulin or basal-bolus regimens.

- In persons with T2D who are treated with basal-bolus insulin therapy, adding a GLP-1 RA, or switching to a fixed-ratio combination of a GLP-1 RA and a basal insulin, or adding an SGLT2i or pramlintide (less commonly used) may be able to reduce postprandial hyperglycemia, A1C, and weight. GLP-1 RAs may also allow reduction or discontinuation of bolus insulin in some individuals.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Type 2 Diabetes Mellitus report, along with their recommendations

Table 6: List of the Additional Guidelines

Additional Guidelines
Saudi Diabetes Clinical Practice Guidelines by the Saudi National Diabetes Center (SNDC) at the Saudi Health Council [2021]
Australian Evidence Based Clinical Guidelines for Diabetes [2021]
Diabetes Canada Clinical Practice Guidelines Pharmacologic Glycemic Management of Type 2 Diabetes in Adults [2020]

1.2.1 Saudi Diabetes Clinical Practice Guidelines by the Saudi National Diabetes Center (SNDC) at the Saudi Health Council **[2021]**

The SNDC has issued the recommendations below[6]:

- Metformin is the preferred initial pharmacologic agent for the treatment of T2DM.
- Continue metformin unless not tolerated or contraindicated.
- Consider periodic measurement of vitamin B12 level in-patient on long-term therapy with metformin as it may cause vitamin B12 deficiency, especially in those with anemia or peripheral neuropathy.
- Metformin therapy should be temporarily halted on the day of radiocontrast administration and restarted a day or two later after confirmation that renal function has not deteriorated.
- Advise initiating insulin therapy if there is evidence of ongoing catabolism (weight loss), or symptoms of hyperglycemia are present, or when HbA1c levels 10%.
- Dual therapy should be considered in patients with newly diagnosed T2DM if HbA1c > 1.5% above their glycemic target.
- Use a patient-centered approach for the choice of pharmacologic agents. Consider comorbidities such as ASCVD, HF, CKD, hypoglycemia risk, impact on weight, cost, the risk for side effects, and patient preferences.
- Recommend SGLT-2i or GLP1-RA with demonstrated CVD benefit for patients with T2DM and established ASCVD.
- Use SGLT-2i in patients with ASCVD at high risk of HF or in whom HF failure coexists.
- Use SGLT-2i or GLP1-RA, which is shown to reduce the risk of CKD progression, cardiovascular events, or both in patients with T2DM and CKD.
- Use of GLP1-RA in patients who need a greater glucose-lowering effect of an injectable medication.

- Intensification of treatment in T2DM should not be delayed for patients not meeting treatment goals.
- Re-evaluate and adjust medication regimen every 3–6 months.

1.2.2 Australian Evidence Based Clinical Guidelines for Diabetes **[2021]**

The 2021 Australian Evidence Based Clinical Guidelines have opted for the following Grading Scheme/Level of Evidence:

Table 7. Australian Diabetes Society Grading/Level of Evidence

Recommendation For/Against
Recommendation for (Green) A strong recommendation is given when there is high-quality evidence showing that the overall benefits of the intervention are clearly greater than the disadvantages. This means that all, or nearly all, people with diabetes will want the recommended intervention.
Recommendation against (Red) A strong recommendation against the intervention is given when there is high-quality evidence showing that the overall disadvantages of the intervention are clearly greater than the benefits. A strong recommendation is also used when the examination of the evidence shows that an intervention is not safe.
Conditional Recommendation for (Yellow) A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when people with diabetes' preferences vary.
Conditional Recommendation against (Orange) A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when people with diabetes' preferences vary.

The Australian Diabetes Society has issued the recommendations below[6,29]:

Optimal Initial Medication:

- The use of metformin is suggested as first-line monotherapy in adults with type 2 diabetes.

Optimal Add-On Medication:

- The addition of an SGLT-2 inhibitor to other glucose lowering medication(s) is recommended in adults with type 2 diabetes who also have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease.

- The addition of a GLP-1 receptor agonist to other glucose lowering medication(s) is recommended in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor due to either intolerance or contraindication.
- The addition of a DPP-4 inhibitor to other glucose lowering medication(s) is suggested in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor or a GLP-1 receptor agonist due to either intolerance or contraindication.
- The addition of either an SGLT-2 inhibitor, GLP-1 receptor agonist or a DPP-4 inhibitor to metformin is suggested in adults with type 2 diabetes who do not have cardiovascular disease, multiple cardiovascular risk factors or kidney disease, and are unable to achieve optimal blood glucose levels.
- It is suggested that a sulfonylurea should not be the first-choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of severe hypoglycemia.
- It is suggested that a thiazolidinedione should not be the first-choice medication to add to metformin as dual therapy in adults with type 2 diabetes as it may increase the risk of hospitalization for heart failure.

1.2.3 Diabetes Canada Clinical Practice Guidelines Pharmacologic Glycemic Management of Type 2 Diabetes in Adults **[2020]**

The 2020 Diabetes Canada Clinical Guidelines have opted for the following Grading Scheme/Level of Evidence:

Table 8. Diabetes Canada Grading/Level of Evidence

Criteria for assigning levels of evidence to the published studies	
*** In cases where such blinding was not possible or was impractical (e.g. intensive vs. conventional insulin therapy), the blinding of individuals who assessed and adjudicated study outcomes was felt to be sufficient.**	
***RCT*, randomized controlled trial.**	
Level	***Criteria***
Studies of diagnosis	
Level 1	a. Independent interpretation of test results (without knowledge of the result of the diagnostic or gold standard) b. Independent interpretation of the diagnostic standard (without knowledge of the test result) c. Selection of people suspected (but not known) to have the disorder d. Reproducible description of both the test and diagnostic standard

	e. At least 50 patients with and 50 patients without the disorder
Level 2	Meets 4 of the Level 1 criteria
Level 3	Meets 3 of the Level 1 criteria
Level 4	Meets 1 or 2 of the Level 1 criteria
Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs a. Comprehensive search for evidence b. Authors avoided bias in selecting articles for inclusion c. Authors assessed each article for validity d. Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators a. Patients were randomly allocated to treatment groups b. Follow up at least 80% complete c. Patients and investigators were blinded to the treatment * d. Patients were analyzed in the treatment groups to which they were assigned e. The sample size was large enough to detect the outcome of interest
Level 1B	Non-randomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Non-randomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies
Level 4	Other
Studies of prognosis	
Level 1	a. Inception cohort of patients with the condition of interest, but free of the outcome of interest b. Reproducible inclusion/exclusion criteria c. Follow up of at least 80% of subjects d. Statistical adjustment for extraneous prognostic factors (confounders) e. Reproducible description of outcome measures
Level 2	Meets criterion a) above, plus 3 of the other 4 criteria
Level 3	Meets criterion a) above, plus 2 of the other criteria
Level 4	Meets criterion a) above, plus 1 of the other criteria

Diabetes Canada has issued the recommendations below[29]:

Treatment of People With Newly Diagnosed Type 2 Diabetes:

- Healthy behavior interventions should be initiated at type 2 diabetes diagnosis and reinforced and maintained throughout. Metformin may be introduced at the time of diagnosis, in conjunction with healthy behavior interventions.

- If glycemic targets are not achieved within 3 months using healthy behavior interventions alone, anti- hyperglycemic therapy should be added to reduce the risk of microvascular complications. Metformin should usually be selected before other agents due to its low risk of hypoglycemia and weight gain, and long-term experience with this agent.
- If A1C values are ≥1.5% above target, initiating metformin in combination with a second antihyperglycemic agent should be considered to increase the likelihood of reaching target.
- Individuals with metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss) should receive insulin with or without metformin, until glycemic control is achieved OR type of diabetes is established.

Reassessment and Monitoring:

- Glycemic control, cardiovascular and renal status should be reviewed regularly (at least annually). Healthy behavior interventions should be reinforced and supported. Efficacy, side effects and adherence to existing antihyperglycemic therapy should be assessed.
- Dose adjustments, substitutions and/or addition of anti- hyperglycemic medications should be made in order to maintain A1C or attain target A1C within 3 to 6 months.
- If glycemic targets are not achieved with existing antihyperglycemic medication(s), or the individual's clinical status changes, other classes of agents should be used (either by addition or replacement) to reduce cardiorenal outcomes and/or improve glycemic control; or glycemic targets should be reassessed.
- For adults with type 2 diabetes with metabolic decompensation (e.g. marked or symptomatic hyperglycemia, ketosis or unintentional weight loss), insulin should be used.

Advancement or Adjustment of Treatment in People With Type 2 Diabetes:

- In adults with type 2 diabetes WITH ASCVD, HF and/or CKD, treatment should include agents from the following classes with demonstrated CV or renal benefits.
    - In adults with type 2 diabetes and ASCVD, a GLP1-RA or SGLT2i with CV or renal benefit should be used to reduce the risk of:

        MACE

        HHF

        Progression of nephropathy

- In adults with type 2 diabetes and a history of HF (reduced ejection fraction 40%):

    An SGLT2i should be used to reduce the risk of HHF or CV death, if the eGFR is >30 mL/min/ 1.73m2

    TZD and saxagliptin should be avoided due to their higher risk of HF

- In adults with type 2 diabetes and CKD and an estimated eGFR >30 mL/min/1.73m^2:

An SGLT2i should be used to reduce the risk of:

(1) Progression of nephropathy

(2) HHF

(3) MACE

A GLP1-RA may be considered to reduce the risk of MACE

- In adults with type 2 diabetes requiring treatment advancement or adjustment to improve glycemic control, the choice of antihyperglycemic medication should be individualized according to clinical priorities
- In adults with type 2 diabetes aged 60 years or older with at least 2 CV risk factors, inclusion of the following classes in glycemic management should be considered:

    A GLP1-RA with proven CV outcome benefit to reduce the risk of MACE

    OR

    An SGLT2i with proven cardiorenal outcome benefit if estimated GFR is >30 mL/min/1.73m^2 to reduce the risk of:

(1) HHF

(2) Progression of nephropathy

- If reducing risk of hypoglycemia is a priority: Incretin agents (DPP4i or GLP1-RA), SGLT2i, acarbose and/or pioglitazone should be considered as add-on medication to improve glycemic control with a lower risk of hypoglycemia than other agents.
- If weight loss is a priority: A GLP1-RA and/or SGLT2i should be considered as add-on medication to improve glycemic control with more weight loss than other agents.

Initiating Insulin Treatment in Patients With Type 2 Diabetes:

- In people not achieving glycemic targets on existing noninsulin antihyperglycemic medication(s), the addition of a basal insulin regimen should be considered over premixed insulin or bolus-only regimens, if lower risk of hypoglycemia and/or preventing weight gain are priorities.
- In adults with type 2 diabetes treated with basal insulin therapy, if minimizing risk of hypoglycemia is a priority:

  Long-acting insulin analogues (insulin glargine U-100, glargine U-300, detemir, degludec) should be considered over NPH insulin to reduce the risk of nocturnal and symptomatic hypoglycemia.

  Insulin degludec or insulin glargine U-300 may be considered over insulin glargine U-100 to reduce overall and nocturnal hypoglycemia.

Treatment Advancement or Adjustment for People With Type 2 Diabetes Treated With Insulin:

- In adults with type 2 diabetes receiving insulin, doses should be adjusted and/or additional antihyperglycemic medication(s) should be added if glycemic targets are not achieved.
  - A GLP1-RA should be considered as add-on therapy [Grade A, Level 1A], before initiating bolus insulin or intensifying insulin to improve glycemic control with potential benefits of weight loss and lower hypoglycemia risk compared to single or multiple bolus insulin injections.
  - An SGLT2i should be considered as add-on therapy to improve glycemic control with potential benefits of weight loss and lower hypoglycemia risk compared to additional insulin.
  - A DPP4i may be considered as add-on therapy to improve glycemic control with potential benefits of less weight gain and lower hypoglycemia risk compared to additional insulin.
- When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be considered over short-acting (regular) insulin for greater improvement in glycemic control.
- Bolus insulin may be initiated using a stepwise approach (starting with 1 injection at 1 meal and additional meal-time injections as needed) to achieve similar A1C reduction with lower hypoglycemia risk compared to initiating bolus injections at every meal.

Section 2.0 Drug Therapy

This section comprises three subsections: the first one contains the newly recommended drugs, the second one covers drug modifications, and the third one outlines the drugs to delist due to withdrawal from the market among others.

2.1 Additions

The following drugs have been newly approved for Type 2 Diabetes Mellitus; some of which are SFDA registered, and others are not. The first section below tackles the SFDA registered new molecules along with their HTA analysis and the second section includes non-SFDA registered new molecules.

SFDA Registered Drugs:

2.1.1 Ertugliflozin

The following table describes the characteristics of Ertugliflozin[7,8]:

Table 9. Drug Therapy with Ertugliflozin

SCIENTIFIC NAME ERTUGLIFLOZIN	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E11
Drug Class	BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS
Drug Sub-class	SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS
ATC Code	A10BK04
Pharmacological Class (ASHP)	Antidiabetic Agent
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	5 mg once daily; may increase to 15 mg once daily after 4 to 12 weeks if needed to achieve glycemic goals
Maximum Daily Dose Adults*	15 mg/day
Dose (pediatrics)	N/A

Maximum Daily Dose Pediatrics*	N/A
Adjustment	Altered Kidney Function: eGFR ≥45 mL/minute/1.73 m : No dosage adjustment necessary. eGFR <45 mL/minute/1.73 m : Use is not recommended. Patients on dialysis: Use is contraindicated. Altered Hepatic Function: Mild or moderate impairment (Child-Pugh class A or B): No dosage adjustment necessary. Severe impairment (Child-Pugh class C): Use is not recommended (has not been studied).
Prescribing edits*	PA, AGE, ST
AGE (Age Edit)	Safety and effectiveness of STEGLATRO in pediatric patients under 18 years of age have not been established.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	Ertugliflozin may be used as an adjunctive agent or alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or who cannot take metformin. It is given as 5mg orally once daily. + Check other prescribing edits (AGE, ST)
QL (Quantity Limit)	N/A
ST (Step Therapy)	Ertugliflozin may be used for patients in whom initial therapy with lifestyle intervention and metformin failed or who cannot take metformin.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Urinary tract infections, Genitourinary fungal infection, Hypoglycemia. **Most serious**: Ketoacidosis, Urinary tract infection with sepsis, angioedema, Necrotizing fasciitis.
Drug Interactions*	There are no **Category X** interactions. **Category D:**

	Insulins Sulfonylureas
Special Population	**Older Adult** Older adults may be predisposed to symptoms related to intravascular volume depletion (eg, hypotension, orthostatic hypotension, dizziness, syncope, dehydration) and renal impairment or failure.
Pregnancy	Due to adverse effects on renal development observed in animal studies, the manufacturer does not recommend use of ertugliflozin during the second and third trimesters of pregnancy. Poorly controlled diabetes during pregnancy can be associated with an increased risk of adverse maternal and fetal outcomes, including diabetic ketoacidosis, preeclampsia, spontaneous abortion, preterm delivery, delivery complications, major malformations, stillbirth, and macrosomia. To prevent adverse outcomes, prior to conception and throughout pregnancy, maternal blood glucose and HbA should be kept as close to target goals as possible but without causing significant hypoglycemia.
Lactation	It is not known if ertugliflozin is present in breast milk. Due to the potential for adverse events in the breastfeeding infant, breastfeeding is not recommended by the manufacturer.
Contraindications	History of serious hypersensitivity reaction to ertugliflozin or any component of the formulation; patients on dialysis.
Monitoring Requirements	Blood glucose; renal function; volume status; genital mycotic infections and urinary tract infections; hypersensitivity reactions; blood pressure; lower limb and feet; if signs/symptoms of ketoacidosis, confirm diagnosis by direct measurement of blood ketones and arterial pH
Precautions	**Bone fractures:** An increased incidence of bone fractures has been observed with other sodium-glucose cotransporter 2 (SGLT2) inhibitors in some clinical trials. **Genital mycotic infections:** May increase the risk of genital mycotic infections. Patients with a history of these infections or uncircumcised males are at greater risk. **Hypotension:** May cause symptomatic hypotension due to intravascular volume depletion

	especially in patients with renal impairment (ie, eGFR <60 mL/minute/1.73 m), older adults, patients on other antihypertensives (eg, diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]), or those with low systolic blood pressure. Assess volume status prior to initiation in patients at risk of hypotension and correct if depleted. **Ketoacidosis:** Cases of ketoacidosis (some fatal) have been reported in patients with type 1 and type 2 diabetes mellitus receiving SGLT2 inhibitors; in some cases, patients have presented with normal or only modestly elevated blood glucose (<250 mg/dL). Before initiating treatment, consider risk factors that may predispose to ketoacidosis. Consider temporary discontinuation of therapy ≥4 days prior to surgery or any event that may precipitate ketoacidosis; ensure risk factors are resolved prior to reinitiating therapy. Patients presenting with nausea/vomiting, abdominal pain, generalized malaise, and/or shortness of breath should be assessed immediately for ketoacidosis. **Lower limb amputation:** There is conflicting data involving the risk of lower limb amputations with SGLT2 inhibitor therapy. Prior to initiation consider risk factors for amputation including prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Counsel patients about the importance of preventative foot care. Discontinue therapy if any of the following occur: signs and symptoms of new infection (including osteomyelitis), new pain or tenderness, or sores/ulcers involving the lower limbs. **Necrotizing fasciitis:** Cases of necrotizing fasciitis of the perineum (Fournier gangrene), a rare but serious and potentially fatal infection, have been reported in patients receiving

	SGLT2 inhibitors. Assess patients presenting with fever or malaise along with genital or perianal pain, tenderness, erythema, or swelling for necrotizing fasciitis. **Renal effects:** Acute kidney injury has been reported. Prior to initiation, consider risk factors for acute kidney injury (eg, hypovolemia, chronic renal insufficiency, heart failure, use of concomitant medications [eg, diuretics, ACE inhibitors, angiotensin receptor blockers, NSAIDs]). Temporarily discontinue use with reduced oral intake or fluid losses; discontinue use if acute kidney injury occurs. Additional abnormalities in renal function (decreased eGFR, increased serum creatinine) and adverse effects related to renal function may occur. **Urinary tract infection:** Serious urinary infections, including urosepsis and pyelonephritis, requiring hospitalization have been reported; treatment with SGLT2 inhibitors increases the risk for urinary tract infections.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Type 2 Diabetes Mellitus treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Ertugliflozin.**

Table 10. Ertugliflozin HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Ertugliflozin	NICE[10]	27 March 2019 – Positive Recommendation: Indirect comparisons with Canagliflozin, dapagliflozin and empagliflozin show that ertugliflozin has similar overall health benefits to canagliflozin, dapagliflozin and empagliflozin. The acquisition cost of ertugliflozin is lower than the acquisition costs of these other drugs. Ertugliflozin is

		therefore recommended as an option for treating type 2 diabetes as monotherapy or with metformin in line with the previous recommendations for SGLT-2 inhibitors.
	CADTH[12]	January 25, 2019 – Negative Recommendation: The CADTH Canadian Drug Expert Committee recommends that ertugliflozin should not be reimbursed as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus to improve glycemic control in those for whom metformin is inappropriate due to contraindications or intolerance (monotherapy), or as add-on combination treatment when metformin alone, or metformin plus sitagliptin do not provide adequate glycemic control.
	HAS[13]	September 5, 2019 – Negative Recommendation: Insufficient clinical benefit to justify its reimbursement in the management of type 2 diabetic patients.
	IQWIG[14]	May 19, 2022 – Negative Recommendation: Ertugliflozin has no proved added benefit for any of the indications it was assessed for in patients attained with Type 2 DM. No suitable data are available for assessing the added benefit of ertugliflozin as an adjunct to diet and exercise versus the ACT in adults with inadequately controlled type 2 diabetes mellitus.
	PBAC[11]	March 2018 – Positive Recommendation: The PBAC recommended the Authority Required (STREAMLINED) listing of the 5 mg dose strength ertugliflozin for dual oral therapy with metformin or a sulfonylurea, and the 2.5 mg ertugliflozin with 500 mg metformin, and 2.5 mg ertugliflozin with 1 g metformin fixed dose combinations, for the treatment of type 2 diabetes in patients

		inadequately controlled with metformin or a sulfonylurea.

CONCLUSION STATEMENT- Ertugliflozin

Ertugliflozin may be used as an adjunctive agent or alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or who cannot take metformin. In patients with established atherosclerotic cardiovascular disease, use has been associated with a reduced risk of hospitalization for heart failure. The use of Ertugliflozin is backed by some HTA bodies as HAS and PBAC. Its use is limited by the increased risk of urinary tract infections and hypoglycemia.

2.1.2 Tirzepatide

The following table describes the characteristics of Tirzepatide[7,8]:

Table 11. Drug Therapy with Tirzepatide

SCIENTIFIC NAME TIRZEPATIDE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E11
Drug Class	BLOOD GLUCOSE LOWERING DRUGS
Drug Sub-class	Glucose-Dependent Insulinotropic Polypeptide (GIP)/Glucagon-Like Peptide (GLP-1) Receptor Agonist
ATC Code	A10BX16
Pharmacological Class (ASHP)	Glucose-Dependent Insulinotropic Polypeptide (GIP)/Glucagon-Like Peptide (GLP-1) Receptor Agonist
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled pen
Route of Administration	Subcutaneous Use
Dose (Adult) [DDD]*	2.5 mg once weekly for 4 weeks, then increase to 5 mg once weekly. May

	increase dose in 2.5 mg/week increments every 4 weeks if needed to achieve glycemic goals
Maximum Daily Dose Adults*	Maximum weekly dose: 15 mg/week
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustments necessary in any case
Prescribing edits*	PA, QL, AGE, MD
AGE (Age Edit)	Safety and effectiveness of Tirzepatide have not been established in pediatric patients (younger than 18 years of age).
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Tirzepatide should be prescribed by a consultant diabetologist, or a consultant endocrinologist who is registered in the Saudi Commission for Health Specialties (SCFHS) and involved in the diagnosis and management of adult patients with T2DM. Tirzepatide may be refilled by a consultant diabetologist or an endocrinologist, or by a family physician.
PA (Prior Authorization)	This treatment recommendation is applicable coverage for adults with insufficiently controlled type 2 diabetes who have already implemented dietary and exercise interventions only if the patients: • Are aged ≥ 18 years • Have an insufficient control of HbA1C for two consecutive readings in 6-months • Have a BMI ≥ 30 kg/m2 or a BMI ≥ 27 kg/m2 with a documented history of comorbidities such as (Hypertension and/or hyperlipidemia and/or chronic kidney disease)

	• Are not tolerant or have a contraindication to triple therapy with metformin and 2 other antidiabetic drugs that include one GLP-1 (Insurance company can modify the coverage criteria and have it as 2nd or 1st line based on their internal analysis cost effectiveness analysis and contractual agreements) • Are prescribed Tirzepatide by a consultant diabetologist, or a consultant endocrinologist who is registered in the Saudi Commission for Health Specialties (SCFHS) and involved in the diagnosis and management of adult patients with T2DM. • This recommendation is not intended to affect treatment with Tirzepatide that was started before this guidance was published. Beneficiaries having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their clinician consider it appropriate to stop.
QL (Quantity Limit)	One-month supply should be dispensed with 2-month refills. Maximum weekly dose of 15 mg/week.
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Decreased appetite, diarrhea, increased serum amylase/lipase, nausea. **Most serious**: Acute kidney injury, diabetic retinopathy, gallbladder

	disease, gastrointestinal symptoms, hypersensitivity reactions, increased heart rate, medullary thyroid carcinoma, pancreatitis.
Drug Interactions*	**<u>Category X:</u>** Liraglutide Semaglutide Tirzepatide is not to be used in combination with GLP-1 agonists or DPP-4 inhibitors. Concomitant use with alpha glucosidase inhibitors, meglitinides is not recommended due to lack of or insufficient data regarding their combined use.
Special Population	No overall differences in safety or efficacy were found between older and younger adults.
Pregnancy	Poorly controlled diabetes during pregnancy can be associated with an increased risk of adverse maternal and fetal outcomes, including diabetic ketoacidosis, preeclampsia, spontaneous abortion, preterm delivery, delivery complications, major malformations, stillbirth, and macrosomia. To prevent adverse outcomes, prior to conception and throughout pregnancy, maternal blood glucose and HbA1c should be kept as close to target goals as possible but without causing significant hypoglycemia. Agents other than Tirzepatide are currently recommended to treat diabetes mellitus in pregnancy.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the

	risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Serious hypersensitivity to tirzepatide or any component of the formulation; a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.
Monitoring Requirements	Plasma glucose; GI adverse reactions; kidney function; signs/symptoms of pancreatitis; signs/symptoms of gallbladder disease; worsening of diabetic retinopathy.
Precautions	**Delayed gastric emptying:** Tirzepatide slows gastric emptying, which may alter the absorption of other medications. Monitor narrow therapeutic index medications for increased or decreased response. **Appropriate use:** Diabetes mellitus: Do not use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis; not a substitute for insulin.
Black Box Warning	**Risk of thyroid C-cell tumors:** Tirzepatide is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of tirzepatide and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent

	hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with tirzepatide.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Type 2 Diabetes Mellitus treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Tirzepatide.**

Table 12. Tirzepatide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Tirzepatide	NICE[15]	Still in development with an expected publication date of October 11, 2023.
	CADTH[16]	N/A; *"Although the price of tirzepatide is currently not available, future cost-effectiveness studies will be necessary to determine if tirzepatide adds value to the existing drug classes already available in Canada."*
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT- Tirzepatide

Tirzepatide is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. However, it has not been studied in patients with a history of pancreatitis and is not indicated for use in patients with type 1 diabetes mellitus. It is usually given as 2.5 mg once weekly for 4 weeks, then increased to 5 mg once weekly. The use of Tirzepatide is limited by the risk of developing acute kidney injury, diabetic retinopathy, gallbladder disease, gastrointestinal symptoms, hypersensitivity reactions, increased heart rate, medullary thyroid carcinoma, and pancreatitis.

2.1.3 Semaglutide

The following table describes the characteristics of Semaglutide[7,8]:

Table 13. Drug Therapy with Semaglutide

SCIENTIFIC NAME SEMAGLUTIDE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E11
Drug Class	BLOOD GLUCOSE LOWERING DRUGS
Drug Sub-class	Biguanide; Dipeptidyl Peptidase 4 (DPP-4) Inhibitor; Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor
ATC Code	A10BJ06
Pharmacological Class (ASHP)	Antidiabetic agent
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled pen Tablet
Route of Administration	Subcutaneous Use, Oral Use
Dose (Adult) [DDD]*	**Oral:** To be administered ≥30 minutes before the first food, beverage, or other medications of the day. Initial: 3 mg once daily for 30 days, then increase to 7 mg once daily; may increase to 14 mg once daily after 30 days on the 7 mg dose if needed to achieve glycemic goals. **SQ:** Initial: 0.25 mg once weekly for 4 weeks, then increase to 0.5 mg once weekly. May increase to 1 mg once weekly after 4 weeks on the 0.5 mg/week dose if needed to achieve glycemic goals; may increase further to 2 mg once weekly after 4 weeks on the 1 mg/week dose if needed to achieve glycemic goals

Maximum Daily Dose Adults*	Maximum: 2 mg/week
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Altered kidney function: Mild to severe impairment: No dosage adjustment necessary Hemodialysis, intermittent (thrice weekly): Unlikely to be dialyzable: No supplemental dose or dosage adjustment necessary Peritoneal dialysis: Unlikely to be dialyzable: No dosage adjustment necessary; use with caution due to limited clinical evidence For hepatic impairment: No dosage adjustment necessary.
Prescribing edits*	PA, QL, AGE, ST
AGE (Age Edit)	Semaglutide still hasn't been approved for children/adolescents with Type 2 DM.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	Semaglutide is recommended to be used as an adjunctive agent or alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or those who cannot take metformin. It is preferred in patients who have or are at risk for atherosclerotic cardiovascular disease (Ozempic only), when weight loss is desired, and/or in patients with an HbA1c relatively far from goal (eg, HbA 9% to 10%) and type 1 diabetes is not likely. It is given as **Oral:** To be administered ≥30 minutes before the first food, beverage, or other medications of the day.

	Initial: 3 mg once daily for 30 days, then increase to 7 mg once daily; may increase to 14 mg once daily after 30 days on the 7 mg dose if needed to achieve glycemic goals. OR **SQ:** Initial: 0.25 mg once weekly for 4 weeks, then increase to 0.5 mg once weekly. May increase to 1 mg once weekly after 4 weeks on the 0.5 mg/week dose if needed to achieve glycemic goals; may increase further to 2 mg once weekly after 4 weeks on the 1 mg/week dose if needed to achieve glycemic goals + Check other prescribing edits (AGE, QL, ST)
QL (Quantity Limit)	The patient is advised not to receive more than 2mg/week.
ST (Step Therapy)	May be used as an adjunctive agent or alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or those who cannot take metformin.
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Abdominal pain, constipation, diarrhea, nausea. **Most serious**: Acute kidney injury, diabetic retinopathy, gallbladder disease, gastrointestinal symptoms, hypersensitivity reactions, medullary thyroid carcinoma, pancreatitis.
Drug Interactions*	**Category X:** Glucagon-Like Peptide-1 Agonists Liraglutide
Special Population	Per the manufacturer, no differences in safety, efficacy, or pharmacokinetics

	were noted between older and younger adults.
Pregnancy	Poorly controlled diabetes during pregnancy is associated with an increased risk of adverse maternal and fetal outcomes, including diabetic ketoacidosis, preeclampsia, spontaneous abortion, preterm delivery, delivery complications, major malformations, stillbirth, and macrosomia. To prevent adverse outcomes, prior to conception and throughout pregnancy, maternal blood glucose and HbA1c should be kept as close to target goals as possible but without causing significant hypoglycemia. Agents other than Semaglutide are currently recommended to treat diabetes mellitus during Pregnancy.
Lactation	It is not known if Semaglutide is present in breast milk. The oral formulation also contains salcaprozate sodium (SNAC); it is not known if SNAC is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy with injectable semaglutide should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Breastfeeding during therapy with oral semaglutide is not recommended due to the unknown risks associated with potential accumulation of SNAC in the infant.
Contraindications	Hypersensitivity to semaglutide or any component of the formulation;

	personal or family history of medullary thyroid carcinoma (MTC); patients with multiple endocrine neoplasia syndrome type 2 (MEN2) Pregnancy and breastfeeding
Monitoring Requirements	Plasma glucose; heart rate; renal function; signs/symptoms of pancreatitis; triglycerides; signs/symptoms of gallbladder disease; worsening of diabetic retinopathy.
Precautions	**Psychiatric effects:** Suicidal behavior has been reported with other medications used for weight management. Avoid use in patients with history of suicidal attempts or active suicidal ideation. **Delayed gastric emptying:** Semaglutide slows gastric emptying, which may alter the absorption of other medications. Monitor narrow therapeutic index medications for increased or decreased response. **Multiple dose injection pens (Ozempic):** According to the CDC, pen-shaped injection devices should never be used for more than one person (even when the needle is changed) because of the risk of infection. The injection device should be clearly labeled with individual patient information to ensure that the correct pen is used. **Diabetes mellitus:** Do not use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis; not a substitute for insulin.
Black Box Warning	**Risk of thyroid C-cell tumors:** Semaglutide is contraindicated in patients with a personal or family

	history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of semaglutide and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Type 2 Diabetes Mellitus treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Semaglutide.**

Table 14. Semaglutide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Semaglutide	NICE	Not applicable
	CADTH[17]	May 2019 – Positive Recommendation: The CADTH Canadian Drug Expert Committee recommends that semaglutide be reimbursed for the treatment of type 2 diabetes mellitus to improve glycemic control, if the following conditions are met: **Conditions for Reimbursement** **Initiation Criteria** 1. Adult patients diagnosed with type 2 diabetes mellitus with inadequate glycemic control. **Administration Criteria** 1. In combination with metformin alone, when diet and exercise plus maximal tolerated dose of metformin do not

		achieve adequate glycemic control. 2. Semaglutide should not be reimbursed for use as add-on therapy to metformin and another antihyperglycemic drug. **Pricing conditions** 1. Drug plan costs for semaglutide should not exceed the drug plan costs of the least costly currently reimbursed drug used when metformin alone is insufficient to achieve glycemic control in the treatment of patients with type 2 diabetes mellitus.
	HAS[18]	August 26, 2021 – Positive Recommendation for SQ formulation and Negative Recommendation for oral formulation: The Committee maintained a favorable opinion for maintenance of reimbursement in the indications previously recommended for semaglutide for injection (OZEMPIC), except as dual therapy with a sulfonylurea and as triple therapy with insulin and metformin. However, the unfavorable opinion for reimbursement of oral semaglutide (RYBELSUS) was maintained.
	IQWIG[20]	28 January 2021 – Negative Recommendation: The company provided no relevant data for the assessment of semaglutide as monotherapy in adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycemic control and the use of metformin is considered inappropriate due to intolerance or contraindication. This resulted in no hint of an added benefit of semaglutide in comparison with the ACT. An added benefit is therefore not proven.
	PBAC[19]	November 2019 – Positive Recommendation: The PBAC recommended the listing of semaglutide (injectable) for treatment of patients with

		type 2 diabetes who have inadequate glycemic control, as dual therapy in combination with metformin or a sulfonylurea where either of these is contraindicated or not tolerated; or triple therapy in combination with metformin and a sulfonylurea. The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of semaglutide would be acceptable if it were cost-minimized against dulaglutide.

CONCLUSION STATEMENT- Semaglutide

Semaglutide is recommended to be used as an adjunctive agent or alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or those who cannot take metformin. It is preferred in patients who have or are at risk for atherosclerotic cardiovascular disease (Ozempic only), when weight loss is desired, and/or in patients with an HbA1c relatively far from goal and type 1 diabetes is not likely. Its use is backed by CADTH, PBAC and HAS (Only for the SQ formulation). Its use is limited by the risk of acute kidney injury, diabetic retinopathy, gallbladder disease, gastrointestinal symptoms, hypersensitivity reactions, medullary thyroid carcinoma, and pancreatitis.

2.1.4 Degludec-Liraglutide Combination **(Xultophy®)**

The following table describes the characteristics of the Degludec-Liraglutide combination[7,8]:

Table 15. Drug Therapy with Degludec-Liraglutide

SCIENTIFIC NAME DEGLUDEC-LIRAGLUTIDE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E11

Drug Class	BLOOD GLUCOSE LOWERING DRUGS
Drug Sub-class	Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist; Insulin, Long-Acting
ATC Code	A10AE56
Pharmacological Class (ASHP)	Antidiabetic agent
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous Use
Dose (Adult) [DDD]*	Patients naive to basal insulin or a GLP-1 agonist: 10 units (insulin degludec 10 units/liraglutide 0.36 mg) once daily. Patients currently on basal insulin or a GLP-1 agonist: 16 units (insulin degludec 16 units/liraglutide 0.58 mg) once daily.
Maximum Daily Dose Adults*	Maximum dose: 50 units (insulin degludec 50 units/liraglutide 1.8 mg)/day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling (combination product has not been studied). Insulin requirements may be reduced due to changes in insulin clearance or metabolism; monitor blood glucose closely.
Prescribing edits*	AGE, ST
AGE (Age Edit)	Safety and effectiveness of XULTOPHY 100/3.6 have not been established in pediatric patients.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	XULTOPHY is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal

	insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypoglycemia, antibody development, diarrhea, headache. **Most serious**: Increased heart rate, hypokalemia, angioedema.
Drug Interactions*	**Category X:** Glucagon-Like Peptide-1 Agonists Macimorelin Rosiglitazone Semaglutide
Special Population	N/A
Pregnancy	XULTOPHY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.
Contraindications	Hypersensitivity to insulin degludec, liraglutide, or any component of the formulation; history of or family history of medullary thyroid carcinoma (MTC); patients with multiple endocrine neoplasia syndrome type 2 (MEN2); during episodes of hypoglycemia Pregnant or breastfeeding women
Monitoring Requirements	Plasma glucose; electrolytes; renal function; hepatic function; weight; signs/symptoms of pancreatitis; triglycerides; signs/symptoms of gallbladder disease. Monitor HbA1c at least twice yearly in patients who have stable glycemic control and are meeting treatment goals; monitor quarterly in patients in whom treatment goals have not been met, or with therapy change.
Precautions	**Antibody formation:** Development of antibodies to insulin and liraglutide may occur. **Gallbladder disease:** Cholelithiasis and cholecystitis have been reported in patients treated with liraglutide, with the majority of patients requiring hospitalization or

	cholecystectomy; gallbladder studies and further clinical assessment are indicated if cholelithiasis is suspected. **GI symptoms:** Most common reactions are gastrointestinal related; these symptoms may be dose-related and may decrease in frequency/severity with gradual titration and continued use. **Glycemic control:** Hyper- or hypoglycemia may result from changes in insulin strength, manufacturer, type, and/or administration method. **Hypersensitivity:** Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with liraglutide and with insulin degludec; discontinue use if hypersensitivity reactions occur and treat promptly as indicated. **Hypokalemia:** Insulin (especially IV insulin) causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia. Monitor serum potassium and supplement potassium when necessary. **Pancreatitis:** Cases of acute and chronic pancreatitis have been reported with GLP-1 receptor agonists; monitor for signs and symptoms of pancreatitis. If pancreatitis is suspected, discontinue use. Do not resume unless an alternative etiology of pancreatitis is confirmed. **Renal effects:** Acute renal failure and chronic renal failure exacerbation have been reported with liraglutide; Renal dysfunction was usually reversible with appropriate corrective measures, including discontinuation of liraglutide. Risk may be increased in patients receiving concomitant medications affecting renal function and/or hydration status. **Thyroid tumors:** Patients should be counseled on the potential risk of MTC with the use of liraglutide and informed of symptoms of thyroid tumors. Use is contraindicated in patients with a personal or a family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2 (MEN2). Patients who develop elevated calcitonin concentrations or have thyroid nodules detected during imaging studies or physical exams should be further evaluated. Routine

	monitoring of serum calcitonin or using thyroid ultrasound monitoring is of uncertain value for early detection of MTC in patients treated with liraglutide. **Cardiac disease:** Concurrent use with peroxisome proliferator-activated receptor (PPAR)-gamma agonists, including thiazolidinediones (TZDs) may cause dose-related fluid retention and lead to or exacerbate heart failure, particularly when used in combination with insulin. If PPAR-gamma agonists are prescribed, monitor for signs and symptoms of heart failure. If heart failure develops, consider PPAR-gamma agonist dosage reduction or therapy discontinuation. **Gastroparesis:** Liraglutide slows gastric emptying. **Hepatic impairment:** Use with caution in patients with hepatic impairment, insulin requirements may be reduced due to changes in insulin clearance or metabolism; monitor blood glucose closely. Dosage adjustments may be necessary. **Renal impairment:** Use with caution in patients with renal impairment. Dosage adjustments may be necessary. **Appropriate use:** Not approved for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. **Patient education:** Diabetes self-management education (DSME) is essential to maximize the effectiveness of therapy.
Black Box Warning	**Thyroid C-Cell Tumor Risk:** Insulin degludec/liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of insulin degludec/liraglutide and inform them of symptoms of thyroid tumors. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with insulin degludec/liraglutide.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Type 2 Diabetes Mellitus treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for the Degludec-Liraglutide combination.**

Table 16. Degludec-Liraglutide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Degludec-Liraglutide	NICE[30]	Not applicable – The available guidance discusses clinical effectiveness.
	CADTH[21]	October 2019 – Positive Recommendation: The CADTH Canadian Drug Expert Committee (CDEC) recommends that insulin degludec and liraglutide (IDegLira) should be reimbursed as an adjunct to lifestyle modification, for the once-daily treatment of adults with T2DM to improve glycemic control in combination with metformin (MET), with or without sulfonylurea (SU), when these, combined with basal insulin (at doses of 20 to 50 units per day) do not provide adequate glycemic control, only if the following conditions are met: **Conditions for Reimbursement** **Discontinuation criteria** IDegLira should be discontinued if the patient does not achieve a desirable level of glycemic control despite receiving a maximum dose of IDegLira (50 units of insulin degludec [IDeg] and 1.8 mg of liraglutide) after 26 weeks of treatment. **Pricing condition** Drug plan costs for IDegLira should not exceed the cost of the least costly glucagon-like peptide-1 receptor agonist (GLP-1 RA) plus the least costly basal insulin administered separately or in combination.

	HAS[22]	August 26, 2021 – Positive Recommendation: The Committee maintained a favorable opinion on maintaining reimbursement in the indications previously recommended for the fixed liraglutide/insulin degludec combination (XULTOPHY).
	IQWIG[23]	November 16, 2015 – Negative Recommendation: The manufacturer presented no relevant data for the assessment of the added benefit of insulin degludec/liraglutide versus the ACT. Hence no added benefit can be derived from the dossier. The manufacturer itself also claimed no added benefit for this therapeutic indication of the fixed combination.
	PBAC	N/A

CONCLUSION STATEMENT- Degludec-Liraglutide

The Degludec-Liraglutide combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily). Due to the lack of additive glycemic benefit, patients should avoid concomitant use with a dipeptidyl peptidase-4 inhibitor. A dose reduction or discontinuation of insulin secretagogues (sulfonylureas, meglitinides) is considered to avoid hypoglycemia. The combination is given as 10 units (insulin degludec 10 units/liraglutide 0.36 mg) once daily for patients naive to basal insulin or a GLP-1 agonist and is given as 16 units (insulin degludec 16 units/liraglutide 0.58 mg) once daily for patients currently on basal insulin or a GLP-1 agonist. Its use is backed by some HTA bodies (CADTH and HAS). Limitations to the use of this combination product include the risks for hypoglycemia, increased heart rate and angioedema.

2.1.5 Glargine-Lixisenatide Combination (Soliqua®)

The following table describes the characteristics of Glargine-Lixisenatide [7,8]:

Table 17. Drug Therapy with Glargine-Lixisenatide

SCIENTIFIC NAME GLARGINE-LIXISENATIDE	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	E11
Drug Class	BLOOD GLUCOSE LOWERING DRUGS
Drug Sub-class	Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist; Insulin, Long-Acting
ATC Code	A10AE04 A10BJ03
Pharmacological Class (ASHP)	Antidiabetic agent
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled syringe
Route of Administration	Subcutaneous Use
Dose (Adult) [DDD]*	**Insulin glargine 100 units/lixisenatide 33 mcg per mL pen injector ("30 to 60" pen):** **Patients naive to basal insulin or a GLP-1 agonist, or currently on a GLP-1 agonist or <30 units of basal insulin/day:** 15 units (insulin glargine 15 units/lixisenatide 5 mcg) once daily. **Patients currently on 30 to 60 units of basal insulin/day, with or without a GLP1 agonist:** 30 units (insulin glargine 30 units/lixisenatide 10 mcg) once daily. **Insulin glargine 100 units/lixisenatide 50 mcg per mL pen injector ("10 to 40" pen)** **Patients naive to basal insulin or currently on <20 units of basal insulin/day:** 10 units (insulin glargine 10 units/lixisenatide 5 mcg) once daily. **Patients currently on 20 to <30 units of basal insulin/day:** 20 units (insulin glargine 20 units/lixisenatide 10 mcg) once daily. **Patients currently on ≥30 units of basal insulin/day:** Do not use the "10 to 40" pen; see dosing above for insulin glargine 100

	units/lixisenatide 33 mcg per mL pen injector (the "30 to 60" pen).
Maximum Daily Dose Adults*	**Insulin glargine 100 units/lixisenatide 33 mcg per mL pen injector:** Maximum dose: 60 units (insulin glargine 60 units/lixisenatide 20 mcg)/day. **Insulin glargine 100 units/lixisenatide 50 mcg per mL pen injector:** Maximum dose: 40 units (insulin glargine 40 units/lixisenatide 20 mcg) per day.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** eGFR ≥15 mL/minute/1.73 m to <90 mL/minute/1.73 m : There are no specific dosage adjustments provided in the manufacturer's labeling for the combination product; insulin requirements may be reduced due to changes in insulin clearance or metabolism; monitor blood glucose closely. eGFR <15 mL/minute/1.73 m : Use is not recommended (has not been studied). **Hepatic Impairment:** There are no specific dosage adjustments provided in the manufacturer's labeling for the combination product; insulin requirements may be reduced due to changes in insulin clearance or metabolism; monitor blood glucose closely.
Prescribing edits*	AGE
AGE (Age Edit)	Safety and effectiveness of SOLIQUA 100/33 have not been established in pediatric patients below 18 years of age.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A

EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Hypoglycemia, antibody development, nausea, diarrhea. **Most serious**: Upper respiratory tract infection, anaphylaxis, angioedema, acute kidney injury.
Drug Interactions*	**Category X:** Liraglutide Macimorelin Rosiglitazone Semaglutide
Special Population	**Older Adults:** Age was highly correlated with creatinine clearance; dose adjustments should be made based on renal function. Adverse events reported in clinical trials were more common in patients with renal impairment, particularly nausea, vomiting, and diarrhea. Intensive glucose control (HbA1c <6.5%) has been linked to increased all-cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. How "tightly" to control a geriatric patient's blood glucose needs to be individualized. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.
Pregnancy	SOLIQUA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

Contraindications	History of serious hypersensitivity to insulin glargine, lixisenatide, or any component of the formulation; during episodes of hypoglycemia. Patients with a personal or family history of medullary thyroid carcinoma; patients with multiple endocrine neoplasia syndrome type 2; pregnancy; breastfeeding.
Monitoring Requirements	Plasma glucose; electrolytes; hepatic function; weight; potassium; renal function; signs/symptoms of pancreatitis; signs/symptoms of gallbladder disease; gallbladder studies and further clinical assessment are indicated if cholelithiasis is suspected. HbA1c: Monitor at least twice yearly in patients who have stable glycemic control and are meeting treatment goals; monitor quarterly in patients in whom treatment goals have not been met, or with therapy change.
Precautions	**Antibody formation:** Development of antibodies to insulin and lixisenatide may occur; consider alternative antidiabetic therapy in patients not achieving targeted glycemic control or with worsening glycemic control and/or significant allergic or injection site reactions. **Gallbladder disease:** Use of glucagon-like peptide-1 (GLP-1) agonists may increase risk of gallbladder and bile duct disease, including cholelithiasis and cholecystitis. **Hypersensitivity:** Serious hypersensitivity reactions including anaphylaxis and angioedema have been reported with lixisenatide and with insulin glargine; discontinue use if hypersensitivity reactions occur and treat promptly as indicated. **Hypoglycemia:** The most common adverse effect of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. **Hypokalemia:** Insulin (especially IV insulin) causes a shift of potassium from the

	extracellular space to the intracellular space, possibly producing hypokalemia. Monitor serum potassium and supplement potassium when necessary. **Pancreatitis:** Cases of acute pancreatitis have been reported with GLP-1 receptor agonists; monitor for signs and symptoms of pancreatitis. If pancreatitis is suspected, discontinue use. Do not resume unless an alternative etiology of pancreatitis is confirmed. Consider alternative antidiabetic therapy in patients with a history of pancreatitis. **Cardiac disease:** Concurrent use with peroxisome proliferator-activated receptor (PPAR)- gamma agonists, including thiazolidinediones (TZDs) may cause dose-related fluid retention and lead to or exacerbate heart failure, particularly when used in combination with insulin. If PPAR-gamma agonists are prescribed, monitor for signs and symptoms of heart failure. If heart failure develops, consider PPAR-gamma agonist dosage reduction or therapy discontinuation. **Gastroparesis:** Lixisenatide slows gastric emptying and is not recommended for use in patients with gastroparesis; do not initiate therapy in patients with severe gastroparesis. **Renal impairment:** Use with caution in patients with renal impairment. Dosage adjustments may be necessary. Patients with mild to moderate renal impairment (eGFR ≥30 to 89 mL/minute/1.73 m) may be at increased risk of adverse effects which may lead to dehydration, acute kidney injury, and worsening of chronic renal failure. There is limited experience with severe impairment (eGFR 15 to <30 mL/minute/1.73 m); lixisenatide exposure may be increased in these patients. Monitor all patients with renal impairment closely for decreasing renal function. Use is not

	recommended in patients with end-stage renal disease (eGFR <15 mL/minute/1.73 m) (has not been studied). **Hepatic impairment:** Use with caution in patients with hepatic impairment. Dosage adjustments may be necessary. **Appropriate use:** Not approved for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. **Patient education:** Diabetes self-management education (DSME) is essential to maximize the effectiveness of therapy.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Type 2 Diabetes Mellitus treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for the Glargine-Lixisenatide combination.**

Table 18. Glargine-Lixisenatide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Glargine-Lixisenatide	NICE	N/A
	CADTH[24]	January 3, 2019 – Positive Recommendation: The CADTH Canadian Drug Expert Committee recommends that insulin glargine and lixisenatide (iGlarLixi) be reimbursed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, if the following condition is met: **Condition** Drug plan costs for iGlarLixi should not exceed the combined drug plan costs of lixisenatide and insulin glargine provided separately in jurisdictions that reimburse both drugs for the treatment of type 2 diabetes mellitus.

	HAS[25]	August 26, 2021 – Negative Recommendation: unfavorable opinion for reimbursement of lixisenatide/insulin glargine (SULIQUA). The negative recommendation is attributed to the lack of evidence and absence of conclusive new data. (Insufficient clinical benefit)
	IQWIG	N/A
	PBAC[26]	March 2019 – Negative Recommendation: The PBAC did not recommend the listing of insulin glargine with lixisenatide fixed ratio combination (FRC) for treatment of adults with type 2 diabetes mellitus who have inadequate glycaemic control with basal insulin on the basis that the proposed price was unacceptably high given the residual uncertainty around the claim of noninferiority and the appropriate equi-effective doses. The PBAC considered that on balance, cost-effectiveness had not been demonstrated and noted that there was no strong clinical need for insulin glargine with lixisenatide due to other PBS listed treatment options.

CONCLUSION STATEMENT- Glargine-Lixisenatide

The Glargine-Lixisenatide combination is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The two different formulations used are the **Insulin glargine 100 units/lixisenatide 33 mcg per mL pen injector** and the **Insulin glargine 100 units/lixisenatide 50 mcg per mL pen injector**. Its use is backed by one HTA body (HAS). Limitations for the use of the Glargine-Lixisenatide combination include the risk for hypoglycemia, upper respiratory tract infections, anaphylaxis, angioedema, and acute kidney injury.

Other Drugs

The following drugs discussed are newly approved drugs which are FDA approved; however, are regarded as non-SFDA registered new molecules.

For Non-SFDA Registered New Molecules:

Bexagliflozin (Brenzavvy®)

Bexagliflozin was approved by the FDA on January 23, 2023. It still hasn't been approved by the EMA. Bexagliflozin may be used as an adjunctive agent or

alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or who cannot take metformin. It is usually given as 20 mg once daily in the morning.

Empagliflozin/Linagliptin/Metformin (Trijardy XR®)

The Empagliflozin/Linagliptin/Metformin combination was approved by the FDA on January 27, 2020. It still hasn't been approved by the EMA. The combination is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is given as follows: Its administration and regimen are individualized based on the patient's current antidiabetic regimen.

Patients not taking empagliflozin are to be switched to the combination product containing a similar total daily dose of metformin, empagliflozin 10 mg/day, and linagliptin 5 mg/day given once daily.

Patients taking empagliflozin are to be switched to the combination product containing a similar total daily dose of metformin, same total daily dose of empagliflozin, and linagliptin 5 mg/day given once daily.

The dose may be gradually titrated based on effectiveness and tolerability; maximum: empagliflozin 25 mg/linagliptin 5 mg/metformin 2 g once daily.

2.2 Modifications

The following modifications and adjustments have been implemented since the 2019 report:

Modifications In Step Therapy:

Most persons with T2D who require further intensification of antihyperglycemic therapy should initially be prescribed a GLP-1 RA rather than insulin first.

SGLT-2 Inhibitors of GLP-1 Ras are recommended as additional glucose-lowering medications after lifestyle interventions particularly if there are concerns about hypoglycemia or weight gain.

In patients with a previous stroke/TIA, GLP-1 RAs or Pioglitazone are indicated.

2.3 Delisting

The medications below are no longer SFDA registered[7], therefore, it is recommended to delist the following drugs from CHI formulary:

- Exenatide
- Exenatide Extended Release
- Albiglutide

Section 3.0 Key Recommendations Synthesis

- Metformin is the first-line medication for management of type 2 diabetes mellitus and has beneficial effects on A1C, weight, and cardiovascular mortality. (Grade A)
- In patients with contraindications or intolerance of metformin, initial therapy should be based on patient factors; consider a drug from another class: sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitor, sodium glucose cotransporter 2 (SGLT2) inhibitor, GLP-1 receptor agonist (GLP1-RA), or basal insulin. (Grade A)
- Consider initiating stepwise dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5-2.0% above their glycemic target. (Strong Recommendation)
- The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (>300mg/dL [16.7mmol/L]) are very high. (Grade E)
- If insulin is used, combination therapy with a GLP1-RA is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. (Grade A)
- Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. GLP-1 medications with ASCVD benefits: Dulaglutide, Liraqlutide, Semaglutide (SQ). (Grade A)
- If an adult with type 2 diabetes is symptomatically hyperglycemic, consider insulin or a sulfonylurea, and review treatment when blood glucose control has been achieved. (Strong Recommendation)
- In adults with type2 diabetes, if metformin is contraindicated or not tolerated and if they don't have chronic heart failure, established ASCVD, or are at high risk of developing cardiovascular disease, consider initial drug treatment with: a DPP-4 inhibitor, pioglitazone, a sulfonylurea, or an SGLT2 inhibitor. (Strong Recommendation)
- The addition of a DPP-4 inhibitor is suggested to other glucose lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease, and are unable to be prescribed an SGLT-2 inhibitor or a GLP-1 receptor agonist due to either intolerance or contraindication. (Conditional Recommendation, High)
- For adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's

individually agreed threshold for further intervention intensification, consider either: Triple therapy by adding a DPP-4 inhibitor, pioglitazone or a sulfonylurea or an SGLT2 inhibitor OR starting insulin-based treatment. (Strong Recommendation)

- Long-acting basal insulin analogs are the recommended initial choice of insulin therapy for persons with T2D. The insulin analogs glargine (U100 or U300), degludec (U100 or U200), or detemir are preferred**.** (Grade A)
- When control of postprandial hyperglycemia is needed and a basal insulin and a GLP-1 RA are already being used, preference should be given to rapid-acting meal insulins. (Grade A)
- Tirzepatide is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (No stated level of evidence)
- Semaglutide is recommended to be used as an adjunctive agent or alternative monotherapy for patients in whom initial therapy with lifestyle intervention and metformin failed or those who cannot take metformin. It is preferred in patients who have or are at risk for atherosclerotic cardiovascular disease, when weight loss is desired, and/or in patients with an HbA1c relatively far from goal and type 1 diabetes is not likely. (No stated level of evidence)
- The Degludec-Liraglutide combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily). (No stated level of evidence)
- The Glargine-Lixisenatide combination is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (No stated level of evidence)

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Type 2 Diabetes Mellitus report** and aims to provide recommendations to aid in the management of D2M. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with D2M. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. Level of Evidence Description

Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Sort By	Filters	Search Details	Results
((((((((((((((((((((((((((((((Diabetes Mellitus, Type 2[MeSH Terms]) OR (Diabetes Mellitus, Noninsulin-Dependent[Title/Abstract])) OR (Diabetes Mellitus, Ketosis-Resistant[Title/Abstract])) OR (Diabetes Mellitus, Ketosis Resistant[Title/Abstract])) OR (Ketosis-Resistant Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Non-Insulin Dependent[Title/Abstract])) OR (Diabetes Mellitus, Non-Insulin-Dependent[Title/Abstract])) OR (Non-Insulin-Dependent Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Stable[Title/Abstract])) OR (Stable Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Type II[Title/Abstract])) OR (NIDDM[Title/Abstract])) OR (Diabetes Mellitus, Noninsulin Dependent[Title/Abstract])) OR (Diabetes Mellitus, Maturity-Onset[Title/Abstract])) OR (Diabetes Mellitus, Maturity Onset[Title/Abstract]))		Meta-Analysis, Systematic Review, in the last 5 years	("diabetes mellitus, type 2"[MeSH Terms] OR "diabetes mellitus noninsulin dependent"[Title/Abstract] OR (("diabetes mellitus"[MeSH Terms] OR ("Diabetes"[All Fields] AND "Mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND "Ketosis-Resistant"[Title/Abstract]) OR (("diabetes mellitus"[MeSH Terms] OR ("Diabetes"[All Fields] AND "Mellitus"[All Fields]) OR "diabetes mellitus"[All Fields]) AND "Ketosis-Resistant"[Title/Abstract]) OR "ketosis resistant diabetes mellitus"[Title/Abstract] OR "diabetes mellitus non-insulin dependent"[Title/Abstract] OR "diabetes mellitus non-insulin dependent"[Title/Abstract] OR "nonnon-insulin dependent diabetes mellitus"[Title/Abstract] OR "diabetes mellitus stable"[Title/Abstract] OR "stable diabetes mellitus"[Title/Abstract] OR "diabetes mellitus type ii"[Title/Abstract] OR "NIDDM"[Title/Abstract]	3,888

OR (Maturity-Onset Diabetes Mellitus[Title/Abstract])) OR (Maturity Onset Diabetes Mellitus[Title/Abstract])) OR (MODY[Title/Abstract])) OR (Diabetes Mellitus, Slow-Onset[Title/Abstract])) OR (Diabetes Mellitus, Slow Onset[Title/Abstract])) OR (Slow-Onset Diabetes Mellitus[Title/Abstract])) OR (Type 2 Diabetes Mellitus[Title/Abstract])) OR (Noninsulin-Dependent Diabetes Mellitus[Title/Abstract])) OR (Noninsulin Dependent Diabetes Mellitus[Title/Abstract])) OR (Maturity-Onset Diabetes[Title/Abstract])) OR (Diabetes, Maturity-Onset[Title/Abstract])) OR (Maturity Onset Diabetes[Title/Abstract])) OR (Type 2 Diabetes[Title/Abstract])) OR (Diabetes, Type 2[Title/Abstract])) OR (Diabetes Mellitus, Adult-Onset[Title/Abstract])) OR (Adult-Onset Diabetes Mellitus[Title/Abstract])) OR (Diabetes Mellitus, Adult Onset[Title/Abstract])			OR "diabetes mellitus noninsulin dependent"[Title/Abstract] OR "diabetes mellitus maturity onset"[Title/Abstract] OR "diabetes mellitus maturity onset"[Title/Abstract] OR "maturity onset diabetes mellitus"[Title/Abstract] OR "maturity onset diabetes mellitus"[Title/Abstract] OR "MODY"[Title/Abstract] OR "diabetes mellitus slow onset"[Title/Abstract] OR "diabetes mellitus slow onset"[Title/Abstract] OR ("Slow-Onset"[All Fields] AND "diabetes mellitus"[Title/Abstract]) OR "type 2 diabetes mellitus"[Title/Abstract] OR "noninsulin dependent diabetes mellitus"[Title/Abstract] OR "noninsulin dependent diabetes mellitus"[Title/Abstract] OR "maturity onset diabetes"[Title/Abstract] OR "diabetes maturity onset"[Title/Abstract] OR "maturity onset diabetes"[Title/Abstract] OR "type 2 diabetes"[Title/Abstract] OR "diabetes type 2"[Title/Abstract] OR "diabetes mellitus adult onset"[Title/Abstract] OR "adult onset diabetes	

			mellitus"[Title/Abstract] OR "diabetes mellitus adult onset"[Title/Abstract]) AND ((y_5[Filter]) AND (meta-analysis[Filter] OR systematicreview[Filter]))	

Appendix D. Scope Table

The following table describes all the changes and additions made to the previous 2019 D2M report; extracted from the Scope Document.

Comparison of the 2019 and the 2023 Report

2019 Version	Changes Performed	2023 (current version)	Rationale
Not available	New section	Scope	Summarize the main changes and updates between the 2019 and 2023 versions
Executive Summary	Updated	Background	Update based on the new guideline updates: ADA, EASD, AACE, NICE, SNDC, Australian, Canadian
Section 1.0 – Type 2 Diabetes Clinical Guidelines			
The American Diabetes Association (ADA) the pharmacologic approaches to glycemic treatment: standard of medical care in diabetes-2019 and Consensus Report of The American Diabetes Association (ADA) with the European Association for the Study of Diabetes (EASD) guidelines 2018	Added recommendations + Updated	American Diabetes Association (ADA) pharmacologic approaches to glycemic treatment: standards of care in diabetes – 2023 and Consensus Report of The American Diabetes Association (ADA) with the European Association for the Study of Diabetes (EASD) guidelines 2022	ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S140-S157. doi:10.2337/dc23-S009 Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2022;65(12):1925-1966. doi:10.1007/s00125-022-05787-2AACE
NICE guidelines 2015 with last update 2019	Added recommendations + Updated	NICE Type 2 Diabetes in Adults: Management (Published in 2015 – Last Updated in 2022)	*Type 2 diabetes in adults: management*. London: National Institute for Health and Care Excellence (NICE); June 29, 2022.
The American Association of Clinical Endocrinologists, the	Added recommendations + Updated	American Association of Clinical Endocrinology Clinical Practice	Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-

American College of Endocrinology guidelines 2019		Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan – 2022 Update	2022 Update [published correction appears in Endocr Pract. 2023 Jan;29(1):80-81]. *Endocr Pract*. 2022;28(10):923-1049. doi:10.1016/j.eprac.2022.08.002
Not available	New section	American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm – 2023 Update	Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm. *Endocr Pract*. 2023;29(5):305-340.doi: 10.1016/j.eprac.2023.02.001
Not available	New section	Saudi Diabetes Clinical Practice Guidelines by the Saudi National Diabetes Center (SNDC) at the Saudi Health Council – First Edition 2021	Saudi Diabetes Clinical Practice Guidelines by the Saudi National Diabetes Center (SNDC) at the Saudi Health Council – First Edition 2021
Not available	New section	Australian Evidence Based Clinical Guidelines for Diabetes 2021	Australian Evidence Based Clinical Guidelines for Diabetes 2021
Not available	New section	Diabetes Canada Clinical Practice Guidelines – Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update	Diabetes Canada Clinical Practice Guidelines Expert Committee, Lipscombe L, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. *Can J Diabetes*. 2020;44(7):575-591. doi:10.1016/j.jcjd.2020.08.001
Section 2.0 – Drug therapy in Type 2 Diabetes			
SGLT2 inhibitors	Addition of two medications	Ertugliflozin Bexagliflozin	
GLP-1 receptor agonists	Addition of a medication	Semaglutide (SQ and PO)	
Not available	Addition of a drug class	GLP-1/GIP dual agonist: Tirzepatide	
Not available	Addition of a drug class	Insulin/GLP-1 RAs fixed ration combinations: Degludec-Liraglutide	

		Glargine-Lixisenatide	
Not available	New section	Section 3.0 – Key Recommendation Synthesis	
Section 5.0 – Conclusion	New section	Section 4.0 – Conclusion	
Section 3.0 – References	Updated	Section 5.0 – References	
Section 4.0 – Appendix	Updated	Section 6.0 – Appendices	

Appendix E. Treatment Algorithm

The following treatment algorithm is adapted from the 2023 ADA Standards of Care in Diabetes 2023 and the Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[4,31]