Diabetic Retinopathy

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

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To the CHI Original Diabetic Retinopathy Clinical Guidance-Issued May 2020

Contents

List of Tables 3
Related Documents 3
Abbreviations 4
Executive Summary 5
Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence 9
1.1 Revised Guidelines 9
1.1.1 American Academy of Ophthalmology: Diabetic Retinopathy Preferred Practice Pattern (March 2022 Update) 9
1.1.2 American Diabetes Association (ADA) Guidelines Standards of Care in Diabetes—2023 11
1.2 Additional Guidelines 13
1.2.1 Saudi National Diabetes Center (SNDC) 2021 Saudi Diabetes Clinical Practice Guidelines (SDCPG) 13
1.2.2 2018 Clinical Practice Guidelines Retinopathy Diabetes Canada Clinical Practice Guidelines Expert Committee 15
1.2.3 Japanese Clinical Practice Guideline for Diabetes (2019) 18
Section 2.0 Drug Therapy in Diabetic Retinopathy 19
2.1 Additions 19
2.1.1 Faricimab 19
2.1.2 Brolucizumab 27
2.2 Modifications 32
2.3. Delisting 32
Section 3.0 Key Recommendation Synthesis 33
Section 4.0 Conclusion 33
Section 5.0 References 34
Section 6.0 Appendices 36
Appendix A. Prescribing Edits Definition 36
Appendix B. Diabetic Retinopathy Scope 37
Appendix C. MeSH Terms PubMed 40
Appendix D. Treatment Algorithm 41

List of Tables

Table 1. General Recommendations for the Management of Diabetic Retinopathy.....6
Table 2. Guidelines Requiring Revision 9
Table 3. Definitions and levels of evidence based on the Scottish Intercollegiate Guideline Network1 (SIGN) 9
Table 4. Quality of Evidence Recommendations as Defined by GRADE.....10
Table 5. American Academy of Ophthalmology Grading Scheme for Recommendations 10
Table 6. ADA Grading System for Standards of Care in Diabetes.....12
Table 7. List of Additional Guidelines.....13
Table 8. Grading System for Japanese Clinical Practice Guideline for Diabetes 2019.18
Table 9. Drug Therapy with Faricimab 19
Table 10. HTA Analysis of Faricimab 25
Table 11. Drug Therapy with Brolucizumab 27
Table 12. HTA Analysis of Brolucizumab.....31

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

Abbreviations

ACEI	Angiotensin-Converting Enzyme Inhibitor
ADA	American Diabetes Association
AMD	Age-related Macular Degeneration
ARB	Angiotensin Receptor Blocker
BCVA	Best-Corrected Visual Acuity
BP	Blood Pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CI-DME	Center-Involved Diabetic Macular Edema
CPG	Clinical Practice Guideline
CST	Central subfield thickness
CV	Cardiovascular
DM	Diabetes Mellitus
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
HAS	Haute Autorité de Santé
HDL	High-Density Lipoprotein
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IQWIG	The Institute for Quality and Efficiency in Healthcare
nAMD	Neovascular (wet) Age-Related Macular Degeneration
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PRP	Panretinal Photocoagulation
RAAS	Renin-Angiotensin-Aldosterone System
RR	Risk Ratio
SDCPG	Saudi Diabetes Clinical Practice Guidelines
SFDA	Saudi Food and Drug Authority
SNDC	Saudi National Diabetes Center
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
VEGF	Vascular Endothelial Growth Factor

Executive Summary

Diabetic retinopathy (DR) is a common complication in type 1 and type 2 diabetes characterized by changes to the retinal blood vessels which can lead to bleeding, leakage of fluid and vision loss. DR is divided into two major forms: non-proliferative and proliferative, named for the absence or presence of abnormal new blood vessels in the retina which can also be classified according to severity[1].

It is considered as one of the most important causes of visual loss worldwide and is the principal cause of impaired vision in patients between 20 and 74 years of age. Of an estimated 285 million people with diabetes mellitus worldwide, approximately one third have signs of DR and of these, a further one third of DR is vision-threatening DR[2].

In 2015, Saudi Arabia had the highest prevalence (17.6%) of DM in the Middle East and North Africa Region. The overall global prevalence of DR is estimated to be around 34.6%, accounting for 4.8% of blindness in the world. In Saudi Arabia, the prevalence of DR was found to be 19.7%, with 53% of them reported to have proliferative diabetic retinopathy (PDR). Other studies from different regions of Saudi Arabia have reported a high prevalence of DR ranging from 27.8% to 36%[3].

Prevention can be done through good glycemic and blood pressure control and lipid lowering therapy. The goals of treatment of diabetic retinopathy include improvement in vision, preservation of vision, and reduction in the rate of progression and frequency of retinopathy, vitreous hemorrhage, and macular edema. Treatment options include: intravitreal agents that inhibit the vascular endothelial growth factor (VEGF) such as ranibizumab, aflibercept, and brolucizumab, laser therapy and intravitreal glucocorticoids[3].

CHI issued Diabetic Retinopathy clinical guidance after thorough review of renowned international and national clinical guidelines in May 2020. 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 Diabetic retinopathy clinical guidance and seeks to offer guidance for the effective management of diabetic retinopathy. It provides an **update on the Diabetic Retinopathy 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** namely **American Diabetes Association (ADA)** Guidelines Standards of Care in Diabetes—**2023**. Moreover, **new guidelines are added to the report** such as. **Saudi Diabetes Clinical Practice**

Guidelines (SDCPG) Saudi National Diabetes Center (SNDC) **2021**, **2018 Clinical Practice Guidelines Retinopathy Diabetes Canada Clinical Practice Guidelines** Expert Committee, Japanese Clinical Practice Guideline for Diabetes **2019**.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drugs **Brolucizumab (BEOVU®) and** , **Faricimab (Vabysmo®)** in the CHI formulary.

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 therapeutic management of diabetic retinopathy.

Below is a table summarizing the major changes based on the different diabetic retinopathy guidelines used to issue this report:

Table 1. General Recommendations for the Management of Diabetic Retinopathy

Management of Diabetic Retinopathy		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
In order to decrease the chance of diabetic retinopathy (DR), optimization of blood pressure, glycemic and serum lipid control are necessary.	Not graded	Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC) 2021[4]
An initial comprehensive eye examination by an ophthalmologist within five years after the onset of Type 1 Diabetes Mellitus (T1DM) and at the time of Type 2 Diabetes Mellitus (T2DM) diagnosis is needed.	Not graded	Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC) 2021[4]
If eye exam was normal for more than one time and glycemia is controlled, screening can be done every 1-2 years.	Level of evidence B	American Diabetes Association (ADA) Guidelines

		Standards of Care in Diabetes—2023 [5]
Laser photocoagulation is recommended for patients with high-risk proliferative DR or severe non-proliferative DR in order to reduce vision loss.	Not graded	Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC) 2021[4]
Intra-vitreous injections of anti–vascular endothelial growth factor are considered as a reasonable alternative to traditional panretinal laser photocoagulation in some patients with proliferative DR and proved to reduce vision loss in these patients.	Not graded	Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC) 2021[4]
If diabetic macular edema is not resolved despite treatment with anti–vascular endothelial growth factor agents or in specific cases that are not candidates for first-line therapies, **macular focal/grid photocoagulation and intravitreal injections of corticosteroid** would be reasonable alternatives.	Level of evidence A	American Diabetes Association (ADA) Guidelines Standards of Care in Diabetes—2023[5]

Certain drugs were found to be associated with an increased risk of developing, or with the worsening and diabetic retinopathies and mainly include thiazolidinediones and the GLP-1 agonist semaglutide.

- Thiazolidinediones have been associated with an increased risk of incident or worsening diabetic macular edema, although this risk is believed to be low[6]
- In general, glucagon-like peptide 1 (GLP-1) agonists, also known as incretins, are beneficial for managing diabetes. However, it is noteworthy that semaglutide, a GLP-1 agonist, has been linked to higher rates of diabetic retinopathy complications[6].

- The SUSTAIN-6 trial, while not primarily designed to evaluate diabetic retinopathy (DR), did reveal a statistically significant increased risk of new onset or worsening DR. In the semaglutide group, there was a 3% incidence of DR, compared to 1.8% in the placebo group[7].
- Despite patients with proliferative diabetic retinopathy being excluded from PIONEER 6, a 0.8% increase in diabetic retinopathy was observed with oral semaglutide[8].
- A dedicated ophthalmic trial (FOCUS) of 5 years treatment duration will assess the long-term effect of semaglutide on diabetic retinopathy development and progression[9].
- Although diabetic retinopathy (DR) has been identified as a potential adverse effect of semaglutide, the overall benefit-risk profile remains positive when the medication is used in accordance with FDA-approved prescribing information. As per the American Diabetes Association guidelines, individuals newly diagnosed with type 2 diabetes should undergo a comprehensive eye examination at the time of diagnosis, followed by annual eye exams thereafter. For patients recently started on semaglutide, particularly those with a history of retinopathy, healthcare providers should exercise vigilance and closely monitor for any signs of new or worsening retinopathy[9].

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

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the May 2020 CHI Diabetic retinopathy Report and the corresponding recommendations.

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 **2019** American Academy of Ophthalmology: **Diabetic Retinopathy Preferred Practice Pattern**	1.1.1 American Academy of Ophthalmology: Diabetic Retinopathy Preferred Practice Pattern (March 2022 Update)[6]
1.2 **The Royal College of Ophthalmologists** Diabetic Retinopathy Guidelines December **2012**	N/A*
1.3 Diabetic Retinopathy: A Position Statement by the **American Diabetes Association 2017**	1.1.2 **American Diabetes Association (ADA)** Guidelines Standards of Care in Diabetes—**2023**[5]

**: No update available*

1.1.1 American Academy of Ophthalmology: Diabetic Retinopathy Preferred Practice Pattern (March 2022 Update)

The American Academy of Ophthalmology: Diabetic Retinopathy Preferred Practice Pattern (March 2022 Update)[6] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 3. Definitions and levels of evidence based on the Scottish Intercollegiate Guideline Network1 (SIGN)

Definitions and levels of evidence	
I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias

I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

Table 4. Quality of Evidence Recommendations as Defined by GRADE

Quality of evidence	
Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

Table 5. American Academy of Ophthalmology Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not.
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

- Educating patients about the visual consequences of early glucose control is crucial and should commence right from the onset of the disease.

- A healthy diet and lifestyle, which incorporates regular exercise and maintaining a healthy weight, can help reduce the risk of developing diabetes in certain individuals.
- Multiple, high quality clinical trials have demonstrated that anti-VEGF therapy is more effective in improving vision in CI-DME than monotherapy with focal laser treatment, supplanting it as the first-line therapy.
- A meta-analysis provided additional evidence that both ranibizumab and aflibercept have superior efficacy for DME treatment compared with conventional laser. (I++, Good Quality, Strong Recommendation)
- The YOSEMITE and RHINE trials illustrated that patients who received faricimab-svoa for diabetic macular edema (DME), administered every 8 weeks, achieved comparable improvements in visual acuity to those receiving aflibercept at the same interval. The FDA granted approval to faricimab-svoa on January 28, 2022. Vabysmo (faricimab-svoa), a humanized bispecific monoclonal antibody designed for intravitreal use, works by concurrently inhibiting angiopoietin-2 (ANG-2) and vascular endothelial growth factor A (VEGF-A). This medication is indicated for treating individuals with DME.
- Using topical povidone iodine is advised for intravitreal injections due to the reported significant risk of endophthalmitis when it is not used. However, the routine application of antibiotic eye drops before or after intravitreal injections is not recommended since it does not lower the risk of endophthalmitis.
- A 2018 Cochrane systematic review has reported that there is “moderate certainty evidence” of safety of anti-VEGF injections and as of 2019 no studies have shown a definite increased risk.212 (I+, Moderate quality, Strong recommendation).

1.1.2 American Diabetes Association (ADA) Guidelines Standards of Care in Diabetes—2023

The American Diabetes Association (ADA) released its 2023 standards of care in diabetes to guide prevention, diagnosis, and treatment for people living with diabetes. The grading system used is detailed in table 3, and the main recommendations pertaining to diabetic retinopathy are summarized below[5].

Table 6. ADA Grading System for Standards of Care in Diabetes

Level	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis 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

- If the eye exam was normal for more than one time and glycemia is controlled, screening can be done every 1-2 years. (Level of evidence B)
- **Intra-vitreous injections of anti–vascular endothelial growth factor agents** are considered as a reasonable alternative to traditional panretinal laser photocoagulation in some patients with proliferative DR and proved to reduce vision loss in these patients. (Level of evidence A).
- If diabetic macular edema is not resolved despite treatment with anti–vascular endothelial growth factor agents or in specific cases that are not candidates for first-line therapies, **macular focal/grid photocoagulation** and **intravitreal**

injections of corticosteroid would be reasonable alternatives. (Level of evidence A).

- Intravitreal injections of anti-VEGF proved effectiveness in delaying the progress of proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal photocoagulation (PRP) over 2 years of follow-up (Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others). (Ungraded)
- Observational studies have shown that Ranibizumab contributed to less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications, and a lower risk of developing diabetic macular edema. (Ungraded)
- However, the disadvantage of anti-VEGF therapy to manage proliferative disease is that patients were required to have a greater number of visits and received a greater number of treatments than is usually required for management with panretinal laser, which may not be very convenient for some individuals. (Ungraded)

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Diabetic Retinopathy report, along with their recommendations.

Table 7. List of Additional Guidelines

Additional Guidelines
Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC) 2021[4]
2018 Clinical Practice Guidelines Retinopathy Diabetes Canada Clinical Practice Guidelines Expert Committee[7]
Japanese Clinical Practice Guideline for Diabetes 2019[8]

1.2.1 Saudi National Diabetes Center (SNDC) 2021 Saudi Diabetes Clinical Practice Guidelines (SDCPG)

The Saudi National Diabetes Center (SNDC) published its Saudi Diabetes Clinical Practice Guidelines (SDCPG) in 2021. The main recommendations are detailed below[4]:

- In order to decrease the chance of diabetic retinopathy (DR), optimization of blood pressure, glycemic and serum lipid control are necessary.

- An initial comprehensive eye examination by an ophthalmologist within five years after the onset of Type 1 Diabetes Mellitus (T1DM) and at the time of Type 2 Diabetes Mellitus (T2DM) diagnosis is needed.
- Follow-up should be conducted every three years. If retinopathy was detected, follow-up should be done annually or more frequently.
- Counselling on the risk of DR should be provided for pregnant women or those planning pregnancy with T1DM or T2DM as well as eye examinations every trimester, then 1-year postpartum according to the degree of DR.
- DM patients with any level of macular edema, severe non-proliferative DR, or any proliferative DR should be examined by an ophthalmologist.
- Lifestyle management is a cornerstone of diabetes care, and it should be collaboratively developed with the patient and adjusted regularly, beginning with the initial visit. It encompasses various components, including diabetes self-management education and support, nutritional therapy, physical activity, sleep health, counseling for smoking and alcohol cessation, and psychosocial care.
- **Laser photocoagulation** is recommended for patients with high-risk proliferative DR or severe non-proliferative DR in order to reduce vision loss.
- **Intra-vitreous injections of anti–vascular endothelial growth factor** ranibizumab are not inferior to traditional panretinal laser photocoagulation, and are indicated to reduce the risk of vision loss in patients with proliferative DR.
- Intra-vitreous injections of anti-vascular endothelial growth factor are indicated for central involved macular edema.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARBs) showed to be effective treatments in DR.
- The addition of fenofibrate can delay the progression of DR in patients with dyslipidemia, especially those with very mild baseline nonproliferative DR.
- The use of aspirin for cardio-protection is not contraindicated in cases of diabetic retinopathy.
- In cases of proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy, engaging in vigorous-intensity aerobic or resistance exercises is contraindicated. This is because such exercises can elevate the risk of vitreous hemorrhage or retinal detachment in individuals with these eye conditions.

1.2.2 2018 Clinical Practice Guidelines Retinopathy Diabetes Canada Clinical Practice Guidelines Expert Committee

The following recommendations are retrieved from 2018 Clinical Practice Guidelines Retinopathy Diabetes Canada Clinical Practice Guidelines Expert Committee[7]:

Screening Recommendations for Diabetic Retinopathy

When to initiate screening

- T1DM: 5 years after diagnosis in all individuals ≥ 15 years
- T2DM: children, adolescents and adults at diagnosis

Screening methods

- 7-standard filed, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard)
- Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil
- Digital fundus photography

If retinopathy is present

- Diagnose retinopathy severity and establish appropriate monitoring intervals (1 year or less)
- Treat sight-threatening retinopathy with laser, pharmacological or surgical therapy
- Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines
- Screen for other diabetes complications

If retinopathy is not present

- T1DM: rescreen annually
- T2DM: rescreen every 1 to 2 years
- Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines
- Screen for other diabetes complications

Treatment

- Steroids are an alternate class of drug utilized in the management of DME. Injectable agents include triamcinolone, dexamethasone and fluocinolone.

- Treatments with intraocular steroids are associated with increased rates of glaucoma and cataract formation.
- Fenofibrate could added to statins in patients with type 2 diabetes to regress the progression of retinopathy although not usually recommended for CVD prevention or treatment, in addition to statin therapy, may be used in people with type 2 diabetes to slow the progression of established retinopathy [Grade A, Level 1A]
- The effect of the fenofibrate peroxisome proliferator-activated receptor-alpha agonist was studied in 2 large-scale randomized controlled trials.
- The objective of the **Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)** study was to evaluate whether long-term lipid-lowering therapy with fenofibrate could delay the progression of retinopathy and the need for laser treatment in individuals diagnosed with type 2 diabetes mellitus.
- Individuals were eligible for inclusion if they were aged between 50 and 75 years, had type 2 diabetes according to WHO criteria, and had an initial plasma total cholesterol concentration of 3·0–6·5 mmol/L and a total cholesterol/HDL-cholesterol ratio of 4·0 or more, or a plasma triglyceride concentration of 1·0–5·0 mmol/L, without requiring lipid-modifying treatment at study entry.
- Fenofibrate 200 mg daily reduced both the requirement for laser therapy (a pre-specified tertiary endpoint) and retinopathy progression among people with pre-existing retinopathy[9].
- The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study was designed to evaluate the effects of the three interventions on the development and progression of diabetic retinopathy in a subset of ACCORD Study participants.
- In the ACCORD Eye study, the addition of fenofibrate 160 mg daily to simvastatin was associated with a 40% reduction in the primary outcome of retinopathy progression over 4 years.
- From the study's control and event rates, the number of people needed to treat with combination statin and fenofibrate therapy to prevent 1 retinopathy progression event is estimated at 27 over the 4-year period.
- The mechanism for any beneficial effect of fenofibrate in diabetic retinopathy has not been established.
- Active treatment with fenofibrate was associated with an increase in high-density lipoprotein cholesterol (HDL-C) and decrease in serum triglycerides in

ACCORD Eye; however, in the FIELD study, any beneficial effect of fenofibrate was independent of plasma lipid concentrations.

- Thus, the addition of fenofibrate to statin therapy could be considered in people with type 2 diabetes to slow the progression of established retinopathy[10].
- Retinopathy complicated with non-clearing vitreous bleeding in diabetes should be treated with Vitreoretinal surgery, persistent neovascularization (especially post PRP laser +/- VEGF injectables) and vitreoretinal traction, especially with retinal detachment threatening the macula.
- A systematic review and meta-analysis were carried out to evaluate the effect(s) of RAAS inhibition on diabetic retinopathy, and to compare between ACE inhibitors and ARBs.
- The study included 21 randomized controlled clinical trials and 13,823 participants. Results of these analyses suggest that RAAS inhibition was associated with reduced risk of incidence and progression of diabetic retinopathy, and that ACE inhibitors were better than ARBs at reducing these risks.
- Studies meeting the following selection criteria were included: randomized controlled trial; individuals with type 2 diabetes or type 1 diabetes; comparison of ACE inhibitor or ARB monotherapy with other antihypertensive drugs (eg, β blockers, calcium channel blockers, or diuretics) or placebo; had at least one of incidence, progression, or regression of diabetic retinopathy as outcomes, and reported number of patients and events in each treatment group or reported the risk ratio (RR) with corresponding 95% CI; time of follow-up was more than 3 months; and appropriate initial doses of RAS inhibitors (ranging from a quarter of the recommended dose to the maximum recommended dose) for blood pressure control.
- However, the study did not evaluate the effect(s) of RAAS inhibition in participants with multiple medical comorbidities (the subgroup of participants that are more likely to benefit from RAAS blockade), or the optimal dosage and duration of specific RAAS inhibitors.
- Thus, while BP lowering (including use of RAAS blockers) reduces retinopathy rates and is an important component of cardiovascular (CV) protection (see Cardiovascular Protection in People with Diabetes chapter, p. S162), there is insufficient evidence to recommend specific routes of RAAS blockade as primary prevention for retinopathy for all normotensive people with diabetes[11].

1.2.3 Japanese Clinical Practice Guideline for Diabetes (2019)

The grading system used by the Japanese clinical practice guidelines for diabetes in detailed in table 5, and the main recommendations issued are summarized below[8]:

Table 8. Grading System for Japanese Clinical Practice Guideline for Diabetes 2019

Strength of Recommendation	Grading	Note
Strongly recommend	Grade A	Positive rating is ahead for the 4 items below*
Weakly recommend	Grade B	Negative rating is ahead for the 4 items below*
*Certainty of overall evidence, balance of benefits and harms, patient preferences and values, costs		

- The use of fenofibrates proved to delay the progression of diabetic retinopathy in patients with type 2 diabetes complicated by dyslipidemia. (Grade B: 85% agreement)
- The use of antiplatelet agents did not show clinical evidence for suppressing the onset/progression of diabetic retinopathy. (Ungraded)
- Diabetic retinopathy is a risk factor for diabetic nephropathy and macroangiopathy. (Ungraded)

Section 2.0 Drug Therapy in Diabetic Retinopathy

This section comprises three subsections: the first contains the newly recommended drugs, the second covers drug modifications, and the third outlines the drugs that have been withdrawn from the market.

2.1 Additions

2.1.1 Faricimab

This section includes pertinent information regarding the use of Faricimab (Vabysmo®) in for the treatment of wet age-related macular degeneration (AMD) and diabetic macular edema (DME) (Lexicomp 2023).

Table 9. Drug Therapy with Faricimab

SCIENTIFIC NAME **Faricimab**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	H36.0, H35.2, H35.1, H35.0, E14.34, E14.33, E14.32, E14.31, E13.34, E13.33, E13.32, E13.31, E11.34, E11.33, E11.32, E11.31, E10.34, E10.33, E10.31, E10.32
Drug Class	Angiopoietin-2 Inhibitor; Ophthalmic Agent
Drug Sub-class	Vascular endothelial growth factor inhibitor (Anti-VEGF)
ATC Code	S01LA
Pharmacological Class (ASHP)	52:56 - Vascular Endothelial Growth Factor Antagonists
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravitreal use
Dose (Adult) [DDD]*	**Age-related macular degeneration, neovascular (wet):** - Intravitreal: Initial: 6 mg once every 4 weeks (approximately

	every 28 days) for 4 doses. Subsequent doses are individualized based on visual assessments, and are administered as one of the following regimens: o Every-8-week regimen: 6 mg on weeks 20, 28, 36, and 44 o Every-12-week regimen: 6 mg on weeks 24, 36, and 48 o Every-16-week regimen: 6 mg on weeks 28 and 44 **Macular edema, diabetic:** Doses may be administered based on one of the following regimens: - Fixed interval regimen: Intravitreal: 6 mg once every 4 weeks (approximately every 28 days) for 6 doses, followed by 6 mg once every 8 weeks - Variable interval regimen: Intravitreal: 6 mg once every 4 weeks (approximately every 28 days) for at least 4 doses, followed by 6 mg every 4 to 16 weeks (based on visual assessments)
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	<u>Renal Impairment:</u> - CrCl ≥15 mL/minute/1.73 m2: No dosage adjustment necessary. - CrCl <15 mL/minute/1.73 m2: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

	Hepatic Impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	MD, ST, PA
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): It can only be obtained with a prescription and must be given by a qualified doctor who is experienced in giving intravitreal injections.	
PA (Prior Authorization): This medication is expensive, needs to be prescribed by a specialized physician and is usually used as second-line therapy if other agents have failed.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Should be used as second like after other agents have failed.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Cataract Most serious: - Ophthalmic events: Cataract, conjunctival hemorrhage, increased intraocular pressure (IOP), intraocular inflammation (including iridocyclitis, iritis, uveitis, vitritis), retinal pigment epithelium tear, and vitreous opacity, Conjunctival hyperemia, corneal abrasion, decreased visual acuity (may be transient), endophthalmitis, ocular hyperemia, rhegmatogenous retinal detachment, retinal hole without detachment, and vitreous hemorrhage. - Thromboembolic events: Arterial thromboembolism, including acute myocardial

	infarction and cerebrovascular accident.
Drug Interactions*	No interactions of Risk Level A or greater identified.
Special Population	N/A
Pregnancy	Based on the mechanism of action, in utero exposure to faricimab may cause fetal harm. Faricimab is a vascular endothelial growth factor (VEGF) inhibitor; VEGF is required to achieve and maintain normal pregnancies. Reproductive considerations: Based on the mechanism of action, faricimab may affect fertility. Patients who may become pregnant should use effective contraception during treatment and for at least 3 months after the last dose of faricimab.
Lactation	It is not known if faricimab is present in breast milk. 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 (eg, rash, pruritus, urticaria, erythema, severe intraocular inflammation) to faricimab or any component of the formulation; ocular or periocular infections; active intraocular inflammation.
Monitoring Requirements	Monitor intraocular pressure (via tonometry) and optic nerve head perfusion immediately following administration; symptoms of endophthalmitis and retinal detachment (eg, eye redness/pain, photophobia, blurred vision, other vision changes).

Precautions	Retinal vasculitis/retinal vascular occlusion: Cases of retinal vasculitis and/or retinal vascular occlusion have been reported with other vascular endothelial growth factor inhibitors (eg, brolucizumab) but not faricimab.
Black Box Warning	N/A
REMS*	N/A

Clinical Trials – Faricimab

1. **Neovascular (wet) Age-Related Macular Degeneration (nAMD)**

TENAYA and LUCERNE were randomised, double-masked, non-inferiority trials across 271 sites worldwide[12].

Patients aged 50 years or older at randomisation (day 1) were eligible to participate. Treatment-naive patients were randomly assigned (1:1) to intravitreal faricimab 6·0 mg up to every 16 weeks, based on protocol-defined disease activity assessments at weeks 20 and 24, or aflibercept 2·0 mg every 8 weeks. Randomisation was performed through an interactive voice or web-based response system using a stratified permuted block randomisation method. Patients, investigators, those assessing outcomes, and the funder were masked to group assignments. The primary endpoint was mean change in best corrected visual acuity (BCVA) from baseline averaged over weeks 40, 44, and 48 (prespecified non-inferiority margin of four letters), in the intention-to-treat population[12].

Across the two trials, 1329 patients were randomly assigned between Feb 19 and Nov 19, 2019 (TENAYA n=334 faricimab and n=337 aflibercept), and between March 11 and Nov 1, 2019 (LUCERNE n=331 faricimab and n=327 aflibercept). BCVA change from baseline with faricimab was non-inferior to aflibercept in both TENAYA (adjusted mean change 5·8 letters [95% CI 4·6 to 7·1] and 5·1 letters [3·9 to 6·4]; treatment difference 0·7 letters [−1·1 to 2·5]) and LUCERNE (6·6 letters [5·3 to 7·8] and 6·6 letters [5·3 to 7·8]; treatment difference 0·0 letters [–1·7 to 1·8]). Rates of ocular adverse events were comparable between faricimab and aflibercept (TENAYA n=121 [36·3%] vs n=128 [38·1%], and LUCERNE n=133 [40·2%] vs n=118 [36·2%])[12].

The positive visual outcomes achieved through faricimab administered every 16 weeks highlight its ability to significantly prolong the treatment interval while maintaining effectiveness. This has the potential to decrease the treatment frequency and burden for individuals with nAMD[12].

2. Diabetic Macular Edema (DME)

The safety and efficacy of VABYSMO were assessed in two randomized, multi-center, double-masked, active comparator-controlled 2-year studies (YOSEMITE – NCT03622580 and RHINE – NCT03622593) in patients with DME[13].

The inclusion criteria were the following:

- Macular thickening secondary to DME involving the center of the fovea, with Central subfield thickness (CST) ≥325 µm
- BCVA between 25 and 73 Early Treatment Diabetic Retinopathy Study (ETDRS) letters
- Sufficiently clear ocular media and adequate pupillary dilatation to allow acquisition of good-quality CFP images (including ETDRS 7 modified fields or 4 wide-angle fields to permit grading of DR and assessment of the retina) and other imaging methods[13].

These studies were designed to evaluate 3 treatment groups: faricimab 6.0 mg dosed either at fixed dosing every 8 weeks after initial treatment with 6 intravitreal doses at 4-week intervals, or faricimab 6.0 mg dosed according to personalized treatment interval after initial treatment with 4 every-4-week doses, compared with aflibercept 2.0 mg dosed every 8 weeks after 5 initial every-4-week doses. The primary end point of the studies was change from baseline in best-corrected visual acuity at 1 year, averaged over weeks 48, 52, and 56[13].

The YOSEMITE and RHINE trials thus should provide further insights on the efficacy and safety of faricimab for the treatment of DME, as well as on the potential benefits of an algorithm-based PTI regimen allowing for up to every16-week dosing with faricimab. The 2-year outcomes will allow a deeper assessment of the potential for faricimab, through dual angiopoietin-2 and VEGF-A inhibition, to improve retinal stability and to deliver sustained efficacy in the long term[13].

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of diabetic macular edema and neovascular (wet) age-related macular degeneration 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 are for Faricimab.**

Table 10. HTA Analysis of Faricimab

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Faricimab	NICE	**Diabetic Macular Edema** 06/2022: Faricimab is recommended as an option for treating visual impairment due to diabetic macular oedema in adults, only if: - the eye has a central retinal thickness of 400 micrometres or more at the start of treatment the company provides faricimab according to the commercial arrangement.[14] **Wet age-related macular degeneration** 06/2022: Faricimab is recommended as an option for treating wet age-related macular degeneration in adults, only if: - the eye has a best-corrected visual acuity between 6/12 and 6/96 - there is no permanent structural damage to the central fovea the lesion size is 12-disc areas or less in greatest linear dimension - there are signs of recent disease progression (for example, blood vessel growth as shown by fluorescein angiography, or recent visual acuity changes) - the company provides faricimab according to the commercial arrangement[15]
	CADTH	**Diabetic macular edema** 10/2022: Vabysmo should only be reimbursed if prescribed by an ophthalmologist with experience managing DME and if the cost of Vabysmo is not more than the least costly anti-VEGF drug covered by the public drug plans for the treatment of DME.[16] **Neovascular (wet) age-related macular degeneration**

		08/2022: Vabysmo should only be reimbursed if prescribed by an ophthalmologist with experience managing nAMD and if the cost per administration is not more than the least costly drug covered by the public drug plans for the treatment of nAMD.[17]
	HAS	**Neovascular (wet) retrofoveal age-related macular degeneration** 01/2023: Favourable opinion for reimbursement "the treatment of neovascular (wet) retrofoveal age-related macular degeneration (AMD) in adults".[18] **Diabetic macular edema** 01/2023: Favorable opinion for reimbursement only in "the treatment of adult patients with visual impairment due to diabetic macular oedema (DME), in the event of diffuse forms or leakages close to the centre of the macula, in adults with a visual acuity of ≤ 5/10 and in whom diabetes management has been optimised."[19]
	IQWIG	Not available
	PBAC	**Diabetic macular edema** 01/2023: Patient must have visual impairment due to diabetic macular oedema, AND - Patient must have documented visual impairment defined as a best corrected visual acuity score between 78 and 39 letters based on the early treatment diabetic retinopathy study chart administered at a distance of 4 meters (approximate Snellen equivalent 20/32 to 20/160), in the eye proposed for treatment, AND The condition must be diagnosed by optical coherence tomography; OR

		The condition must be diagnosed by fluorescein angiography, AND The treatment must be as monotherapy; OR The treatment must be in combination with laser photocoagulation, AND The treatment must be the sole PBS-subsidised therapy for this condition.[20]

Conclusion Statement – Faricimab

Faricimab is recommended as an option for the treatment of diabetic macular edema and neovascular (wet) age-related macular degeneration. NICE, CADTH, PBAC and HAS recommend the use of Faricimab under specific conditions. However, no relevant information could be retrieved from IQWIG.

2.1.2 Brolucizumab

This section includes pertinent information regarding the use of Brolucizumab (BEOVU®) in Diabetic Macular Edema (Lexicomp 2023).

Table 11. Drug Therapy with Brolucizumab

SCIENTIFIC NAME **Brolucizumab**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	No
PMDA	No
Indication (ICD-10)	H36.0, H35.2, H35.1, H35.0, E14.34, E14.33, E14.32, E14.31, E13.34, E13.33, E13.32, E13.31, E11.34, E11.33, E11.32, E11.31, E10.34, E10.33, E10.31, E10.32
Drug Class	Antiangiogenic ophthalmic agent, Monoclonal Antibody
Drug Sub-class	Vascular endothelial growth factor inhibitor (Anti-VEGF)
ATC Code	S01LA
Pharmacological Class (ASHP)	52:56 - Vascular Endothelial Growth Factor Antagonists

DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Intravitreal use
Dose (Adult) [DDD]*	Intravitreal: 6 mg every 6 weeks (approximately every 39 to 45 days) for 5 doses, followed by 6 mg once every 8 to 12 weeks.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal Impairment: No dosage adjustment necessary Hepatic Impairment: No dosage adjustment necessary
Prescribing edits*	MD, ST, PA
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): It can only be obtained with a prescription and must be given by a qualified doctor who is experienced in giving intravitreal injections.	
PA (Prior Authorization): This medication is expensive, needs to be prescribed by a specialized physician and is usually used as second-line therapy if other agents have failed.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Should be used as second like after other agents have failed.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Immunologic: Antibody development Most serious: Arterial thromboembolism, blindness
Drug Interactions*	There are no known significant interactions

Special Population	N/A
Pregnancy	Based on findings in animal reproduction studies and on the mechanism of action, brolucizumab may cause fetal harm if administered to a pregnant female. Reproductive considerations: Evaluate pregnancy status prior to use in females of reproductive potential. Females of reproductive potential should use highly effective contraception (methods with pregnancy rates <1%) during therapy and for ≥1 month following the last brolucizumab dose.
Lactation	It is not known if brolucizumab is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for ≥1 month following the last brolucizumab dose.
Contraindications	Hypersensitivity (e.g., rash, pruritus, urticaria, erythema, severe intraocular inflammation) to brolucizumab or any component of the formulation; ocular or periocular infections; active intraocular inflammation
Monitoring Requirements	Intraocular pressure (via tonometry) and optic nerve head perfusion immediately following administration; symptoms of endophthalmitis and retinal detachment; symptoms of retinal vasculitis and retinal vascular occlusion (especially in patients with intraocular inflammation), vision changes.

Precautions	- Endophthalmitis and retinal detachment - Increased intraocular pressure. - Retinal vasculitis/retinal vascular occlusion Thromboembolic events
Black Box Warning	N/A
REMS*	N/A

Clinical Trials – Brolucizumab

Two randomized trials (KESTREL – NCT03481634 and KITE - NCT03481660) were conducted to compare the efficacy and safety of brolucizumab with aflibercept in patients with diabetic macular edema (DME).

Subjects were randomized 1:1:1 to brolucizumab 3 mg/6 mg or aflibercept 2 mg in KESTREL (n = 566) or 1:1 to brolucizumab 6 mg or aflibercept 2 mg in KITE (n = 360). Brolucizumab groups received 5 loading doses every 6 weeks (q6w) followed by 12-week (q12w) dosing, with optional adjustment to every 8 weeks (q8w) if disease activity was identified at predefined assessment visits; aflibercept groups received 5 doses every 4 weeks (q4w) followed by fixed q8w dosing.

Eligible participants were aged ≥18 years with type 1 or 2 diabetes mellitus, glycosylated hemoglobin (HbA1c) ≤10%, and who presented with (i) BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts at an initial testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening and baseline; and (ii) central-involved DME with central subfield thickness (CSFT) of ≥320 µm on spectral domain optical coherence tomography (SD-OCT) at screening.

At Week 52, brolucizumab 6 mg was non-inferior (NI margin 4 letters) to aflibercept in mean change in BCVA from baseline (KESTREL: +9.2 letters vs +10.5 letters; KITE: +10.6 letters vs +9.4 letters; P < .001), more subjects achieved central subfield thickness.

Brolucizumab 6 mg showed robust visual gains and anatomical improvements with an overall favorable benefit/risk profile in patients with DME[21].

doses every 4 weeks (q4w) followed by fixed q8w dosing.

Eligible participants were aged ≥18 years with type 1 or 2 diabetes mellitus, glycosylated hemoglobin (HbA1c) ≤10%, and who presented with (i) BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts at an initial testing distance of 4 meters (approximate Snellen equivalent of 20/32 to

20/320) at screening and baseline; and (ii) central-involved DME with CSFT of ≥320 µm on spectral domain optical coherence tomography (SD-OCT) at screening.

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Brolucizumab 6 mg showed robust visual gains and anatomical improvements with an overall favorable benefit/risk profile in patients with DME[21].

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of of diabetic macular edema 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 are for brolucizumab.**

Table 12. HTA Analysis of Brolucizumab

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Brolucizumab	NICE[22]	07/2022: Brolucizumab is recommended as an option for treating visual impairment due to diabetic macular oedema in adults, only if the eye has a central retinal thickness of 400 micrometers or more at the start of treatment and the company provides brolucizumab according to the commercial arrangement.
	CADTH[23]	01/2023: Beovu should only be reimbursed if prescribed by an ophthalmologist with experience in managing DME and if its cost is not more than the least costly anti-VEGF drug covered by the public drug plans for the treatment of DME.
	HAS[24]	09/2022: Approval of reimbursement, in adults, for the treatment of visual impairment due to diabetic macular oedema, in the case of diffuse forms or leakages near the center of the macula,

		in patients with visual impairment of 5/10 or less and for whom diabetes management has been optimized.
	IQWIG[25]	07/2022: The overall consideration shows neither positive nor negative effects for brolucizumab in comparison with aflibercept. In summary, there is no proven added benefit of brolucizumab in comparison to aflibercept for adults with visual impairment due to DMO
	PBAC	Not available

Conclusion Statement – Brolucizumab

Brolucizumab is recommended as an option for the treatment of diabetic macular edema. NICE, CADTH and HAS recommend the use of Brolucizumab (Beovu) under specific conditions. As for IQWIG, their position is neutral as no clear benefit for brolucizumab in comparison to aflibercept was proven yet.

2.2 Modifications

No modifications have been made to the medications since May 2020.

2.3. Delisting

No drugs were delisted from the SFDA list.

Section 3.0 Key Recommendation Synthesis

- To reduce the likelihood of diabetic retinopathy (DR), it is essential to optimize the management of blood pressure, glycemic levels, and serum lipid levels[4].
- It is necessary to undergo a thorough eye examination by an ophthalmologist within five years of the start of Type 1 Diabetes Mellitus (T1DM) and at the time of Type 2 Diabetes Mellitus (T2DM) diagnosis[4].
- Regular follow-up examinations should take place every three years. However, if retinopathy has been identified, follow-up should occur annually or more frequently[4].
- Patients with diabetes mellitus (DM) who have macular edema at any level, severe non-proliferative diabetic retinopathy (DR), or any form of proliferative DR should be referred to an ophthalmologist[4].
- Anti-VEGF drugs have become first-line therapy in the management of centre-involving DME[7].
- The addition of fenofibrate can delay the progression of DR in patients with dyslipidemia, especially those with very mild baseline nonproliferative DR[4].
- There is no contraindication to the use of aspirin for cardio-protection in cases of diabetic retinopathy[4].
- If diabetic macular edema persists even after receiving treatment using anti-vascular endothelial growth factor medications or in situations where certain individuals are not suitable for initial therapies, it would be reasonable to consider using macular focal/grid photocoagulation and intravitreal corticosteroid injections as alternative options[5].
- Injectable agents include triamcinolone, dexamethasone and fluocinolone[7].
- There is insufficient evidence to recommend the use of ACEI and ARB as primary prevention for retinopathy for all normotensive people with diabetes[7].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Diabetic Retinopathy report** and aims to provide recommendations to aid in the management of Diabetic Retinopathy. 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 Diabetic Retinopathy. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Altomare F, Kherani A, Lovshin J. Retinopathy. *Can J Diabetes*. 2018;42:S210-S216. doi:10.1016/j.jcjd.2017.10.027
2. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye and Vision*. 2015;2(1). doi:10.1186/s40662-015-0026-2
3. Al-Shehri AM, Aldihan KA, Aljohani S. Reasons for the Late Presentation of Diabetic Retinopathy in Saudi Arabia: A Survey of Patients Who Presented with Advanced Proliferative Diabetic Retinopathy to a Tertiary Eye Hospital. *Clinical Ophthalmology*. 2022;16:4323-4333. doi:10.2147/opth.s394146
4. *Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC).*; 2021.
5. standards-of-care-2023. Published online 2023.
6. Saw M, Wong VW, Ho I Van, Liew G. New anti-hyperglycaemic agents for type 2 diabetes and their effects on diabetic retinopathy. *Eye (Basingstoke)*. 2019;33(12):1842-1851. doi:10.1038/s41433-019-0494-z
7. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2016;375(19):1834-1844. doi:10.1056/nejmoa1607141
8. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2019;381(9):841-851. doi:10.1056/nejmoa1901118
9. Semaglutide Carries Potential Risk of Worsening Diabetic Retinopathy. Accessed September 6, 2023. https://www.pharmacytimes.com/view/semaglutide-carries-potential-risk-of-worsening-diabetic-retinopathy
10. Flaxel CJ, Adelman RA, Bailey ST, et al. Diabetic Retinopathy Preferred Practice Pattern®. *Ophthalmology*. 2020;127(1):P66-P145. doi:10.1016/j.ophtha.2019.09.025
11. Altomare F, Kherani A, Lovshin J. Retinopathy. *Can J Diabetes*. 2018;42:S210-S216. doi:10.1016/j.jcjd.2017.10.027
12. Araki E, Goto A, Kondo T, et al. Japanese Clinical Practice Guideline for Diabetes 2019. *Diabetol Int*. 2020;11(3):165-223. doi:10.1007/s13340-020-00439-5
13. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Published online 2007. doi:10.1016/S0140
14. Chew EY, Davis MD, Danis RP, et al. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: The action to control cardiovascular risk in diabetes (ACCORD) eye study. *Ophthalmology*. 2014;121(12):2443-2451. doi:10.1016/j.ophtha.2014.07.019

15. Wang B, Wang F, Zhang Y, et al. Effects of RAS inhibitors on diabetic retinopathy: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(4):263-274. doi:10.1016/S2213-8587(14)70256-6

16. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *The Lancet*. 2022;399(10326):729-740. doi:10.1016/S0140-6736(22)00010-1

17. Eter N, Singh RP, Abreu F, et al. YOSEMITE and RHINE: Phase 3 Randomized Clinical Trials of Faricimab for Diabetic Macular Edema: Study Design and Rationale. *Ophthalmology Science*. 2022;2(1). doi:10.1016/j.xops.2021.100111

18. *Faricimab for Treating Diabetic Macular Oedema*.; 2022. www.nice.org.uk/guidance/ta799

19. *Faricimab for Treating Wet Age-Related Macular Degeneration*.; 2022. www.nice.org.uk/guidance/ta800

20. CADTH Reimbursement Recommendation Faricimab (Vabysmo) 2.

21. CADTH Reimbursement Recommendation Faricimab (Vabysmo) 2.

22. *HAS-Evaluation and Access to Innovation Department New Indication What Therapeutic Improvement? Role in the Care Pathway?* www.has-sante.fr

23. *HAS-Evaluation and Access to Innovation Department New Indication Key Points*. www.has-sante.fr

24. FARICIMAB. Published 2023. Accessed August 30, 2023. https://www.pbs.gov.au/medicine/item/13177M-13183W-13195L-13198P

25. Brown DM, Emanuelli A, Bandello F, et al. KESTREL and KITE: 52-Week Results From Two Phase III Pivotal Trials of Brolucizumab for Diabetic Macular Edema. *Am J Ophthalmol*. 2022;238:157-172. doi:10.1016/j.ajo.2022.01.004

26. *Brolucizumab for Treating Diabetic Macular Oedema*.; 2022. www.nice.org.uk/guidance/ta820

27. CADTH Reimbursement Recommendation Brolucizumab (Beovu) 2. Published online 2023.

28. *HAS-Evaluation and Access to Innovation Department*.; 2022.

29. for Quality I, in Health Care E. *Brolucizumab (Visual Impairment Due to Diabetic Macular Oedema)-Benefit Assessment According to §35a Social Code Book V 1*.; 2022. www.iqwig.de

30. Standards of Care in Diabetes-2023. Published online 2022. https://diabetesjournals.org/care

31. *Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC)*.

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

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. Diabetic Retinopathy Scope

Section	Rationale/Updates
Section 1.1.1 1.1.1 American Academy of Ophthalmology: Diabetic Retinopathy Preferred Practice Pattern (March 2022 Update)[6]	• Multiple, high quality clinical trials have demonstrated that anti-VEGF therapy is more effective in improving vision in CI-DME than monotherapy with focal laser treatment, supplanting it as the first-line therapy. • A meta-analysis provided additional evidence that both ranibizumab and aflibercept have superior efficacy for DME treatment compared with conventional laser. (I++, Good Quality, Strong Recommendation) • The YOSEMITE and RHINE trials illustrated that patients who received faricimab-svoa for diabetic macular edema (DME), administered every 8 weeks, achieved comparable improvements in visual acuity to those receiving aflibercept at the same interval. The FDA granted approval to faricimab-svoa on January 28, 2022. Vabysmo (faricimab-svoa), a humanized bispecific monoclonal antibody designed for intravitreal use, works by concurrently inhibiting angiopoietin-2 (ANG-2) and vascular endothelial growth factor A (VEGF-A). This medication is indicated for treating individuals with DME. • Using topical povidone iodine is advised for intravitreal injections due to the reported significant risk of endophthalmitis when it is not used. However, the routine application of antibiotic eye drops before or after intravitreal injections is not recommended since it does not lower the risk of endophthalmitis. • A 2018 Cochrane systematic review has reported that there is “moderate certainty evidence” of safety of anti-VEGF injections and as of 2019 no studies have shown a definite increased risk.212 (I+, Moderate quality, Strong recommendation).
Section 1.1.2	- If diabetic macular edema is not resolved despite treatment with anti–vascular endothelial growth factor agents or in specific cases that are not candidates for first-line therapies, macular focal/grid

ADA Guidelines Standards of Care in Diabetes—2023 [26]	photocoagulation and intravitreal injections of corticosteroid would be reasonable alternatives. - Intravitreal injections of anti-VEGF proved effectiveness in delaying the progress of proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others). - Observational studies have shown that Ranibizumab contributed to less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications, and a lower risk of developing diabetic macular edema. - However, the disadvantage of anti-VEGF therapy to manage proliferative disease is that patients were required to have a greater number of visits and received a greater number of treatments than is usually required for management with panretinal laser, which may not be very convenient for some individuals.
Section 1.2.1 **Saudi Diabetes Clinical Practice Guidelines (SDCPG) Saudi National Diabetes Center (SNDC) 2021**[31]	- Intra-vitreous injections of anti–vascular endothelial growth factor ranibizumab showed to be noninferior to traditional panretinal laser photocoagulation, and are used to lower the risk of vision loss in patients with proliferative Diabetic retinopathy. - ACE inhibitors and ARBs showed effectiveness as treatments for DR. The addition of fenofibrate in patients with dyslipidemia can delay the progression of DR mostly in cases with very mild baseline nonproliferative DR. -

Section 1.2.2 **2018 Clinical Practice Guidelines**	- Fenofibrate could added to statins in patients with type 2 diabetes to regress the progression of retinopathy although not usually recommended for CVD prevention or treatment, in addition to statin

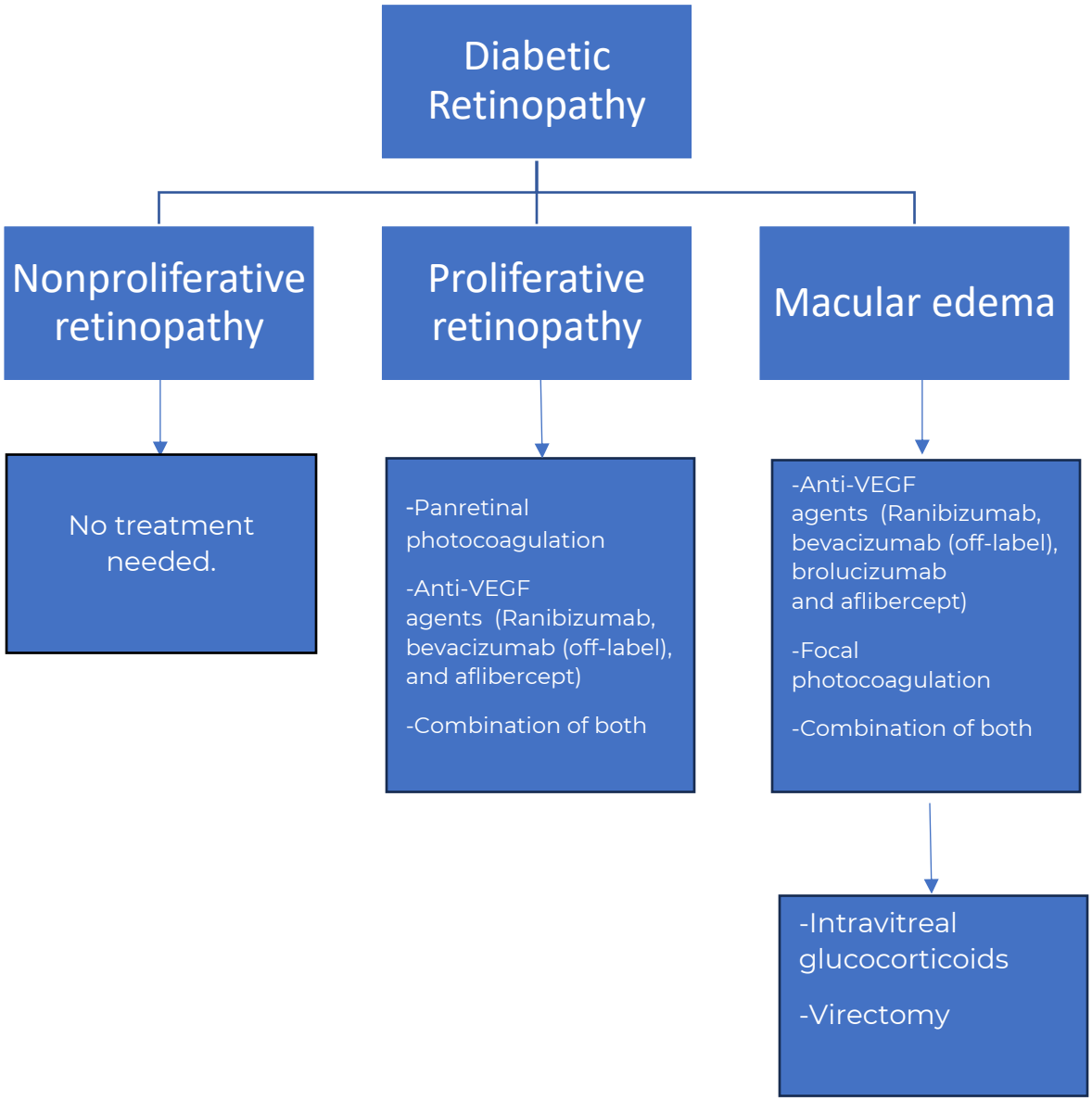
Retinopathy Diabetes Canada Clinical Practice Guidelines Expert Committee[1]	therapy, may be used in people with type 2 diabetes to slow the progression of established retinopathy - Focular macular laser is used to reduce the probability of further vision loss, however Treatment of centre-involving DME with intravitreal anti-VEGF agents showed to improve vision and reduce macular edema. - Retinopathy complicated with non-clearing vitreous bleeding in diabetes should be treated with Vitreoretinal surgery, persistent neovascularization (especially post PRP laser +/- VEGF injectables) and vitreoretinal traction, especially with retinal detachment threatening the macula.
Section 1.2.3 **Japanese Clinical Practice Guideline for Diabetes 2019**[12]	- The use of fenofibrates proved to delay the progression of diabetic retinopathy in patients with type 2 diabetes complicated by dyslipidemia. - The use of antiplatelet agents did not show clinical evidence for suppressing the onset/progression of diabetic retinopathy.

Appendix C. MeSH Terms PubMed

The following is the result of the PubMed search conducted for diabetic retinopathy guideline search:

Query	Filters	Search Details	Results
(((Diabetic Retinopathy [MeSH Terms]) OR (Diabetic Retinopathies [Title/Abstract])) OR (Retinopathies, Diabetic [Title/Abstract])) OR (Retinopathy, Diabetic [Title/Abstract])	Guideline, in the last 5 years	"Diabetic Retinopathy" [MeSH Terms]) OR "Diabetic Retinopathies" [Title/Abstract OR "Retinopathies, Diabetic" [Title/Abstract] OR "Retinopathy, Diabetic" [Title/Abstract]	5

Appendix D. Treatment Algorithm



Note: In patients with severe non-proliferative diabetic retinopathy and significant areas of retinal nonperfusion on fluorescein angiography, panretinal laser photocoagulation may reduce the risk of progression to proliferative diabetic retinopathy