New Drug Overview

Lipfendra (enlicitide)

PDL Category: Antihyperlipidemics

Introduction

- **Disease background**
  - Hypercholesterolemia is a condition described primarily by elevated serum levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B (ApoB) (*Roeters van Lennep et al 2026*). Direct measurement of plasma LDL is uncommon in routine clinical practice, thus calculated plasma LDL-C is instead used as a surrogate measure and has become the primary focus for cardiovascular risk assessment (*Ference et al 2017*).
  - In the U.S., approximately 86 million adults aged 20 years and older have total cholesterol greater than 200 mg/dL, nearly 25 million have levels 240 mg/dL or higher, 10% of adults have high total cholesterol, 17% have low high-density lipoprotein cholesterol (HDL-C), which is less than 40 mg/dL, and about 7% of children and adolescents aged 6 to 19 years are affected with high total cholesterol *(CDC 2024).*
  - Sustained exposure to elevated LDL-C promotes lipid retention within the vessel wall, triggering inflammation and atherosclerotic plaque formation, which increases the risk for cardiovascular diseases like coronary heart disease (CHD), ischemic stroke, and peripheral artery disease (PAD) (*Burnett et al 2025, Domanski et al 2020, Stein and Tattersall 2026*).
  - Familial hypercholesterolemia (FH) is an autosomal dominant genetic condition characterized by persistently elevated LDL-C levels from birth (*Osei et al 2026*).
    - FH is most frequently linked to pathogenic variants in the low-density lipoprotein receptor (LDLR) gene, accounting for approximately 85 – 90% of cases, followed by mutations in ApoB and proprotein convertase subtilisin/kexin type 9 (PCSK9). Some less common variants have also been identified in LDL receptor adaptor protein 1 (LDLRAP1), signal-transducing adaptor family member 1 (STAP1), and apolipoprotein E (ApoE) (*Abifadel and Boileau 2022, Bouhairie and Goldberg 2015, Ison et al 2025*).
    - Under normal physiological conditions, LDL particles are cleared from circulation when ApoB binds to LDLR on hepatocytes, enabling hepatic uptake and degradation. In FH, mutations affecting LDLR, ApoB, PCSK9, or LDLRAP1 impair this clearance mechanism, resulting in persistently elevated LDL-C and accelerated accumulation of LDL within the arterial wall, contributing to atherosclerotic cardiovascular disease (ASCVD) risk (*Rocha and Santos 2021, Suryawanshi and Warbhe 2023*).
    - FH encompasses a spectrum of clinical phenotypes determined by the underlying genetic variant and its effect on LDLR function (*Ahmad et al 2026, Sturm et al 2018*):
      - Heterozygous FH (HeFH) is typically caused by a pathogenic variant in a single allele of LDLR, ApoB, or PCSK9, with LDLR variants being the most common.
      - Homozygous FH (HoFH) results from biallelic pathogenic variants, usually in LDLR, and is characterized by markedly elevated LDL-C (> 400 mg/dL) and early onset ASCVD.
      - Globally, HeFH affects approximately 1 in 311 individuals, with substantially higher prevalence among patients with established ASCVD, affecting approximately 1 in 17 individuals (*Hu et al 2020*). HoFH is considerably rarer, with an estimated global prevalence of approximately 1 in 300,000 individuals (*Hu et al 2020, Osei et al 2026*).
    - Individuals with the FH phenotype (LDL-C ≥ 190 mg/dL) experience an acceleration in CHD risk of 1 to 20 years in males and 20 to 30 years in females compared with the general population (*Tsao et al 2022*).
  - Hypercholesterolemia and FH are generally silent in terms of symptoms, with most patients unaware of elevated LDL-C until identified on a screening lipid panel or after a cardiovascular event (*CDC 2024*). However, individuals with homozygous or compound heterozygous patients may present characteristic physical findings such as xanthomas,

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

xanthelasmas, or corneal arcus, and are at increased risk of premature CVD (*Abifadel and Boileau 2022, Sciammarella 2026*).
  - Diagnosis and risk assessment rely on routine lipid panel screening paired with a validated ASCVD risk calculator to guide statin initiation. For FH specifically, panel-based genetic testing for pathogenic or likely pathogenic variants is recommended to confirm diagnosis, distinguish FH from polygenic or acquired hypercholesterolemia, and enable cascade screening of first-degree relatives. Coronary artery calcium (CAC) scoring may be used selectively to help guide treatment decisions in cases of clinical uncertainty (*Ahmad et al 2026, Blumenthal et al 2026, Patel et al 2025*).
  - Standard of care follows a stepwise approach, beginning with statin therapy as first-line management. Ezetimibe is subsequently added if LDL-C goals are not achieved, followed by PCSK9-targeted therapy in patients with FH or those who remain above goal. Treatment targets generally specify an LDL-C level below 70 mg/dL for patients with ASCVD or elevated risk, tightening to below 55 mg/dL for patients with FH who have clinical ASCVD or are otherwise at very high risk (*Ahmad et al 2026, Blumenthal et al 2026, Patel et al 2025*).
  - PCSK9-targeted therapy has been available within the guideline-directed pathway, but existing agents are limited to injectable formulations (*Ahmad 2026*).
  - Lipfendra was FDA approved in 2026.

- **Pharmacology/usage**
  - Lipfendra (enlicitide) is a PCSK9 inhibitor.
    - Enlicitide is a macrocyclic peptide that binds to PCSK9. PCSK9 binds to the LDLR on the surface of hepatocytes to promote LDLR degradation within the liver. By inhibiting the binding of PCSK9 to LDLR, enlicitide increases the number of LDLRs available to clear LDL-C, thereby lowering LDL-C levels.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Lipfendra (enlicitide)
As an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in adults with hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH) [a]	✔

[a] Cardiovascular outcomes trials have demonstrated that reducing LDL-C lowers the risk for major adverse cardiovascular events (MACE) in adults at increased risk when treated with statins or monoclonal antibody PCSK9 inhibitors as an add-on to statin therapy

(Prescribing information: Lipfendra 2026)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinically efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations, strengths	Route	Usual Recommended Frequency	Comments
Lipfendra (enlicitide)	Tablets: 20 mg	Oral	20mg PO QD	• Assess LDL-C when clinically appropriate. The LDL-C lowering effect of Lipfendra may be

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

	-Swallow whole; do not split, crush, or chew the tablet			measured as early as 4 weeks after initiation. • Take on an empty stomach in the morning with water, black coffee, or plain tea • After taking the tablet, wait at least 30 minutes before eating food or drinking beverages other than water, black coffee, or plain tea • Can be taken with other medications • If a dose is missed, take the missed dose as soon as possible, at least 30 minutes before the next food or drink (other than water, black coffee, or plain tea). Do not take 2 doses on the same day.

See the current prescribing information for full details.

Clinical Efficacy Summary

- **Primary Hypercholesterolemia in Adults: Trial 1**
  - The efficacy of Lipfendra was evaluated in a multicenter, double-blind, randomized, placebo-controlled trial (CORALreef Lipids) that included patients (N = 2904) with hypercholesterolemia (including those with and without HeFH) and a history of a major ASCVD event or increased risk for development of a first major ASCVD event.
    - In this trial, patients were randomized to receive Lipfendra 20 mg orally once daily or placebo for 52 weeks. Patients required additional LDL-C lowering despite receiving stable moderate- or high-intensity statin therapy (unless statin intolerance was documented), with or without other lipid-modifying therapy.
    - Patients taking other PCSK9 inhibitors were excluded from the trial.
    - The mean age of participants was 63 years (range 19 to 89), with 47% being 65 years or older. In addition, 39% were female and 54% were White. At baseline, 50% had diabetes mellitus (49% type 2 diabetes mellitus), 58% had a history of an ASCVD event, and 42% were at increased risk for a ASCVD event. At baseline, 97% were receiving statin therapy (54% high-intensity, 41% moderate-intensity, 1% low-intensity). The mean baseline LDL-C was 96 mg/dL.
    - The primary efficacy endpoint was the percent change from baseline to Week 24 in LDL-C.
      - Results suggested that the difference between Lipfendra and placebo groups in mean percent change in LDL-C from baseline to week 24 was -56% ($p < 0.001$).
      - Results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy Results for Trial 1

Efficacy Parameter	Lipfendra (N = 1935)	Placebo (N = 969)	Rate Difference & p-value
Percent Change in LDL-C at Week 24	-57	3	-56 ($p < 0.001$)
Non-HDL-C	-54	3	-53
ApoB	-50	3	-50

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Mean % Change in LDL-C at Week 52 (*ClinicalTrials.gov [NCT05952856]*)	-50.4	4.0	-47.6 (p < 0.001)

- **Heterozygous Familial Hypercholesterolemia in Adults: Trial 2**
  - The efficacy of Lipfendra for patients with HeFH (N=303) was evaluated in a multicenter, double-blind, randomized, placebo-controlled trial (CORALreef HeFH).
    - In this trial, patients with HeFH were randomized to receive either Lipfendra 20 mg orally once daily or placebo for 52 weeks. Patients required additional LDL-C lowering despite stable moderate- or high-intensity statin therapy, with or without other lipid-modifying therapy. The diagnosis of HeFH was made by clinical criteria or genotyping.
      - The mean age of participants was 52 years (range 20 to 84), with 20% being 65 years or older. In addition, 51% were female and 70% were White. At baseline, 12% had type 2 diabetes mellitus, and all patients were receiving statin therapy (82% high-intensity). In addition, 64% received cholesterol-absorption inhibitors (eg, ezetimibe). The mean baseline LDL-C was 119 mg/mL.
      - The mean baseline LDL-C was 119 mg/dL.
    - The primary efficacy outcome measure in Trial 2 was the percent change from baseline to Week 24 in LDL-C.
      - Results suggested that the difference between the Lipfendra and placebo groups in mean percent change in LDL-C from baseline to Week 24 was -59% (p < 0.001).
    - Results are presented on the table below, which was adapted from the prescribing information.

Table 4. Efficacy Results for Trial 2

Efficacy Parameter	Lipfendra (N = 202)	Placebo (N = 101)	Rate Difference & p-value
Percent Change in LDL-C at Week 24	-58	3	-59 (p < 0.001)
Non-HDL-C	-52	2	-53
ApoB	-48	2	-49
Mean % Change in LDL-C at Week 52 (*ClinicalTrials.gov NCT05952869]*)	-55.3	8.7	-61.5 (p < 0.001)

Clinical guidelines

- Lifestyle and dietary modification are recommended as a foundational, lifelong intervention across every guideline and risk level, alongside integrated management of all cardiometabolic risk factors together (*Ahmad et al 2026, Bittner et al 2024, Blumenthal et al 2026, Patel et al 2025*).
- Statin therapy is consistently positioned as first-line pharmacotherapy across all guidelines, categorized by expected LDL-C reduction as high-, moderate-, or low-intensity, with ezetimibe as the typical first add-on when goals are not met on maximally tolerated statin (*Ahmad et al 2026, Bittner et al 2024, Blumenthal et al 2026, Patel et al 2025*).
- Guidelines converge on a general LDL-C target under 70 mg/dL for patients with ASCVD or elevated ASCVD risk, with further intensification in higher-risk subgroups discussed below (*Blumenthal et al 2026, Patel et al 2025*).
- **2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines** (*Blumenthal et al 2026*).
  - Primary prevention statin intensity scales with 10-year ASCVD risk: low risk (< 3%) favors counseling alone, though a moderate-intensity statin becomes reasonable if LDL-C is 160 – 189 mg/dL or 30-y risk is ≥ 10%; borderline risk (3% to < 5%) supports a moderate-intensity statin if a shared decision is made to initiate treatment; intermediate risk (5% to < 10%) recommends at least a moderate-intensity statin outright, with high-intensity favored toward the upper

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

end of this range; high risk (≥ 10%) warrants high-intensity statin targeting ≥ 50% reduction, with ezetimibe and then PCSK9 monoclonal antibody or bempedoic acid added if goals remain unmet.
    - Severe hypercholesterolemia (LDL-C ≥ 190 mg/dL) requires ruling out secondary causes and then maximally tolerated statin therapy regardless of ASCVD status. Add-on therapy (ezetimibe, a PCSK9 monoclonal antibody, and/or bempedoic acid) is layered on top, with the LDL-C goal tightening based on risk:
        - No HeFH, subclinical atherosclerosis, or added risk factors: goal is < 100 mg/dL
        - HeFH, subclinical atherosclerosis, added risk factors, or coronary calcification: goal is < 70 mg/dL
        - Clinical ASCVD present: goal is < 55 mg/dL
        - Inclisiran may be added as an alternative when LDL-C remains ≥ 100 mg/dL despite statin with or without ezetimibe
            - Cardiovascular outcomes data for inclisiran are still pending, and it is considered a second-line PCSK9 inhibitor for LDL-C lowering only.
    - For secondary prevention, patients with clinical ASCVD not at very high risk start high-intensity statin therapy targeting ≥ 50% LDL-C reduction, LDL-C < 70 mg/dL, and non-HDL-C < 100 mg/dL.
        - If not at goal, ezetimibe, a PCSK9 monoclonal antibody, and/or bempedoic acid is added, chosen by degree of lowering needed and patient preference; inclisiran substitutes for a PCSK9 monoclonal antibody specifically when the patient cannot tolerate, obtain, or adhere to it.
        - Goals may then be tightened further to LDL-C < 55 mg/dL and non-HDL-C < 85 mg/dL using the same add-on options.
    - Patients with clinical ASCVD at very high risk (including ASCVD with CKD) start at the stricter goal from the outset: LDL-C < 55 mg/dL and non-HDL-C < 85 mg/dL, with an optional apoB goal < 55 mg/dL.
    - Ezetimibe and/or a PCSK9 monoclonal antibody is added first if goals are not met, with inclisiran as the substitute when PCSK9 monoclonal antibody access or tolerance is the barrier, followed by bempedoic acid if goals still are not reached.
- **Update on familial hypercholesterolemia: An expert clinical consensus from the National Lipid Association** (*Ahmad et al 2026*).
    - All FH patients should achieve at least a 50% LDL-C reduction from baseline as a minimum threshold, regardless of numeric goal.
    - Goals are stratified by clinical scenario, with lower targets reserved for higher-risk presentations:
        - Primary prevention in adults with FH: LDL-C < 70 mg/dL, non-HDL-C < 100 mg/dL, apoB < 70 mg/dL.
        - Secondary prevention in adults with FH with ASCVD or high plaque burden: LDL-C < 55 mg/dL, non-HDL-C < 85 mg/dL, apoB < 55 mg/dL.
        - Recurrent event (second vascular event within 2 years despite maximal therapy): LDL-C < 40 mg/dL.
        - Extreme risk in South Asian individuals with FH, given the elevated background ASCVD risk in this population: LDL-C < 30 mg/dL.
        - Pediatric HeFH goal is LDL-C < 100 mg/dL, while pediatric HoFH is LDL-C < 100 mg/dL for primary prevention, tightening to < 70 mg/dL if ASCVD is present.
    - Pharmacologic escalation follows a consistent sequence: statin (high-, moderate-, or low-intensity by expected LDL-C reduction) is initiated first, followed by ezetimibe 10 mg/day as the first add-on, then PCSK9-targeted therapy as second- or third-line, followed by bempedoic acid, with LDLR-independent agents (evinacumab, lomitapide) used as appropriate for HeFH or HoFH if goals remain unmet.
    - PCSK9 monoclonal antibodies (alirocumab, evolocumab) have demonstrated ASCVD event reduction in high-risk primary and secondary prevention, while non-monoclonal antibody options (lerodalcibep and inclisiran) are recognized within this same treatment tier. Enlicitide decanoate was the first oral PCSK9 inhibitor recognized as an option, but FDA approval was still pending at the time of this update.
- **American Association of Clinical Endocrinology Consensus Statement: Algorithm for Management of Adults with Dyslipidemia – 2025 Update** (*Patel et al 2025*).

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- FH, along with other certain groups, is automatically classified as moderate-to-high risk regardless of calculated score, while for everyone else primary prevention risk is stratified using a validated calculator.
- This guideline targets LDL-C < 70 mg/dL for patients with ASCVD or increased risk, explicitly weighing medication cost and polypharmacy burden when individualizing this goal
- For primary prevention pharmacotherapy, low risk favors lifestyle medication alone, while intermediate and high-risk support moderate- and high-intensity statin therapy. Ezetimibe is added if LDL-C stays above goal on maximally tolerated statin.
- For secondary prevention, add-on options like bempedoic acid, PCSK9-based therapy, and bile acid resins, are selected through shared decision-making, with an emphasis that not all agents carry equal evidence for ASCVD risk reduction.

- **Managing Hypercholesterolemia in Adults Other than 75 Years Without a History of Atherosclerotic Cardiovascular Disease: An Expert Clinical Consensus from the National Lipid Association and the American Geriatrics Society** (*Bittner et al 2025*).
  - In adults over 75 with an LDL-C of 70 to 189 mg/dL and there is clinical uncertainty about statin initiation, CAC is used to help guide the decision.
    - Statin therapy is withheld if CAC is 0, while shared decision-making regarding statin is reasonable if CAC is ≥ 100 or above the 75th percentile for age, sex, and race.
  - Shared decision-making anchors patient evaluation (incorporating mortality indexes, CAC when uncertain, and competing-risk-adjusted models), followed by statin initiation when appropriate and not precluded by life-limiting illness, followed by routine LDL-C monitoring, with ezetimibe or bempedoic acid available as alternatives when statin therapy is insufficient or not tolerated, and deprescribing revisited as clinical circumstances evolve.

Safety summary

- **Contraindications:** None.

- **Boxed warnings:** None.

- **Warnings and Precautions:** None.

- **Common adverse drug reactions**
  - Listed % incidence for adverse drug reactions = reported % incidence for drug (Lipfendra) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo
    - The most frequently reported adverse events included diarrhea (5%) and dizziness (5%).

- **Drug interactions:** None.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that treatment should be discontinued when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.
  - The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- Hypercholesterolemia is characterized by elevated levels of lipoproteins, particularly LDL-C, and remains a major contributor to cardiovascular disease burden. Its high prevalence in both adults and children underscores the importance of effective lipid-lowering strategies to reduce long-term cardiovascular risk (*CDC 2024, Roeters van Lennep et al 2026*).

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- FH is an inherited disorder marked by persistently elevated LDL-C levels from birth, most commonly resulting from pathogenic variants in the LDLR gene, although ApoB, PCSK9, and other genes may also be involved. Clinical severity varies according to the underlying genetic defect, ranging from HeFH to the more severe HoFH, and is associated with a markedly increased risk of ASCVD (*Abifadel and Boileau 2022, Ahmad et al 2026, Bouhairie and Goldberg 2015, Hu et al 2020, Ison et al 2025, Sturm et al 2018*).
- Lipfendra (enlicitide) is an oral PCSK9 inhibitor indicated as an adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, including HeFH.
  - Cardiovascular outcomes trials have demonstrated that reducing LDL-C lowers the risk for major adverse cardiovascular events (MACE) in adults at increased risk when treated with statins or monoclonal antibody PCSK9 inhibitors as an add-on to statin therapy.
- The efficacy of Lipfendra was evaluated in a multicenter, double-blind, randomized, placebo-controlled trial involving adults with hypercholesterolemia, including patients with and without HeFH, who required additional LDL-C lowering despite background lipid-lowering therapy.
  - The primary endpoint was the percent change in LDL-C from baseline to Week 24.
    - Results demonstrated a significant reduction in LDL-C with Lipfendra compared to placebo at Week 24, with a treatment difference of -56% ($p < 0.001$).
    - Reductions in LDL-C were sustained through Week 52 and were accompanied by favorable changes in non-HDL-C and ApoB.
- The efficacy of Lipfendra in patients with HeFH was further evaluated in a multicenter, double-blind, randomized, placebo-controlled trial.
  - The primary endpoint was the percent change in LDL-C from baseline to Week 24.
    - Results demonstrated a greater reduction in LDL-C with Lipfendra compared to placebo at Week 24, with a treatment difference of -59% ($p < 0.001$).
    - Reduction in LDL-C was maintained throughout Week 52 as well, with concurrent reductions in non-HDL-C and ApoB.
- Although Lipfendra (enlicitide) had not yet received FDA approval at the time the cited guidelines were published, current guideline recommendations already support PCSK9-targeted therapy as part of the standard escalation pathway for patients who remain above LDL-C goal on maximally tolerated statin and ezetimibe.
- Lipfendra is the first and only oral PCSK9 inhibitor FDA-approved to reduce LDL-C in adults with hypercholesterolemia, including HeFH. Where existing PCSK9-targeted options require subcutaneous administration, Lipfendra offers a once daily oral tablet, expanding the route of administration options available. However, no head-to-head trial has directly compared Lipfendra to an injectable PCSK9 inhibitor to date.

- There is no evidence to suggest that Lipfendra is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Lipfendra remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.
- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred with conditions

References

- Abifadel M, Boileau C. Genetic and molecular architecture of familial hypercholesterolemia. *J Intern Med*. 2022;293(2):144-165. doi:10.1111/joim.13577
- Ahmad Z, Agarwala A, Cuchel M, et al. Update of familial hypercholesterolemia: An expert consensus from the National Lipid Association. *J Clin Lipidol*. 2026;20(4):708-737. doi:10.1016/j.jacl.2026.01.011

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Bittner V, Linnebur SA, Dixon DL, et al. Managing hypercholesterolemia in adults older than 75 years without a history of atherosclerotic cardiovascular disease: An Expert Clinical Consensus from the National Lipid Association and the American Geriatrics Society. *J Clin Lipidol*. 2025;19(2):215-237. doi:10.1016/j.jacl.2024.09.005
- Blumenthal RS, Morris PB, Gaudino M, et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of dyslipidemia: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;153(17). doi:10.1161/CIR.0000000000001423
- Bouhairie VE, Goldberg AC. Familial hypercholesterolemia. *Cardiol Clin*. 2015;33(2):169-179. doi:10.1016/j.ccl.2015.01.001
- Burnett H, Cichewicz A, Natani H, et al. Comparative efficacy of non-statin lipid-lowering therapies in patients with hypercholesterolemia at increased cardiovascular risk: an updated network meta-analysis. *J Cardiovasc Pharmacol.* 2025;86(3):251-258. doi:10.1097/FJC.0000000000001712
- Centers for Disease Control and Prevention. High cholesterol facts. CDC. May 15, 2024. Accessed August 25, 2026. https://www.cdc.gov/cholesterol/data-research/facts-stats/index.html
- ClinicalTrials.gov. A study of enlicitide decanoate (MK-0616 oral PCSK9 inhibitor) in adults with hypercholesterolemia (MK-0616-013) CORALreef lipids. ClinicalTrials.gov identifier: NCT05952856. Updated August 6, 2026. Accessed August 17, 2026. https://clinicaltrials.gov/study/NCT05952856
- ClinicalTrials.gov. A study of enlicitide decanoate (MK-0616 oral PCSK9 inhibitor) in adults with heterozygous familial hypercholesterolemia (MK-0616-017/CORALreef HeFH). ClinicalTrials.gov identifier: NCT05952869. Updated February 24, 2026. Accessed August 17, 2026. https://clinicaltrials.gov/study/NCT05952869
- Domanski MJ, Tian X, Wu C, et al. Time Course of LDL Cholesterol Exposure and Cardiovascular Disease Event Risk. *J Am Coll Cardiol*. 2020;76(13):1507-1516. doi:10.1016/j.jacc.2020.07.059
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. Accessed August 17, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/.
- Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J.* 2017 Apr 24;38(32):2459–2472. doi:10.1093/eurheartj/ehx144
- Hu P, Dharmayat KI, Stevens CA, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Circulation.* 2020;141(22):1742-1759. doi:10.1161/CIRCULATIONAHA.119.044795
- Ison HE, Clarke SL, Knowles JW. Familial hypercholesterolemia. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews®* [Internet]. University of Washington, Seattle; 1993-2025. Updated January 30, 2025. Accessed August 25, 2026. https://www.ncbi.nlm.nih.gov/books/NBK174884/
- Lipfendra. Package insert. Merck Sharp & Dohme; July 2026.
- Osei J, Kodukula SS, Otchere B, et al. Opportunities and Challenges in Translating Genomics into Population Health Impact: Lessons from Familial Hypercholesterolemia. *Public Health Genomics*. 2026;29(1):269-277. doi:10.1159/000553208
- Patel SB, Wyne KL, Afreen S. American Association of Clinical Endocrinology clinical practice guideline on pharmacologic management of adults with dyslipidemia. *Endocr Pract.* 2025;31(2):236-262. doi:10.1016/j.eprac.2024.09.016.
- Rocha VZ, Santos RD. Past, Present, and Future of Familial Hypercholesterolemia Management. *Methodist Debakey Cardiovasc J*. 2021;17(4):28-35. Published 2021 Sep 24. doi:10.14797/mdcvj.887
- Roeters van Lennep JE, Robbins J, Standord FC et al. Hypercholesterolemia. Dynamed Website. Updated July 28, 2026. Accessed August 17, 2026. https://www.dynamed.com.
- Sciammarella M, Oettgen P, et al. Familial Hypercholesterolemia in Adults. Dynamed Website. Updated July 27, 2026. Accessed August 14, 2026. https://www.dynamed.com
- Stein J, Tattersall M. Familial Hypercholesterolemia. *JAMA.* 2026;336(8):699-700. doi:10.1001/jama.2026.8822
- Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia. *J Am Coll Cardiol*. 2018;72(6): 662-680. doi:10.1016/j.jacc.2018.05.044
- Suryawanshi YN, Warbhe RA. Familial Hypercholesterolemia: A Literature Review of the Pathophysiology and Current and Novel Treatments. *Cureus*. 2023;15(11):e49121. Published 2023 Nov 20. doi:10.7759/cureus.49121
- Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. Circulation. 2022;145(8):e153-e639. doi: 10.1161/CIR.0000000000001052

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Publication Date: September 2026.

This information is considered confidential and proprietary to Iowa Medicaid's PBM provider and property of Iowa Medicaid, which may not be reproduced without permission. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the new drug overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.