

# Cholesterol absorption inhibitors

Agents that lower LDL cholesterol by acting in the gut rather than the hepatocyte, led by ezetimibe's blockade of the NPC1L1 sterol transporter and most often used alongside a statin.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/ezetimibe-and-absorption-inhibitors>

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## Quick revision

One Liner: Ezetimibe blocks the NPC1L1 sterol transporter at the intestinal brush border, so less cholesterol reaches the liver, hepatic stores fall and LDL clearance rises - a gut-level route to the same end point a statin reaches inside the hepatocyte.

1. Mechanism: selective inhibition of cholesterol absorption at the brush border of the small intestine, mediated by the sterol transporter Niemann-Pick C1-Like 1. [1]
2. Reduced cholesterol delivery to the liver lowers hepatic cholesterol stores and increases clearance of cholesterol from the blood. [1]
3. Net lipid effect: total cholesterol, LDL and triglycerides all decrease, and HDL increases modestly. [1]
4. As monotherapy the LDL reduction is modest, in the region of 13% to 20%. [1]
5. Approved for primary and mixed hyperlipidaemia, familial hypercholesterolaemia and homozygous sitosterolaemia, and for use in combination with a statin. [1]
6. Rhabdomyolysis is a rare but recognised risk, particularly when ezetimibe is combined with a statin. [1]
7. Metabolism proceeds by glucuronidation with enterohepatic recycling and minimal cytochrome P450 involvement, which limits drug interactions. [1]
8. Ciclosporin markedly increases ezetimibe exposure, by a factor reported between about 2.3 and 12. [1]
9. Bile acid sequestrants form a second absorption-directed group, binding bile acids in the intestine to interrupt their reabsorption. [3][2]

## Overview

1. This group lowers LDL cholesterol by interfering with what the gut delivers to the liver, rather than with what the liver makes. Ezetimibe is the defining agent: a selective cholesterol-absorption inhibitor that blocks the Niemann-Pick C1-Like 1 sterol transporter at the brush border of the small intestine. Less cholesterol reaching the liver means lower hepatic cholesterol stores and greater clearance of cholesterol from the blood, with total cholesterol, LDL and triglycerides all falling and HDL rising modestly. [1]
2. Approved use covers primary hyperlipidaemia, mixed hyperlipidaemia, familial hypercholesterolaemia and homozygous sitosterolaemia, with combination use alongside a statin formally indicated for primary or mixed lipid disorders and for the homozygous familial form. Because a statin reduces synthesis and ezetimibe reduces absorption, the two act on separate supply routes; in the IMPROVE-IT trial, adding ezetimibe to statin therapy lowered LDL cholesterol by 24% and reduced the risk of cardiovascular events. [1]
3. A second absorption-directed group, the bile acid sequestrants, binds bile acids in the intestine and prevents their reabsorption. Interrupting that recycling drives hepatic conversion of cholesterol into bile acids and upregulates hepatic LDL receptors. Their limitation is practical rather than mechanistic: they reduce the bioavailability of many co-administered drugs and of the fat-soluble vitamins, and they raise triglycerides. [3][2]

## Classification and drug examples

Intro: Two mechanisms sit under the heading of absorption inhibition. One blocks the sterol transporter that carries cholesterol into the enterocyte; the other removes bile acids from the intestinal lumen so that cholesterol must be spent

replacing them.

1. Name: NPC1L1 sterol transporter inhibitor

1. Note: Blocks cholesterol uptake at the intestinal brush border, with minimal cytochrome P450 involvement and a half-life long enough for once-daily use.

Name: Ezetimibe

Route: Oral

Note: Rapidly converted to the active ezetimibe-glucuronide; both parent and metabolite have a half-life of about 22 hours. [1] [1]

2. Name: Bile acid sequestrants

2. Note: Bind bile acids in the intestine so that they cannot be reabsorbed, which forces the liver to convert more cholesterol into bile acids and upregulates hepatic LDL receptors.

Name: Colesevelam

Route: Oral

Note: Forms non-absorbable complexes with bile acids; also improves glycaemic control in type 2 diabetes through incretin release, and raises triglycerides. [2] [3][2]

## Mechanism of action

Summary: Ezetimibe selectively inhibits the NPC1L1 sterol transporter at the intestinal brush border, reducing cholesterol absorption and hepatic cholesterol delivery; bile acid sequestrants achieve a related end by binding bile acids so the liver must consume cholesterol to replace them.

Target: Niemann-Pick C1-Like 1 (NPC1L1) sterol transporter of the intestinal brush border

Cidal Static: not applicable

Kill Kinetics: not applicable

1. Step: 1

1. Title: The drug acts at the intestinal brush border

1. Detail: Ezetimibe works locally in the small intestine, where cholesterol absorption is mediated by the NPC1L1 sterol transporter. [1]

2. Step: 2

2. Title: Cholesterol uptake into the enterocyte is blocked

2. Detail: Selective inhibition of that transporter prevents dietary and biliary cholesterol crossing into the enterocyte. [1][3]

3. Step: 3

3. Title: Less cholesterol reaches the liver

3. Detail: Reduced delivery lowers hepatic cholesterol stores, which is the signal the hepatocyte responds to. [1]

4. Step: 4

4. Title: Clearance of cholesterol from the blood increases

4. Detail: Total cholesterol, LDL and triglycerides fall, and HDL rises modestly. [1]

5. Step: 5

5. Title: Sequestrants reach the same end from the bile side

5. Detail: By forming non-absorbable complexes with bile acids, a sequestrant activates 7-alpha-hydroxylase so cholesterol is converted into bile acids, and hepatic LDL receptors are upregulated. [2]

## Major clinical uses

1. Drug: Ezetimibe

1. Organism: Not applicable

1. Indication: Primary hyperlipidaemia and mixed hyperlipidaemia

1. Line: adjunct

1. Note: Indicated to reduce total cholesterol, LDL, apolipoprotein B and non-HDL cholesterol. [1]
2. Drug: Ezetimibe with a statin
2. Organism: Not applicable
2. Indication: Additional LDL lowering when statin therapy alone is insufficient
2. Line: adjunct
2. Note: A formally approved combination; the IMPROVE-IT trial supported a lower LDL target after acute coronary syndrome. [1]
3. Drug: Ezetimibe
3. Organism: Not applicable
3. Indication: Homozygous familial hypercholesterolaemia
3. Line: adjunct
3. Note: Used in combination rather than alone in this setting. [1]
4. Drug: Ezetimibe
4. Organism: Not applicable
4. Indication: Homozygous sitosterolaemia
4. Line: targeted
4. Note: The indication that follows most directly from the mechanism, since the disorder is one of excessive intestinal sterol absorption. [1]
5. Drug: Colesevelam
5. Organism: Not applicable
5. Indication: Primary hyperlipidaemia and heterozygous familial hypercholesterolaemia
5. Line: adjunct
5. Note: Approved in adults and in adolescents within the stated age range. [2]
6. Drug: Colesevelam
6. Organism: Not applicable
6. Indication: Improvement of glycaemic control in type 2 diabetes alongside diet and exercise
6. Line: adjunct
6. Note: Mediated by increased GLP-1 and other incretins through TGR5 activation, which suppresses hepatic glycogenolysis. [2]

## Pharmacokinetics

1. Drug: Ezetimibe
1. Route: Oral
1. Absorption: Peak plasma concentrations within about 4 to 12 hours, with the glucuronide peaking earlier
1. Csf Penetration: Not clinically relevant
1. Metabolism: Rapid glucuronidation to the active ezetimibe-glucuronide, with enterohepatic recycling and minimal cytochrome P450 involvement
1. Elimination: Parent drug largely in faeces, glucuronide in urine
1. Half Life: Approximately 22 hours for both parent and metabolite
1. Dose Adjust: Not recommended in moderate to severe hepatic impairment [1]
2. Drug: Colesevelam
2. Route: Oral
2. Absorption: Acts within the gastrointestinal lumen; forms non-absorbable complexes with bile acids
2. Csf Penetration: Not applicable
2. Metabolism: Not applicable - the drug is not absorbed for systemic effect
2. Elimination: Faecal, as bile acid complexes
2. Half Life: Not clinically relevant by this route

2. Dose Adjust: Administration of other medicines must be separated in time [2]

1. The near-absence of cytochrome P450 metabolism is the practical strength of ezetimibe: it sidesteps the CYP3A4 interactions that complicate statin prescribing, leaving ciclosporin and the bile acid sequestrants as the interactions that genuinely matter. [1]

2. Monitoring consists of a baseline lipid panel and liver function tests, repeated as clinically indicated, with ciclosporin concentrations followed where that drug is co-prescribed. [1]

3. For a bile acid sequestrant, thyroid function is monitored in hypothyroid patients and triglycerides and fat-soluble vitamin status are also followed. [2]

4. This page gives no dose regimens by design. Doses, and the intervals required between a sequestrant and other medicines, depend on the individual product and belong in a prescribing reference used by the treating clinician.

## Adverse effects

1. Effect: Headache and upper respiratory symptoms

1. Detail: Headache, rhinitis and pharyngitis are the most frequently reported adverse effects of ezetimibe. [1]

2. Effect: Musculoskeletal and general symptoms

2. Detail: Myalgia, back pain, arthralgia, chest pain, fatigue and weakness are reported less commonly. [1]

3. Effect: Gastrointestinal effects of sequestrants

3. Detail: Constipation, diarrhoea, nausea, abdominal pain and steatorrhoea are recognised with colestevam. [2]

4. Effect: Rise in triglycerides with sequestrants

4. Detail: A significant increase in triglycerides is a documented concern with colestevam and shapes which patients can receive it. [2]

1. Effect: Rhabdomyolysis

1. Detail: Rare, and described particularly in combination with a statin; the risk is higher in patients over 65, with hypothyroidism or with renal impairment.

1. Action: Suspected rhabdomyolysis prompts immediate discontinuation and urgent assessment. [1]

2. Effect: Hepatotoxicity

2. Detail: Hepatocellular or cholestatic patterns have been reported, along with autoimmune hepatitis and a case of vanishing bile duct syndrome; clinically apparent injury remains rare.

2. Action: Baseline liver tests, with further testing guided by symptoms. [1][4]

3. Effect: Hypersensitivity including angio-oedema

3. Detail: Listed among the rare but serious reactions to ezetimibe.

3. Action: Discontinue and seek urgent assessment if angio-oedema occurs. [1]

1. Drug: Ezetimibe alone

1. Effect: Has not been associated with a higher rate of serum ALT elevation than placebo, with an overall monotherapy rate of roughly 0.5% to 1.5%. [4]

2. Drug: Ezetimibe added to a statin

2. Effect: Associated with a slight increase in the likelihood of serum aminotransferase elevation compared with the statin alone. [4]

3. Drug: Colestevam

3. Effect: Reduces the bioavailability of numerous medicines including statins and levothyroxine, and of the fat-soluble vitamins A, D, E and K. [2]

## Contraindications, precautions and interactions

1. Hypersensitivity to any component of the formulation. [1]

2. Concomitant statin use in the presence of active hepatic disease or unexplained persistent transaminase elevation. [1]

3. Pregnancy and breastfeeding when ezetimibe is combined with a statin. [1]

4. For colesevelam: a history of bowel obstruction, markedly raised serum triglycerides, or a history of hypertriglyceridaemia-induced pancreatitis. [2]
1. Moderate to severe hepatic impairment, in which ezetimibe is not recommended. [1]
2. Age over 65, hypothyroidism and renal impairment, each of which raises myopathy risk when ezetimibe is combined with a statin or fibrate. [1]
3. Treated hypothyroidism when a sequestrant is used, since thyroid hormone absorption is reduced and thyroid function needs following. [2]
1. With: Ciclosporin
  1. Effect: Increases ezetimibe exposure by a factor reported between about 2.3 and 12, and ciclosporin concentrations themselves require monitoring. [1]
2. With: Bile acid sequestrants
  2. Effect: Bind ezetimibe in the gut, so the two must be separated in time rather than taken together. [1]
3. With: Statins and fibrates
  3. Effect: May be co-administered without a time separation, but the risk of myopathy increases. [1]
4. With: Levothyroxine and fat-soluble vitamins
  4. Effect: Their bioavailability is reduced by colesevelam, which is why the timing of administration is separated. [2]

## Comparison tables

Title: Ezetimibe compared with a bile acid sequestrant

Caption: Both act within the gut, but on different molecules and with very different interaction profiles. Therapy choice belongs to the treating clinician working from a current prescribing reference.

1. Key: feature
  1. Label: Feature
    1. Is Row Header: true
  2. Key: eze
    2. Label: Ezetimibe
  3. Key: bas
    3. Label: Bile acid sequestrant
  1. Feature: Molecular target
    1. Eze: NPC1L1 sterol transporter at the brush border
    1. Bas: Bile acids within the intestinal lumen [1][2]
  2. Feature: Systemic absorption
    2. Eze: Absorbed, glucuronidated and enterohepatically recycled
    2. Bas: Not absorbed; acts entirely within the lumen [1][2]
  3. Feature: Effect on triglycerides
    3. Eze: Reduced along with total cholesterol and LDL
    3. Bas: Can rise significantly [1][2]
  4. Feature: Main interaction concern
    4. Eze: Ciclosporin exposure; myopathy alongside a statin or fibrate
    4. Bas: Reduced bioavailability of many co-administered drugs and fat-soluble vitamins [1][2]
  5. Feature: Additional non-lipid effect
    5. Eze: None recorded
    5. Bas: Improved glycaemic control in type 2 diabetes through incretin release [2]

## High-yield exam pearls

1. Pearl: NPC1L1 is the answer to "which transporter?"
1. Why: Ezetimibe acts on the Niemann-Pick C1-Like 1 sterol transporter at the brush border of the small intestine - a

named molecular target that examiners like precisely because it is unique among the lipid-lowering drugs. [1]

2. Pearl: Its role is additive rather than competitive with statins.

2. Why: A statin reduces cholesterol synthesis while ezetimibe reduces cholesterol absorption, so combining them attacks two different supply routes into the hepatocyte; the combination is a formally approved use. [1][3]

3. Pearl: Almost no cytochrome P450 involvement is a genuine clinical advantage.

3. Why: Ezetimibe is glucuronidated and undergoes enterohepatic recycling with minimal cytochrome P450 participation, so it avoids the CYP3A4 interaction problems that dominate statin prescribing. [1]

4. Pearl: Sitosterolaemia is the mechanistic indication.

4. Why: Homozygous sitosterolaemia is a disorder of excessive plant sterol absorption, so a drug that blocks the intestinal sterol transporter treats the underlying defect rather than merely the lipid number. [1]

5. Pearl: Timing matters with a bile acid sequestrant, not with a statin or fibrate.

5. Why: Ezetimibe must be separated in time from a sequestrant, whereas it may be given with a statin or a fibrate without a dosing interval - although the myopathy risk of those combinations still applies. [1]

6. Pearl: Bile acid sequestrants raise triglycerides.

6. Why: A significant increase in triglycerides is a recognised effect of colesvelam, which is why markedly raised triglycerides and a history of hypertriglyceridaemia-induced pancreatitis are contraindications to that group. [2]

## Common exam traps

1. Trap: "Ezetimibe inhibits HMG-CoA reductase in the intestine."

1. Correction: It has no effect on that enzyme. It blocks the NPC1L1 sterol transporter at the intestinal brush border, which is a transport step rather than a synthetic one. [1][3]

2. Trap: "Because it acts in the gut, ezetimibe cannot cause muscle problems."

2. Correction: Myalgia is among the reported adverse effects and rhabdomyolysis is a rare but recognised risk, especially in combination with a statin and in patients over 65, with hypothyroidism or with renal impairment. [1]

3. Trap: "Ezetimibe by itself raises liver enzymes."

3. Correction: Used alone it has not been associated with a higher rate of ALT elevation than placebo. Adding it to a statin is associated with a slight increase in the likelihood of aminotransferase elevation. [4]

4. Trap: "Bile acid sequestrants only affect lipid absorption."

4. Correction: They reduce the bioavailability of many co-administered drugs and of the fat-soluble vitamins A, D, E and K, which is why administration has to be separated in time. [2]

## Self-test questions

1. Question: Which transporter does ezetimibe inhibit, and where?

1. OATP1B1 in the hepatocyte membrane

2. Niemann-Pick C1-Like 1 at the brush border of the small intestine

3. The epithelial sodium channel in the collecting duct

4. ATP-citrate lyase in the hepatocyte cytoplasm

1. Explanation: Ezetimibe is a selective cholesterol-absorption inhibitor acting on the NPC1L1 sterol transporter at the intestinal brush border, which is what makes its mechanism distinct from every other lipid-lowering class. [1]

2. Question: How does blocking intestinal cholesterol absorption lower plasma LDL cholesterol?

1. By binding LDL particles in the gut lumen

2. By reducing cholesterol delivery to the liver, lowering hepatic cholesterol stores and increasing clearance from the blood

3. By inhibiting hepatic cholesterol synthesis directly

4. By increasing biliary excretion of LDL particles

2. Explanation: Less cholesterol arriving from the gut means lower hepatic stores, and the liver compensates by clearing more cholesterol from the circulation. Total cholesterol, LDL and triglycerides fall while HDL rises modestly. [1]

3. Question: What magnitude of LDL reduction does ezetimibe achieve as monotherapy?

1. Around 1% to 3%
2. Around 13% to 20%
3. Around 45% to 65%
4. More than 70%

3. Explanation: Monotherapy reduces LDL cholesterol by roughly 13% to 20%, which is why the drug is usually positioned as an addition to statin therapy rather than a replacement for it. [1]

4. Question: Which co-prescribed drug substantially increases ezetimibe exposure?

1. Ciclosporin
2. Amlodipine
3. Metformin
4. Warfarin

4. Explanation: Ciclosporin increases ezetimibe exposure by a factor reported between about 2.3 and 12, and ciclosporin concentrations themselves require monitoring when the two are combined. [1]

5. Question: Which combination requires the two drugs to be separated in time?

1. Ezetimibe and a statin
2. Ezetimibe and fenofibrate
3. Ezetimibe and a bile acid sequestrant
4. Ezetimibe and aspirin

5. Explanation: Ezetimibe must be given at an interval either before or after a bile acid sequestrant, because the resin binds it. Statins and fibrates may be co-administered without a time separation, though the myopathy risk of those combinations still applies. [1]

6. Question: Which statement about ezetimibe and liver enzymes is correct?

1. Ezetimibe alone roughly doubles the rate of ALT elevation compared with placebo
2. Ezetimibe alone has not been associated with a higher rate of ALT elevation than placebo, while adding it to a statin slightly increases that likelihood
3. Ezetimibe is a common cause of clinically apparent liver injury
4. Liver enzyme testing is unnecessary at any point during therapy

6. Explanation: Monotherapy does not raise the ALT elevation rate above placebo, and combination with a statin produces only a slight increase. Clinically apparent acute liver injury has been reported but is rare. [4]

7. Question: Why are markedly raised triglycerides a contraindication to colesevelam?

1. Because bile acid sequestrants can cause a significant further increase in triglycerides
2. Because sequestrants are inactivated by triglyceride-rich particles
3. Because sequestrants lower HDL to dangerous levels
4. Because sequestrants precipitate in the small intestine when triglycerides are high

7. Explanation: A significant increase in triglycerides is a recognised effect of colesevelam, so both markedly raised triglycerides and a history of hypertriglyceridaemia-induced pancreatitis are listed as contraindications, alongside a history of bowel obstruction. [2]

## Frequently asked questions

1. Question: Is ezetimibe a substitute for a statin?

1. Answer: It is generally an addition rather than a substitute. Monotherapy lowers LDL cholesterol by roughly 13% to 20%, which is well short of what statin therapy achieves, and the approved combination use reflects that positioning. [1][3]

2. Question: Why does ezetimibe have fewer drug interactions than a statin?

2. Answer: Because its metabolism is glucuronidation with enterohepatic recycling and only minimal cytochrome P450 involvement. That avoids the CYP3A4 interactions responsible for most statin interaction warnings. [1]

3. Question: What did IMPROVE-IT show?

3. Answer: Adding ezetimibe to statin therapy lowered LDL cholesterol by 24% and reduced the risk of cardiovascular events, and the finding prompted recommendations for a lower LDL cholesterol target in patients after an acute coronary syndrome. [1]

4. Question: Can ezetimibe cause muscle problems?

4. Answer: Myalgia is among its reported adverse effects, and rhabdomyolysis is a rare risk that is described particularly when it is combined with a statin. Older age, hypothyroidism and renal impairment increase that risk further. [1]

5. Question: Why must bile acid sequestrants be taken apart from other medicines?

5. Answer: Because they reduce the bioavailability of many co-administered drugs, including statins and levothyroxine, as well as the fat-soluble vitamins A, D, E and K. Separating administration in time limits that binding. [2]

## References

[1] Ezetimibe (StatPearls). StatPearls Publishing / NCBI Bookshelf 2026. <https://www.ncbi.nlm.nih.gov/books/NBK532879/>

[2] Colesevelam (StatPearls). StatPearls Publishing / NCBI Bookshelf 2026. <https://www.ncbi.nlm.nih.gov/books/NBK557815/>

[3] Lipid-Lowering Drug Therapy (StatPearls). StatPearls Publishing / NCBI Bookshelf 2026. <https://www.ncbi.nlm.nih.gov/books/NBK541128/>

[4] Ezetimibe (LiverTox). LiverTox, NIDDK / NCBI Bookshelf 2012. <https://www.ncbi.nlm.nih.gov/books/NBK548095/>

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