Drug Update

Ezetimibe (Zetia)

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Description

Ezetimibe (Zetia) is a newly Food and Drug Administration(FDA)-approved medication that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. It is approved for primary hypercholesterolemia (heterozygous familial and nonfamilial hypercholesterolemia) as monotherapy or in combination with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). It is also indicated in combination with atorvastatin or simvastatin for homozygous familial hypercholesterolemia and as an adjunct to diet for homozygous sitosterolemia [1].

Development

Intestinal cholesterol absorption represents a major route for the entry of cholesterol into the body's miscible pools and therefore can potentially impact the plasma LDL-cholesterol concentration. Finding revealed that adenosine triphosphate-binding cassette transporters G5/8 regulate plant sterol absorption and also the secretion into bile of cholesterol and non-cholesterol sterols. Loss of adenosine triphosphate-binding cassette transporter G5/8 function results in sitosterolemia. Ezetimibe, a novel, potent and selective inhibitor of cholesterol absorption which is effective in milligram doses, lowers plasma plant sterol concentrations in sitosterolemic subjects, thus suggesting that this drug might be inhibiting the activity of a putative sterol permease in the brush border membrane of the enterocyte that actively facilitates the uptake of cholesterol as well as other non-cholesterol sterols. After FDA approval, ezetimibe was launched in 2003.

Pharmacology

- Ezetimibe decreases blood cholesterol by inhibiting its absorption in the small intestine.
- It reduces total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B and triglycerides and increases high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolemia. In patients with primary hypercholesterolemia, ezetimibe as monotherapy reduced LDL-C by 18%, reduced total cholesterol by 13%, reduced triglycerides by 9% and raised HDL by 1% [1,2].
- In patients with hypercholesterolemia, ezetimibe added to ongoing HMG-CoA reductase inhibitor therapy significantly lowered total cholesterol, LDL-C, apolipoprotein B and triglycerides and increased HDL-C compared with HMG-CoA reductase inhibitor administration alone. Mean percent change from treated HMG-CoA reductase inhibitor therapy was -17% for total cholesterol, -25% for LDL-C, -14% for triglycerides, and +3% for HDL-C [1,2].

Mechanisms of Action

- Ezetimibe's mechanism of action differs from other classes of cholesterol-reducing medications (including HMG-CoA reductase inhibitors, bile acid resins and plant stanols). It localizes to the brush border of the small intestine where it inhibits absorption of cholesterol thereby decreasing the delivery of intestinal cholesterol to the liver [1]. This decreases cholesterol stores within the liver and ultimately increases clearance of cholesterol from the blood.
- Its unique mechanism of action is complementary to HMG-CoA reductase inhibitors.

Pharmacokinetics

- Following oral administration, ezetimibe is conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide).
- Following a single 10 mg dose, mean peak plasma concentrations of ezetimibe were achieved within 4-12 hours (T_{max}) and peak ezetimibe-glucuronide values were reached between 1-2 hours (T_{max}).
- Ezetimibe can be given with or without food.
- Ezetimibe and ezetimibe-glucuronide are slowly

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eliminated from plasma (half-life of 22 hours for both) with biliary and renal excretion [1].

Contraindications

- Hypersensitivity to ezetimibe.
- Combination of ezetimibe and HMG-CoA reductase inhibitor is contraindicated in patients with active liver disease or unexplained and persistent elevations of serum transaminases.
- Ezetimibe (alone or in combination with HMG-CoA reductase inhibitors) are contraindicated in pregnant and nursing women.

Precautions

- Ezetimibe is not recommended in patients with moderate or severe hepatic insufficiency [1].
- When ezetimibe is administered with an HMG-CoA reductase inhibitor, liver function tests should be monitored according to the recommendations of the HMG-CoA reductase inhibitors.
- Safety and effectiveness of ezetimibe with fibrates have not been established and therefore co-administration of ezetimibe with fibrates is not recommended until further studies are available.
- Cholestyramine decreased mean area under the curve of total ezetimibe by 55% and therefore incremental LDL-C reduction when adding ezetimibe to cholestyramine may be decreased by this drug interaction.
- No clinically significant pharmacokinetic interactions were observed when ezetimibe was co-administered with HMG-CoA reductase inhibitors.
- In one renal transplant patient total ezetimibe level increased 12-fold with administration of cyclosporine. Therefore, patients who receive both drugs should be carefully monitored.
- Some older individuals may be more sensitive to ezetimibe.

Adverse Reactions

Frequency not determined

- Large, hive-like swelling on face, eyelids, lips, tongue, throat, hands, legs, feet and sex organs and skin rash.

More common

- Fever, headache, muscle pain, runny nose and sore throat.

Less common

- Back pain, body aches or pain, chest pain, chills, cold or flu-like symptoms, congestion, coughing, diarrhoea, difficulty in moving, dizziness, dryness or soreness of throat, hoarseness, muscle pain or stiffness, pain in joints, pain or tenderness around eyes and cheekbones, shortness of breath or troubled breathing, stomach pain, stuffy nose, tender, swollen glands in neck, tightness of chest or wheezing, trouble in swallowing, unusual tiredness or weakness and voice changes.

Dosage and administration

- Patients should be on a standard cholesterol-lowering diet.
- Dose is 10 mg ezetimibe once daily.
- Ezetimibe may be given with an HMG-CoA reductase inhibitor for incremental cholesterol-lowering effect.
- No dosage adjustment is necessary in patients with mild hepatic insufficiency, renal insufficiency or in geriatric patients.
- Administer ezetimibe either >/=2 hours before or >/=4 hours after administration of a bile acid sequestrant for those patients receiving both drugs.

Summary

Ezetimibe represents the first cholesterol-lowering drug of a new class that inhibits cholesterol absorption from the small intestine. It can be used as monotherapy for primary hypercholesterolemia but most likely will be used in combination therapy with statins in which it results in incremental lowering of total and LDL cholesterol [1-4]. It can also be used as part of therapy for homozygous familial hypercholesterolemia and homozygous sitosterolemia. It does not increase the incidence of myopathy or rhabdomyolysis when administered with HMG-CoA reductase inhibitors (statins).

References

1. Bruckert E, Giral P, Tellier P. Perspectives in cholesterol-lowering therapy: the role of ezetimibe, a new selective inhibitor of intestinal cholesterol absorption. Circulation 2003;107(25):3124-8.
2. Mauro VF, Tuckerman CE. Ezetimibe for management of hypercholesterolemia. Ann Pharmacother 2003;37(6):839-48.
3. Kastelein JJ. The future of lipid-lowering therapy: the big picture. Neth J Med 2003;61(5 Suppl):35-9.
4. Weston C. Place of ezetimibe in clinical practice. Hosp Med 2003;64(8):473-8.