Heritage Information Systems, Inc.

Clinical Edit Criteria

Drug/Drug Class: **Zetia™ (Ezetimibe) /Antihyperlipidemic**

Prepared for: Missouri Medicaid
Prepared by: Heritage Information Systems, Inc.

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:
The purpose of this monograph is to provide a review of Zetia (ezetimibe) therapy to determine whether this drug should be made available on an open access basis to prescribers, clinical edit or require prior authorization for use.

Dosage Forms & Manufacturer:
10mg tablet
Merck/Schering-Plough Pharmaceuticals

Summary of Findings:
Zetia® (ezetimibe) is a cholesterol-lowering agent that reduces total-C, LDL-C, Apo B, and triglycerides, and increases HDL-C. Cholesterol is lowered by inhibiting cholesterol absorption in the small intestines resulting in decreased delivery of intestinal cholesterol to the liver. Hepatic cholesterol stores are reduced and clearance of blood cholesterol is increased. Clinical studies indicate that as monotherapy, ezetimibe lowers cholesterol by 13%. In combination with ongoing HMG CoA reductase inhibitors therapy, ezetimibe significantly lowers total-C, LDL-C, Apo B and triglycerides, and increases HDL-C compared with an HMG CoA reductase inhibitor given alone. When initiated concurrently with an HMG CoA reductase inhibitor to previously untreated patients with primary hypercholesterolemia, ezetemibe plus all doses of the HMG CoA reductase inhibitor significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of the HMG CoA reductase inhibitor.

Status Recommendation:
☐ Prior Authorization (PA) Required ☐ Open Access
☒ Clinical Edit

Type of PA Criteria:
☐ Increased Risk of ADE ☐ Non-Preferred Agent
☐ Appropriate Indications ☐ PA Not Required

Purpose

The purpose of this monograph is to provide a review of Zetia™ (ezetimibe) therapy to determine whether this drug should be considered a prior authorization drug or not (open access). While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guiding appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Zetia® (ezetimibe) is a cholesterol-lowering agent that reduces total-C, LDL-C, Apo B, and triglycerides, and increases HDL-C. It acts at the brush border of the small intestine and inhibits the absorption of cholesterol, which results in decreased delivery of intestinal cholesterol to the liver. Hepatic cholesterol stores are reduced and clearance of blood cholesterol is increased. Maximal to near maximal response occurs after two weeks of therapy and is maintained with chronic therapy.

Dosage Form(s)

Oral tablet, 10mg

Manufacturer

Merck/Schering-Plough Pharmaceuticals

Indication(s)

- Primary hypercholesterolemia – as monotherapy or combination therapy with an HMG-CoA reductase inhibitor as an adjunct to diet to reduce elevate total-C, LDL-C, and APO B
- Homozygous familial hypercholesterolemia – with atorvastatin or simvastatin to reduce elevated total-C and LDL-C levels as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are not available.
- Homozygous sitosterolemia – as an adjunct to diet to reduce elevated sitosterol and campesterol levels

Clinical Efficacy (mechanism of action/pharmacology, comparative efficacy)

Ezetimibe reduces total-C, LDL-C, Apo B, and triglycerides, and increases HDL-C by acting at the brush border of the small intestine, inhibiting the absorption of cholesterol, which results in decreased delivery of intestinal cholesterol to the liver. Hepatic cholesterol stores are reduced and clearance of blood cholesterol is increased. Maximal to near maximal response occurs after two weeks of therapy and is maintained with chronic therapy.

Monotherapy

The following table[1] summarizes the results of two multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia. Zetia monotherapy significantly reduced cholesterol, APO B, and TG, and increased HDL-C compared to placebo:

Response to ZETIA in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[a])[b]

	Treatment group	N	Total-C	LDL-C	Apo B	TG[c]	HDL-C
Study 1[d]	Placebo	205	+1	+1	-1	-1	-1
	Ezetimibe	622	-12	-18	-15	-7	+1
Study 2[d]	Placebo	226	+1	+1	-1	+2	-2
	Ezetimibe	666	-12	-18	-16	-9	+1
Pooled Data[d] (Studies 1 & 2)	Placebo	431	0	+1	-2	0	-2
	Ezetimibe	1288	-13	-18	-16	-8	+1

[a]Baseline – on no lipid-lowering drug
[b]Table adapted from source 2
[c]For triglycerides, median % change from baseline
[d] Zetia significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to placebo.

Combination Therapy

The following table summarizes the results of a multicenter, double-blind, placebo controlled, 8-week study with 769 patients with primary hypercholesterolemia, known coronary heart disease or multiple cardiovascular risk factors. These patients were on HMG CoA reductase inhibitor therapy but had not met the NCEP ATP II guideline goals. They were randomized to receive either Zetia or placebo in addition to their HMG CoA reductase inhibitor therapy. Zetia added to the ongoing HMG CoA reductase inhibitor therapy, significantly lowered total-C, LDL-C, Apo B and TG, and increased HDL-C compared with an HMG-CoA reductase inhibitor given alone.

Response to the Addition of Zetia to On-going HMG CoA Reductase Inhibitor Therapy[a] in Patients with Primary Hypercholesterolemia[b] (Mean[c] % Change from Treated Baseline[d])

Treatment	N	Total-C	LDL-C	Apo B	TG[c]	HDL-C
On-going HMG CoA Reductase Inhibitor + Placebo[e]	390	-2	-4	-3	-3	+1
On-going HMG CoA Reductase Inhibitor + Zetia[e]	379	-17	-25	-19	-14	+3

[a] 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)
[b] Table adapted from source 2
[c] TG, median % change from baseline
[d]Baseline – on an HMG-CoA reductase inhibitor
[e]Zetia added to the ongoing HMG CoA reductase inhibitor therapy, significantly lowered total-C, LDL-C, Apo B and TG, and increased HDL-C compared with an HMG-CoA reductase inhibitor given alone.

Response to Zetia and Atorvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia[a]
(Mean[b] % Change from Untreated Baseline[c])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[b]	HDL-C
Placebo	60	+4	+4	+3	-6	+4
ZETIA	65	-14	-20	-15	-5	+4
Atorvastatin 10 mg	60	-26	-37	-28	-21	+6
ZETIA + Atorvastatin 10 mg	65	-38	-53	-43	-31	+9
Atorvastatin 20 mg	60	-30	-42	-34	-23	+4
ZETIA + Atorvastatin 20 mg	62	-39	-54	-44	-30	+9
Atorvastatin 40 mg	66	-32	-45	-37	-24	+4
ZETIA + Atorvastatin 40 mg	65	-42	-56	-45	-34	+5
Atorvastatin 80 mg	62	-40	-54	-46	-31	+3
ZETIA + Atorvastatin 80 mg	63	-46	-61	-50	-40	+7
Pooled data (All Atorvastatin Doses)[d]	248	-32	-44	-36	-24	+4
Pooled data (All ZETIA + Atorvastatin Doses)[d]	255	-41	-56	-45	-33	+7

[a] Table adapted from source 2
[b] Tg, median % change from baseline
[c] Baseline – on no lipid lowering drug
[d] Zetia + all doses of pooled atorvastatin (10-80 mg) significantly reduced total-C, LDL-C, Apo-B and TG, and increased HDL-C compared to all doses of atorvastatin pooled (10-80mg)

Response to Zetia and Simvastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia[a]
(Mean[b] % Change from Untreated Baseline[c])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[b]	HDL-C
Placebo	70	-1	-1	0	+2	+1
ZETIA	61	-13	-19	-14	-11	+5
Simvastatin 10 mg	70	-18	-27	-21	-14	+8
ZETIA + Simvastatin 10 mg	67	-32	-46	-35	-26	+9
Simvastatin 20 mg	61	-26	-36	-29	-18	+6
ZETIA + Simvastatin 20 mg	69	-33	-46	-36	-25	+9
Simvastatin 40 mg	65	-27	-38	-32	-24	+6
ZETIA + Simvastatin 40 mg	73	-40	-56	-45	-32	+11
Simvastatin 80 mg	67	-32	-45	-37	-23	+8
ZETIA + Simvastatin 80 mg	65	-41	-58	-47	-31	+8
Pooled data (All Simvastatin Doses)[d]	263	-26	-36	-30	-20	+7
Pooled data (All ZETIA + Simvastatin Doses)[d]	274	-37	-51	-41	-29	+9

[a] Table adapted from source 2
[b] Tg, median % change from baseline
[c] Baseline – on no lipid lowering drug
[d] Zetia + all doses of pooled simvastatin (10-80 mg) significantly reduced total-C, LDL-C, Apo-B and TG, and increased HDL-C compared to all doses of atorvastatin pooled (10-80mg)

Response to Zetia and Pravastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])[c]

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Placebo	65	0	-1	-2	-1	+2
ZETIA	64	-13	-20	-15	-5	+4
Pravastatin 10 mg	66	-15	-21	-16	-14	+6
ZETIA + Pravastatin 10 mg	71	-24	-34	-27	-23	+8
Pravastatin 20 mg	69	-15	-23	-18	-8	+8
ZETIA + Pravastatin 20 mg	66	-27	-40	-31	-21	+8
Pravastatin 40 mg	70	-22	-31	-26	-19	+6
ZETIA + Pravastatin 40 mg	67	-30	-42	-32	-21	+8
Pooled data (All Pravastatin Doses)[d]	205	-17	-25	-20	-14	+7
Pooled data (All ZETIA + Pravastatin Doses)[d]	204	-27	-39	-30	-21	+8

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] Table adapted from source 2
[d] ZETIA + all doses of pravastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG compared to all doses of pravastatin pooled (10-40 mg).

Response to ZETIA and Lovastatin Initiated Concurrently in Patients with Primary Hypercholesterolemia (Mean[a] % Change from Untreated Baseline[b])[c]

Treatment (Daily Dose)	**N**	**Total-C**	**LDL-C**	**Apo B**	**TG[a]**	**HDL-C**
Placebo	64	+1	0	+1	+6	0
ZETIA	72	-13	-19	-14	-5	+3
Lovastatin 10 mg	73	-15	-20	-17	-11	+5
ZETIA + Lovastatin 10 mg	65	-24	-34	-27	-19	+8
Lovastatin 20 mg	74	-19	-26	-21	-12	+3
ZETIA + Lovastatin 20 mg	62	-29	-41	-34	-27	+9
Lovastatin 40 mg	73	-21	-30	-25	-15	+5
ZETIA + Lovastatin 40 mg	65	-33	-46	-38	-27	+9
Pooled data (All Lovastatin Doses)[d]	220	-18	-25	-21	-12	+4
Pooled data (All ZETIA + Lovastatin Doses)[d]	192	-29	-40	-33	-25	+9

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] Table adapted from source 2
[d] ZETIA + all doses of lovastatin pooled (10-40 mg) significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of lovastatin pooled (10-40 mg).

Adverse Effects[2]

Clinical Adverse Events occurring in ≥2% of Patients and at an Incidence Greater than Placebo, Regardless of Causality, in ZETIA/Statin Combination Studies*†

Body System Adverse Event	Placebo (%) n=259	ZETIA 10 mg (%) n=262	All Statins‡(%) n=936	ZETIA + All Statins‡ (%) n=925
Body as a whole				
Chest pain	1.2	3.4	2.0	1.8
Dizziness	1.2	2.7	1.4	1.8
Fatigue	1.9	1.9	1.4	2.8
Headache	5.4	8.0	7.3	6.3
Gastro-intestinal system disorders				
Abdominal pain	2.3	2.7	3.1	3.5
Diarrhea	1.5	3.4	2.9	2.8
Infections				
Pharyngitis	1.9	3.1	2.5	2.3
Sinusitis	1.9	4.6	3.6	3.5
Upper respiratory tract infection	10.8	13.0	13.6	11.8
Musculo-skeletal system disorders				
Arthralgia	2.3	3.8	4.3	3.4
Back pain	3.5	3.4	3.7	4.3
Myalgia	4.6	5.0	4.1	4.5

*Table adapted from source 2

† Includes four placebo-controlled combination studies in which ZETIA was initiated concurrently with an HMG-CoA reductase inhibitor.

‡ All Statins = all doses of all HMG-CoA reductase inhibitors.

Drug Interactions[2]

Cholestyramine: Concomitant administration with ezetimibe decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Co-administration of ZETIA with fibrates is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold.

HMG-CoA reductase inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Cyclosporine: The total ezetimibe level increased 12-fold in one renal transplant patient receiving multiple medications, including cyclosporine. Patients who take both ezetimibe and cyclosporine should be carefully monitored.

Dosage and Administration

A standard cholesterol-lowering diet should be started before initiating during Zetia therapy. The recommended dose of Zetia is 10 mg once daily, administered with or without food.

Zetia® may be administered with an HMG-CoA reductase inhibitor for incremental effect. For convenience, the daily dose of Zetia® may be taken at the same time as the HMG-CoA reductase inhibitor, according to the dosing recommendations for the HMG-CoA reductase inhibitor.

Patients with Hepatic Insufficiency
No dosage adjustment is necessary in patients with mild hepatic insufficiency

Patients with Renal Insufficiency
No dosage adjustment is necessary in patients with renal insufficiency

Geriatric Patients
No dosage adjustment is necessary in geriatric patients

Co-administration with Bile Acid Sequestrants
Dosing of Zetia® should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant

Cost Comparison (at commonly used dosages)

DRUG AND DAILY DOSE	BRAND NAME	AWP/MONTH*
Ezetimibe 10 mg	**Zetia**	**$72**
Lovastatin 10 mg – 80 mg	Mevacor	$23 - $142
Fluvastatin 20 mg – 40 mg	Lescol	$49†
Simvastatin 5 mg – 80 mg	Zocor	$57 - $132
Lovastatin ER‡ 20 mg – 60 mg	Altocor	$62†
Fluvastatin XL 80 mg	Lescol XL	$62†
Atorvastatin 10 mg – 80 mg	Lipitor	$69 - $109
Niacin/lovastatin 1000mg/20mg – 2000mg/40mg	Advicor	$65 - $130
Pravastatin 10 mg – 80 mg	Pravachol	$83 - $130

*Average Wholesale Price: Red Book Update January 2003. Costs rounded to the nearest whole dollar. Generic costs are used if generic products are available (i.e., lovastatin). HCFA maximum allowable prices used where applicable.
†Dose range reflects currently available strengths
‡Equal pricing for all strengths

Conclusion

Zetia® (ezetimibe) is a cholesterol-lowering agent that reduces total-C, LDL-C, Apo B, and triglycerides, and increases HDL-C. Cholesterol is lowered by inhibiting cholesterol absorption in the small intestines resulting in decreased delivery of intestinal cholesterol to the liver. Hepatic cholesterol stores are reduced and clearance of blood cholesterol is increased. Clinical studies indicate that as monotherapy, ezetimibe lowers cholesterol by 13%. In combination with ongoing HMG CoA reductase inhibitors therapy, ezetimibe significantly lowers total-C, LDL-C, Apo B and triglycerides, and increases HDL-C compared with an HMG CoA reductase inhibitor given alone. When initiated concurrently with an HMG CoA reductase inhibitor to previously untreated patients with primary hypercholesterolemia,
ezetemibe plus all doses of the HMG CoA reductase inhibitor significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C compared to all doses of the HMG CoA reductase inhibitor.

Recommendation

Zetia® will be available through a clinical edit.

Approval Criteia

- Diagnosis equals hypercholesterolemia
- Trial and failure on HMG-Co A Reductase Inhibitor

Denial Criteria

- Lack of approval criteria

References

1. Zetia. Merck/Schering-Plough Pharmaceuticals; North Wales, PA. 2002 October.
2. RxList, Zetia. http://www.rxlist.com/cgi/generic/ezetimibe_cp.htm#cs

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