DUR Board Meeting
December 1, 2008
Heritage Center

1pm

North Dakota Medicaid
DUR Board Meeting
Agenda
Heritage Center
December 1, 2008
1pm

1. Administrative items
    - Travel vouchers
    - Board Members Sign In

2. Old Business
    - Review and approval of minutes of 09/08/08 meeting — Chairman
    - Budget update — Brendan
    - Second review of Triptans — HID
    - Second review of Vusion — HID

3. New Business
    - Review of Statins — HID
    - Yearly PA Review — HID
        - Solodyn
        - Oracea
        - Oxycontin
        - Short Acting Beta Agonists
        - Zanaflex capsules
        - Ketek
    - Criteria Recommendations — Brendan
    - Upcoming meeting date/agenda — Chairman

4. Adjourn — Chairman

Please remember to turn all cellular phones and pagers to silent mode during the meeting.

Drug Utilization Review (DUR) Meeting Minutes
September 8, 2008

Members Present: Patricia Churchill, Cheryl Huber, Norman Byers, Carrie Sorenson, Greg Pfister, Bob Treitline, Kim Krohn, Jeffrey Hostetter, John Savageau, Scott Setzepfandt, and Leeann Ness, Carlotta McCleary and Todd Twogood.
Medicaid Pharmacy Department: Brendan Joyce, Gary Betting
HID Staff Present: Candace Rieth

Chair, C. Sorenson, called the meeting to order at 1:05pm. C. Sorenson asked for a motion to approve the minutes from the June meeting. N. Byers moved that the minutes be approved and C. Huber seconded the motion. Chair, C. Sorenson, called for a voice vote to approve the minutes. The motion passed.

Budget Update
B. Joyce had no new information to present regarding the budget.

Summary of Board Recommendations to Legislative Counsel
Previous board recommendations on HIV/AIDS, Oncology, ADHD, Antidepressants, and Antipsychotics were reviewed. C. Huber mentioned that the summary did not include the decision by the board to not make any recommendations regarding anticonvulsants. B. Treitline made a motion that the Summary of Board Recommendations should be modified based on the past meeting's minutes. G. Pfister seconded the motion. Chair, C. Sorenson, called for a voice vote and the motion passed. B. Joyce stated that the completed recommendations will be sent to the legislative council before October 1st to meet the requirements of the law.

Second Review of Chantix
At the June meeting, J. Hostetter made a motion requesting the Department to formulate a smoking cessation plan that would cover all smoking cessation products for recipients enrolled in the ND Tobacco Quitline. B. Joyce presented the smoking cessation plan to the DUR Board. He said it did not include all smoking cessation products as the nicotine inhaler and nicotine nasal spray are not recommended by the Health Department's Quitline. Each smoking cessation product will be covered for a 90 day supply over a 2 year period of time. Chantix will be covered for a 6 month supply over a 2 year period of time. It was recommended by the Board that patients stop smoking during the first three months of therapy with Chantix. Patients will be contacted by the Quitline once a month. After the first three months of Chantix therapy, the Quitline will verify that patients have stopped smoking and a prior authorization will be required for the next three months of therapy. T. Twogood made a motion to remove the age limit from the guidelines. J. Savageau seconded the motion. Chair, C. Sorenson, called for a voice vote to amend the age on the presented plan as well as implement the smoking cessation program as amended. Both the amendment to the motion and the amended motion passed. B. Joyce informed the Board that a State Plan Amendment (SPA) will need to be filed with CMS to gain approval to cover smoking cessation products. Programming changes will also need to be made. It is hoped that the changes will be in place in October which would then allow the products to be covered in the fashion approved by the board.

Second Review of Soma 250
At the June meeting, Board members made two motions regarding carisoprodol. The first was a motion to place Soma 250 on prior authorization. The second motion recommended that all new prescriptions for carisoprodol be limited to 3 weeks supply with one refill per year. Board members suggested sending provider letters for patients taking carisoprodol on a chronic basis offering the option of grandfathering a patient or weaning a patient over a 6 month period of time. Chronic was defined as greater than 5 scripts per year of carisoprodol. B. Treitline amended the motion to include a prior authorization on carisoprodol and an option for grandfathering patients

currently taking carisoprodol. J. Savageau seconded the motion. Chair, C. Sorenson, called for a voice vote to approve the original motion with the amendment. The motion passed.

Review of Triptans
B. Joyce reviewed triptan utilization with Board members. J. Kelloway, representing GSK, spoke on behalf of Treximet. T. Hartman, representing Pfizer, spoke on behalf of Relpax. N. Byers made a motion to make Imitrex first line for North Dakota Medicaid recipients. G. Pfister seconded the motion. This topic will be brought up again at the next Board meeting for finalization.

Review of Intranasal Corticosteroids
B. Joyce reviewed intranasal corticosteroid utilization with Board members. M. Cardenas, representing GSK, spoke on behalf of Veramyst. K. Hesterman, representing Schering-Plough, spoke on behalf of Nasonex. After much discussion, the topic of intranasal corticosteroids was tabled.

Review of Vusion
B. Joyce reviewed Vusion utilization with Board members. There was no public comment. T. Twogood made a motion to prior authorize Vusion. J. Hostetter seconded the motion. This topic will be brought up again at the next Board meeting for finalization.

Yearly PA Review
The Board reviews products annually that have previously been placed on prior authorization. This allows the Board a chance to update the prior authorization forms and criteria. Growth Hormone/IGF-1 products, ARBs/Renin Inhibitors, Brand Medically Necessary, Amrix and Xenical were reviewed. S. Setzepfandt, representing Roche, recused himself as a Board member and spoke on behalf of Xenical suggesting the BMI criteria be changed to 30. Dana Myer, representing Novartis (Sandoz), spoke on behalf of Omnitrope. No changes were made to the forms and criteria for these agents.

Criteria Recommendations
The recommended RDUR criteria enclosed in the packet were developed from product information provided by the manufacturers and usually are consistent with new indications, new drugs added, new warnings, etc. These proposed criteria will be added to the current set of criteria, and will be used in future DUR cycles. J. Savageau moved to approve the new criteria and C. Huber seconded the motion. Chair, C. Sorenson called for a voice vote. The motion passed.

The next DUR board meeting will be held December 1, 2008. C. Huber made a motion to adjourn the meeting and J. Hostetter seconded. Chair C. Sorenson adjourned the meeting at 3:35 pm.

North Dakota Medicaid Oral Triptan Utilization April 2007 - March 2008

Label Name	Rx Num	Total Reimb Amt	Average Cost per script
AMERGE 2.5 MG TABLET	7	$1,459.46	$208.49
AXERT 12.5 MG TABLET	22	$4,163.13	$189.23
FROVA 2.5 MG TABLET	27	$4,820.10	$178.52
IMITREX 100 MG TABLET	478	$91,975.49	$192.42
IMITREX 25 MG TABLET	68	$17,560.75	$258.25
IMITREX 50 MG TABLET	238	$42,365.42	$178.01
MAXALT 10 MG TABLET	122	$24,346.16	$199.56
MAXALT 5 MG TABLET	8	$1,354.83	$169.35
MAXALT MLT 10 MG TABLET	86	$10,726.02	$124.72
MAXALT MLT 5 MG TABLET	6	$956.26	$159.38
RELPAX 20 MG TABLET	40	$4,995.95	$124.90
RELPAX 40 MG TABLET	341	$44,738.87	$131.20
ZOMIG 2.5 MG TABLET	24	$3,036.96	$126.54
ZOMIG 5 MG TABLET	86	$14,872.06	$172.93
ZOMIG ZMT 2.5 MG TABLET	4	$570.93	$142.73
ZOMIG ZMT 5 MG TABLET	14	$1,114.37	$79.60
Total	**1571**	**$269,056.76**	

North Dakota Medicaid Nasal Triptan Utilization April 2007 – March 2008

Label Name	Rx Num	Total Reimb Amt	Average Cost per script
IMITREX 20 MG NASAL SPRAY	36	$6,838.23	$189.95
IMITREX 5 MG NASAL SPRAY	11	$2,128.65	$193.51
ZOMIG 5 MG NASAL SPRAY	9	$1,341.00	$149.00
Total	**56**	**$10,307.88**	

North Dakota Medicaid Injectable Triptan Utilization April 2007 – March 2008

Label Name	Rx Num	Total Reimb Amt	Average Cost per script
IMITREX 4 MG/0.5 ML SYRINGE KIT	1	$38.32	$38.32
IMITREX 6 MG/0.5 ML KIT REFILL	66	$16,793.47	$254.45
IMITREX 6 MG/0.5 ML SYRINGE KIT	38	$6,359.06	$167.34
Total	**105**	**$23,190.85**	

578 Triptan Recipients April 2007 – March 2008

Serotonin (5-HT$_1$) Receptor Agonists - Triptan PA FORM

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving a new prescription for Amerge, Axert, Frova, Maxalt, Relpax, Treximet, or Zomig must try Imitrex (sumatriptan) as first line therapy.

***Note:**

- **Imitrex (sumatriptan) does not require a PA.**
- **Injectables are not subject to a prior authorization at this time.**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code

Requested Drug and Dosage:	**Diagnosis for this request:**
□ AMERGE □ RELPAX □ AXERT □ TREXIMET □ FROVA □ ZOMIG □ MAXALT	

Qualifications for coverage:

□ Failed sumatriptan therapy	Start Date	End Date	Dose	Frequency

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Physician Signature	Date

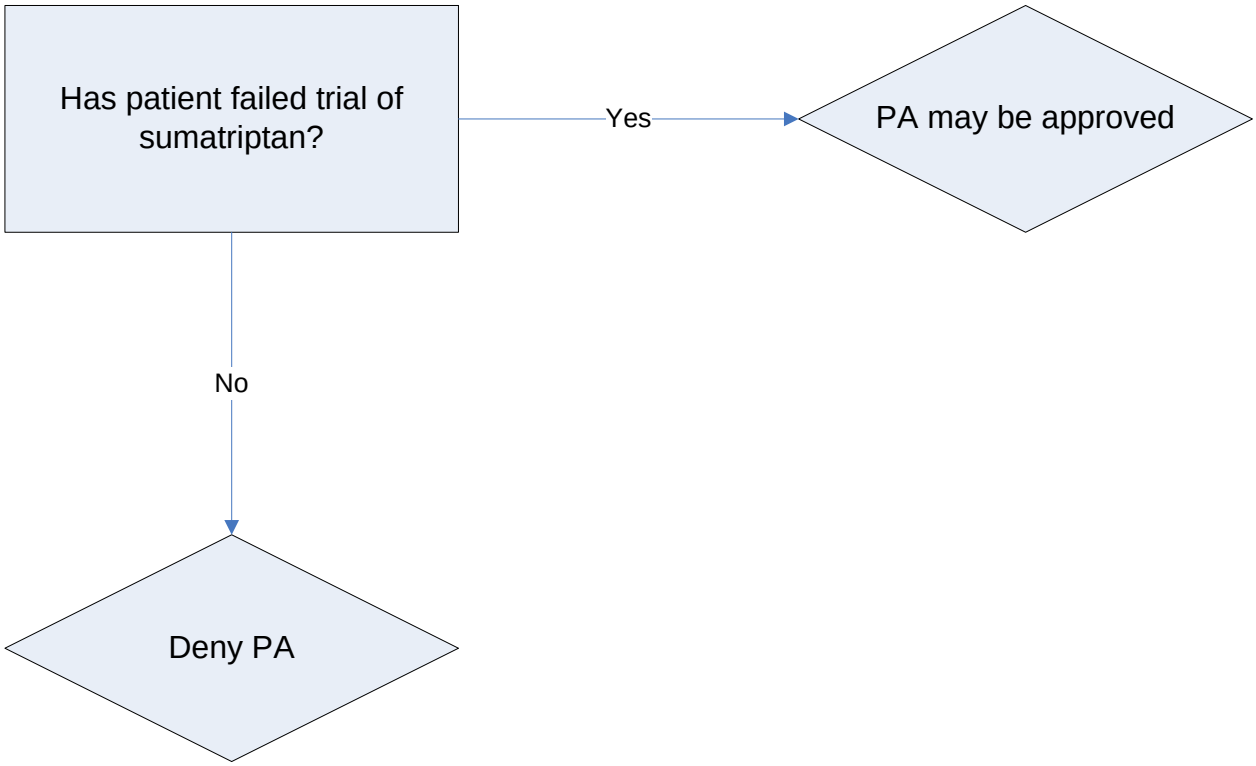
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
Serotonin (5-HT_1) Receptor Agonists
Triptan Prior Authorization Algorithm



Vusion PA FORM

Prior Authorization Vendor for ND Medicaid

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving a new prescription for Vusion must try other topical antifungal products as first line therapy.

***Note: Nystatin and clotrimazole do not require a prior authorization.**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ VUSION	**Diagnosis for this request:**		

Qualifications for coverage:

□ Failed antifungal therapy Name of medication failed: _____	Start Date	End Date	Dose	Frequency

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Physician Signature	Date

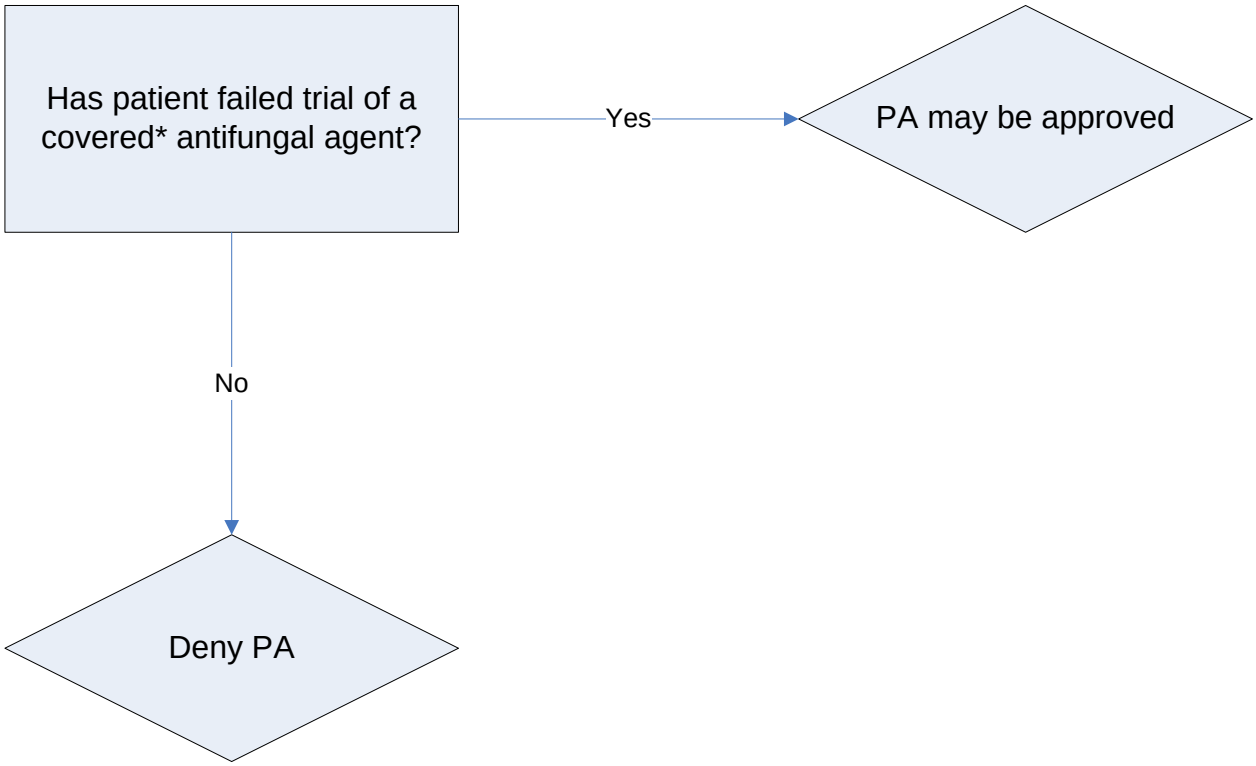
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
Vusion Authorization Algorithm



*Nystatin and clotrimazole do not require a PA

North Dakota Medicaid
Pharmacotherapy Review
Statin and Statin Combinations

I. Overview

The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum low-density lipoprotein (LDL-C) concentrations. They are first line agents for patients who require drug therapy to reduce serum LDL-C concentrations. The statins work by inhibiting HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate in an early step in the biosynthesis of cholesterol. In addition to LDL-C reduction, statins lower total cholesterol as well as triglycerides, and slightly increase high-density lipoprotein (HDL-C).

Lowering total cholesterol and LDL-C and raising HDL-C is important for many reasons. Deposition of cholesterol in the arterial walls is central to the pathogenesis of atherosclerosis in the coronary arteries. A direct correlation exists between total cholesterol, LDL-C, and the risk of developing coronary heart disease (CHD). Each 1% reduction in LDL-C results in approximately a 1% decrease in the risk of a major cardiac event. An inverse relationship exists between HDL-C and the risk of developing CHD; each 1mg/dL decrease in HDL-C results in a 2-3% increase in the risk of CHD.

CHD is the leading cause of death in the United States today, having caused over 800,000 deaths in 2004. From 1993 to 2003, the death rate from both CHD and CVD decreased 30.2% and 22.1% respectively, while the overall mortality rate decreased by 4.6%. Advances have been made in the treatment of CHD, CVD and hyperlipidemia, but there is still work to be done. There are approximately 34.5 million adults in the U.S. with a total cholesterol value of 240mg/dL and greater. The direct and indirect healthcare costs for CVD in 2007 are estimated at $431.8 billion.

Pharmacotherapy that can lower total cholesterol and LDL-C while raising HDL-C is not only worthwhile, but extremely valuable. HMG-CoA reductase inhibitors are considered first-line agents for treating hyperlipidemia.

Table 1 lists the agents included in this review.

Table 1. Statin and Statin Combinations Included in this Review

Generic Name	Brand Name	Dosage Form/Strength	Generic Availability	Manufacturer
Atorvastatin	Lipitor®	Tablets: 10mg, 20mg, 40mg, and 80mg	No	Pfizer
Atorvastatin/amlodipine	Caduet®	Tablets: 2.5mg/10mg, 2.5mg/20mg, 2.5mg/40mg, 5mg/10mg, 5mg/20mg,	No	Pfizer

Generic Name	Brand Name	Dosage Form/Strength	Generic Availability	Manufacturer
		5mg/40mg, 10mg/10mg, 10mg/20mg, 10mg/40mg, and 10mg/80mg		
Fluvastatin	Lescol®, Lescol XL®	Capsules: 20mg, and 40mg; Extended-release tablets: 80mg	No	Novartis
Lovastatin	Mevacor®, Altoprev®	Tablets: 10mg, 20mg, and 40mg; Extended-release tablets: 10mg, 20mg, 40mg, and 60mg	Yes-Mevacor No-Altoprev	Merck, Altoprev-First Horizon, various generic companies
Lovastatin/niacin ER	Advicor®	Tablets: 500mg/20mg, 750mg/20mg, 1000mg/20mg, and 1000mg/40mg	No	Kos
Rosuvastatin	Crestor®	Tablets: 5mg, 10mg, 20mg, and 40mg	No	AstraZeneca
Pravastatin	Pravachol®	Tablets: 10mg, 20mg, 40mg, and 80mg	Yes	Bristol-Myers Squibb, various generic companies
Simvastatin	Zocor®	Tablets: 5mg, 10mg, 20mg, 40mg, and 80mg	Yes	Merck, various generic companies
Simvastatin/ezetimibe	Vytorin®	Tablets:10mg/10mg, 10mg/20mg, 10mg/40mg, and 10mg/80mg	No	Merck/Schering-Plough
Simvastatin/niacin ER	Simcor®	500mg/20mg, 750/20mg, and 1,000mg/20mg	No	Abbott

II. Current Treatment Guidelines

The decision to treat hyperlipidemia generally follows the treatment guidelines of the Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, published in 2002 and updated in 2004. The report stresses that the intensity of treatment should be directed by the degree of cardiovascular risk. Because LDL-C is the major atherogenic lipid component, NCEP-ATP III focuses primarily on achieving target LDL-C levels. For most patients who are prescribed a statin, the target is <130 mg/dL or <100 mg/dL. In ATP-III, patients who have type 2 diabetes without CHD; peripheral or carotid vascular disease; and patients who have multiple risk factors and a 10-year risk of CHD > 20% are said to have 'CHD equivalents.' This means that the criteria for using drug therapy and the LDL-C target is the same for patients who have a history of CHD.

The 2006 update of the American Heart Association/American College of Cardiology consensus statement on secondary prevention states that an LDL-C goal of <70 mg/dL for high risk patients is a therapeutic option. Factors that

place patients in the category of very high risk are the presence of established CVD plus 1) multiple major risk factors (especially diabetes), 2) severe and poorly controlled risk factors (especially continued smoking), 3) multiple risk factors of the metabolic syndrome (especially high triglycerides >200 mg/dL plus non-HDL-C >130 mg/dL with low HDL-C <40 mg/dL, and 4) patients with acute coronary syndromes. If it is not possible to attain LDL-C <70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with either statins or LDL-C lowering drug combinations. The optional goal of <70 mg/dL does not apply to individuals who are not at high risk.

Table 2 summarizes NCEP Treatment Guidelines for LDL-C goals and cutpoints for therapeutic lifestyle changes (TLC), and pharmacotherapy in different risk categories.

Table 2. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for TLC and Pharmacotherapy

Risk Category	LDL Goal	LDL Level to Initiate TLC	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalent (10-year risk > 20%)	< 100 mg/dL	≥ 100 mg/dL	≥ 130 mg/dL (100-129 mg/dL, drug optional)*
2 or more Risk Factors (10-year risk ≤ 20%)	< 130 mg/dL	≥130 mg/dL	≥ 130 mg/dL (for 10-year risk 10-20%) > 160 mg/dL (for 10-year risk < 10%)
0-1 Risk Factors	< 160 mg/dL	≥ 160 mg/dL	≥ 190 mg/dL (160-189 mg/dL, drug optional)**

*Some authorities recommend use of LDL-C lowering drugs in this category if an LDL-C < 100 mg/dL cannot be achieved by TLC. Clinical judgment may also call for deferring drug therapy in this category.
**Factors that favor drug therapy after 3 months of TLC include a severe single risk factor (heavy smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL-C), multiple life-habit risk factors and emerging risk factors, or 10-year risk approaching 10%.

III. Comparative Indications for HMG-CoA Reductase Inhibitors

The Food and Drug Administration (FDA) has approved HMG-CoA reductase inhibitors for use adjunctively with a diet restricted in saturated fat and cholesterol when diet and other nonpharmacological therapies alone have produced inadequate responses.

Table 3 summarizes the FDA-approved indications for HMG-CoA reductase inhibitors included in this review.

Table 3. FDA Approved Indications for the HMG-CoA Reductase Inhibitors

Indication	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Lovastatin ER	Pravastatin	Simvastatin	Rosuvastatin
Primary prevention of coronary events	✓		✓	✓	✓	✓	
Secondary prevention of coronary events	✓	✓	✓	✓	✓	✓	

Indication	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Lovastatin ER	Pravastatin	Simvastatin	Rosuvastatin
Primary hyper-cholesterolemia	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]	✓[a]
Mixed dyslipidemia	✓[b]	✓[b]		✓[b]	✓[b]	✓[b]	✓[b]
Homozygous familial hyperlipidemia	✓					✓	✓
Primary dysbetalipo-proteinemia	✓[c]				✓[c]	✓[c]	
Slow progression of coronary atherosclerosis		✓	✓	✓	✓		✓
Heterozygous familial hyper-cholesterolemia in adolescents	✓	✓	✓		✓	✓	
Hyper-triglyceridemia[d]	✓[e]				✓[e]	✓[e]	✓[e]

a Includes heterozygous familial and nonfamilial hypercholesterolemia..
b Includes Fredrickson types IIA and IIB.
c Includes Frederickson type III.
d Not indicated in hypertriglyceridemia patients with low/normal LDL despite elevated total cholesterol.
e Includes Frederickson type IV.

Combination Product Indications:

1. **Amlodipine/Atorvastatin (Caduet)**
   - Amlodipine: For the treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina (Prinzmetal or Variant angina).
   - Atorvastatin: See indications above.

2. **Niacin (Extended Release)/Lovastatin (Advicor)**
   - Primary hypercholesterolemia/mixed dyslipidemia: For the treatment of primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Frederickson Types IIa and IIb) in the following: Patients treated with lovastatin who require further TG-lowering or HDL-raising who may benefit from having niacin added to their regimen; patients treated with niacin who require further LDL-lowering who may benefit from having lovastatin added to their regimen.

3. **Niacin (Extended Release)/Simvastatin (Simcor)**
   - Hypercholesterolemia: For the reduction total cholesterol, LDL-C, APO B, non-HDL-C, or TG, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson type IIa and IIb) when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

- Hypertriglyceridemia: For the reduction of triglycerides in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia) when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

4. Ezetimibe/Simvastatin (Vytorin)

- Homozygous familial hypercholesterolemia: For reducing elevated total cholesterol and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments.
- Primary hypercholesterolemia and mixed dyslipidemia.

IV. Comparative Pharmacokinetic Parameters of HMG-CoA Reductase Inhibitors

Minor differences exist between the statins with respect to pharmacokinetic parameters. All statins possess low systemic bioavailability indicating extensive first pass metabolism, which is advantageous since the major site of cholesterol synthesis is in the liver. The drug interaction profile for each statin is determined by its cytochrome-based metabolism.

Table 4 summarizes various pharmacokinetic parameters of the statins.

Table 4. Pharmacokinetic parameters of HMG-CoA Reductase Inhibitors

	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Lovastatin ER	Pravastatin	Simvastatin	Rosuvastatin
Elimination Half Life	14 hours (20-30 hours for HMG-CoA reductase inhibitory activity)	<3 hours for IR and 9 hours for XL	2 hours	5.6-8.4 hours	77 hours (pravastatin plus metabolites)	1.9 hours	19 hours
Absolute Bioavailability	~14%	24%-IR 29%-ER	<5%	190% compared to IR lovastatin	17%	<5%	~20%
Food Effect	with or w/o food	with or w/o food	with meals	with or w/o food	with or w/o food	with or w/o food	with or w/o food
Protein Binding	≥98%	98%	>95%	>95%	50%	95%	95%
Main Metabolizing Enzyme	CYP3A4 (hepatic-first pass)	CYP2C9 (75%) (hepatic- first pass)	CYP3A4 (hepatic-extensive first pass)	CYP3A4	various pathways (hepatic-extensive first pass)	CYP3A4 (extensive first pass)	CYP2C9 (not extensively metabolized)

	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin	Lovastatin ER	Pravastatin	Simvastatin	Rosuvastatin
Primary Route of Elimination	Bile	Feces	Feces; Renal	Feces; Renal	Feces; Urine	Feces; Urine	Feces
Effects of Renal/Hepatic Impairment	Plasma levels ↑ in chronic alcoholic liver disease	Plasma levels ↑ with hepatic insufficiency	Plasma levels ↑ in severe renal disease	Plasma levels ↑ in severe renal disease	Plasma levels ↑ with renal or hepatic insufficiency	Plasma levels ↑ with hepatic impairment or severe renal disease	Plasma levels ↑ with hepatic impairment or severe renal disease

V. HMG-CoA Reductase Inhibitor Drug Interactions

Clinically important drug interactions exist for the statins with minor differences between the drugs in this class. Atorvastatin, lovastatin, and simvastatin are metabolized by CYP3A4 and thus have similar drug interaction profiles. Fluvastatin is metabolized primarily by CYP2C9, whereas pravastatin and rosuvastatin are eliminated by other metabolic routes. Each statin should be used cautiously when combined with bile acid sequestrants (due to potential for decreased pharmacological effects of the statin), niacin and fibric acid derivatives such as gemfibrozil (due to increased risk for myopathy and rhabdomyolysis), and azole antifungals (due to increased plasma levels of the statin which could lead to increased side effects and increased risk for rhabdomyolysis). Each statin, with the exception of fluvastatin/fluvastatin XL, should also be used cautiously with cyclosporine (due to increased plasma levels of the statin, which could increase risk for side effects including myopathy and rhabdomyolysis). Dosage reduction of the statin and monitoring for side effects is necessary to properly manage this interaction.

Other clinically significant [rated as 1 (major) or 2 (moderate)] drug interactions for the statins are listed below.

<u>Atorvastatin, Lovastatin, Simvastatin</u>

- Grapefruit juice (> 1 quart/day can increase risk of myopathy)
- Macrolide antibiotics (increase plasma levels of statins, thereby increasing risk of myopathy)
- Nefazodone (increased risk for myopathy and rhabdomyolysis)
- Non-dihydropyridine calcium channel blockers (increased risk of myopathy when used with high doses of statins)
- Oral Contraceptives (atorvastatin only; coadministration increases AUC for norethindrone and ethinyl estradiol)
- Protease Inhibitors (increased risk of myopathy and rhabdomyolysis)
- Rifamycins (concurrent administration decreases the plasma levels of the statin)
- Warfarin (lovastatin and simvastatin only; increased anticoagulant effect)

Fluvastatin/Fluvastatin XL

- Rifamycins (concurrent administration decreases plasma concentrations of the statin)
- Warfarin (increased anticoagulant effect)

Most of the drug interactions listed above can be managed with dosing modifications and monitoring. When considering the general population, use of any statin would not be precluded due to potentially harmful drug interactions. Of note, to avoid any potential harm, the prescribing information for simvastatin and lovastatin offers explicit instructions for proper use and dosage of these medications when used concomitantly with interacting drugs.

VI. Comparative Adverse Effects of HMG-CoA Reductase Inhibitors

Statins are generally well tolerated with the most common side effects being abdominal pain, constipation, flatulence, and headache. More serious but rare side effects of statins include increases in liver enzymes and myopathy accompanied by elevations in creatine kinase, which can progress to rhabdomyolysis and acute renal failure. Routine liver function monitoring is recommended with each statin, with only slight variations in this monitoring parameter existing between statins. Increases in hepatic transaminases (> 3x ULN) have been reported with each statin (0.5%-2.0%) and appear to be dose-dependent (risk increases as the statin dose increases). Elevations in hepatic transaminases frequently reverse with a reduction in dose or suspension of therapy. Upon re-challenge or initiation of another statin, elevations in liver enzymes do not often occur. Myositis (defined as elevated creatine kinase – generally > 10 times the ULN – plus symptomatic muscle aches/weakness) has also been reported with each statin (0.1-0.5%), as has rhabdomyolysis when statins are used as monotherapy (0.04%-0.2%). However, no clear differences exist between the statins in the rates of these rare but serious adverse reactions.

With regard to more minor adverse reactions, no clear differences seem to exist between the drugs in this class. Patients who do not tolerate one statin generally may tolerate another (tolerability differences between statins do exist for unknown reasons).

Table 5 lists adverse reactions reported with the various statins. Incidences of adverse effects are listed as percentages.

Table 5. Adverse Reactions (%) Reported with the HMG-CoA Reductase Inhibitors

Adverse Effects	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin*	Pravastatin	Simvastatin	Rosuvastatin
CNS						
Asthenia	2.2 – 3.8	-	1.2 – 3	-	1.6	2.7
Depression	< 2	-	-	-	-	> 2
Dizziness	> 2	1.9 – 2.2	0.5 – 2	3.3	-	> 2
Headache	2.5 – 16.7	4.7 – 8.9	2.1 – 7	6.2	3.5	5.5

Adverse Effects	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin*	Pravastatin	Simvastatin	Rosuvastatin
Insomnia	> 2	0.9 – 2.7	0.5 – 1	< 1	-	> 2
Paresthesia	< 2	-	0.5 – 1	< 1	-	> 2
GI						
Abdominal pain	2.1 – 3.8	3.7 – 4.9	2 – 2.5	5.4	0.9 – 3.2	> 2
Acid regurgitation	-	-	0.5 – 1	-	-	-
Constipation	1.1 – 2.5	2.3 – 3.1	2 – 3.5	4	2.3	> 2
Diarrhea	2.7 – 5.3	3.5 – 4.9	2.2 – 3	6.2	0.5 – 1.9	3.4
Dry mouth	-	-	0.5 – 1	-	-	-
Dysgeusia	-	-	0.8	-	-	-
Dyspepsia	1.3 – 2.8	3.5 – 7.9	1 – 1.6	-	1.1	3.4
Flatulence	1.1 – 2.8	1.4 – 2.6	3.7 – 4.5	3.3	0.9 – 1.9	> 1
Gastroenteritis	< 2	-	-	-	-	> 2
Heartburn	-	-	1.6	2.9	-	-
Nausea/ Vomiting	> 2/< 2	2.5 – 3.2	1.9 – 2.5/ 0.5 – 1	7.3	0.4 – 1.3	3.4/>1
Tooth disorder	-	1.4 – 2.1	-	-	-	> 1
GU						
Urinary abnormality	-	-	-	2.4	-	-
Urinary tract infection	> 2	1.6 – 2.7	2 – 3	-	-	2.3
Musculoskeletal						
Arthralgia	2 – 5.1	1.3 – 4	0.5 – 1	-	-	> 2
Arthritis	> 2	1.3 – 2.1	-	-	-	> 2
Back pain	1.1 – 3.8	5.7	5	-	-	2.6
Leg pain	< 2	-	0.5 – 1	-	-	-
Localized pain	-	-	0.5 – 1	10	-	-
Muscle cramps/ pain	-	-	0.6 – 1.1	-	-	-
Myalgia	1.3 – 5.6	3.8 – 5	1.8 – 3	2.7	1.2	2.8
Shoulder pain	-	-	0.5 – 1	-	-	-
Respiratory						
Bronchitis	> 2	1.8 – 7.6	-	-	-	> 2
Common cold		-	-	7	-	-
Cough	-	1.9 – 2.4	-	2.6	> 2	-
Pharyngitis	1.3 – 2.5	2.4 – 3.8	-	-	-	-
Rhinitis	> 2	1.5 – 4.7	-	4	-	2.2
Sinusitis	2.5 – 6.4	2.6 – 3.5	4 – 6	-	-	2
URI	-	12.5 – 16.2	-	-	2.1	-
Miscellaneous						
Accidental trauma	1.3 – 4.2	4.2 – 5.1	4 – 6	-	-	> 2
Allergy	0.9 – 2.8	1 – 2.3	-	<1	-	-
Alopecia	< 2	-	0.5 – 1	3.7	-	> 2
Blurred vision/ eye irritation	-	-	0.9 – 1.2	-	-	-
Chest pain	> 2	-	0.5 – 1	3.7	-	> 2
Fatigue	-	1.6 – 2.7	-	3.8	-	-
Flu syndrome	2.2 – 3.2	5.1 – 7.1	5	2.4	-	2.3
Hypertension	< 2	-	-	-	-	> 2
Infection	2.8 – 10.3	-	11 – 16	-	-	> 2
Pain	-	-	3 – 5	-	-	>2
Peripheral edema	> 2	-	-	-	-	>2

Adverse Effects	Atorvastatin	Fluvastatin/ Fluvastatin XL	Lovastatin*	Pravastatin	Simvastatin	Rosuvastatin
Rash/pruritus	1.1 – 3.9/ < 2	1.6 – 2.3	0.8 – 1.3/ 0.5 – 1	4/<1	0.6/0.5	>2/>1

*Immediate release and extended release combined

Table 6 summarizes ezetimibe/simvastatin (Vytorin) adverse reactions.

Table 6. Ezetimibe/Simvastatin Adverse Reactions > 2%

Ezetimibe/Simvastatin Adverse Reactions (>2%)				
Adverse Reaction	Placebo	Ezetimibe 10mg	Simvastatin	Ezetimibe/Simvastatin
Musculoskeletal				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.3	3	2	2.3
Miscellaneous				
Headache	6.4	6	5.9	6.8
Influenza	1	1	1.9	2.6
URI	2.6	5	5	3.9

VII. Dosing and Administration of HMG-CoA Reductase Inhibitors

All statins are dosed once daily with the exception of maximum doses of lovastatin and fluvastatin (non extended-release products), which should be divided into twice daily dosing. Only minor differences in administration exist between the statins and none afford an advantage to one statin.

Table 7 details dosing and administration guidelines for the drugs included in this review.

Table 7. HMG-CoA Reductase Inhibitor Dosing & Administration

	Initial Dose	Dosing Range	Maximum Dose	Administration	Special Considerations
Atorvastatin	10-20mg QD	10-80mg QD	80mg QD	Single dose, may be taken at any time of day	LDL-C reduction ≥ 45%, initiate therapy at 40mg QD
Fluvastatin/ Fluvastatin XL	20mg QD	20-80mg	80mg QD	Single dose, should be taken in the evening	LDL-C reduction ≥ 25%, initiate therapy at 40-80mg QD
Lovastatin/ Lovastatin ER	20mg QD	10-80mg	80mg QD	Best taken once daily with evening meal (morning and evening if BID)	LDL-C > 20%, initiate at 20mg/day
Pravastatin	40mg QD	10-80mg	80mg QD	Single dose, may be taken at any time of day	Initiate at 10mg/day in patients with significant renal or hepatic dysfunction
Simvastatin	20-40mg QD	5-80mg QD	80mg QD	Should be taken in the evening	LDL-C reduction > 45% or is deemed at high risk for

	Initial Dose	Dosing Range	Maximum Dose	Administration	Special Considerations
					CHD event, initiate at 40mg QD
Rosuvastatin	10mg QD	5-40mg QD	40mg QD	Single dose may be taken at any time of day	LDL-C > 190mg/dL, initiate therapy at 20mg QD
Amlodipine/ Atorvastatin	Based on continuation of component being used and the recommended starting dose of the added monotherapy	Initial dose – 10mg/80mg	10mg/80mg QD	Single dose may be taken at any time of day	-
Niacin ER/ Lovastatin	500mg/20mg QD	500mg/20mg-2,000mg/40mg	2,000mg/40mg QD	Take at bedtime with a low-fat snack	Dose of niacin should not be increased more than 500mg daily every 4 weeks.
Niacin ER/Simvastatin	500mg/20mg QD at bedtime	1,000mg/20mg-2,000mg/40mg	2,000mg/40mg QD	Take at bedtime with a low-fat snack.	Dose of niacin should not be increased more than 500mg daily every 4 weeks.
Ezetimibe/ Simvastatin	10mg/20mg QD	10mg/10mg-10mg/80mg	10mg/80mg	Single dose, should be taken in the evening	Use is not recommended in patients with moderate or severe hepatic function impairment.

VIII. Comparative Effectiveness of the HMG-CoA Reductase Inhibitors

Two main factors are typically considered when assessing efficacy of statins: 1) the capacity to reduce lipids, especially LDL-C since this cholesterol component has been identified as a major risk factor for CHD and is the primary target of NCEP-ATP III guidelines; and 2) outcomes data; specifically morbidity and mortality. HMG-CoA reductase inhibitors reduce total cholesterol, LDL-C, and triglycerides while raising HDL-C in a dose dependent manner. Differences do exist, however, between the statins and their cholesterol-lowering capacity (including LDL-C capacity).

Table 8 compares the cholesterol lowering effects of each statin.

Table 8. HMG-CoA Reductase Inhibitors' Effect on Cholesterol Levels

Statin	Mean Changes from Baseline (%)			
	TC	LDL-C	TG	HDL-C
Atorvastatin				
10mg	-25 to 37	- 27 to 39	- 17 to 41	+ 6 to 14

Statin	Mean Changes from Baseline (%)			
	TC	LDL-C	TG	HDL-C
20mg	- 33 to 35	- 30 to 43	- 26 to 39	+ 9 to 11
40mg	-37	- 50	- 29	+ 6
80ng	- 44 to 58	- 41 to 60	- 37 to 53	+ 5 to 7.5
Fluvastatin				
20mg	- 16 to 17	- 22 to 25	- 12 to 17	+ 2 to 6
40mg	- 18 to 19	- 24 to 31	- 14 to 20	+ 4 to 8
80mg IR	- 27	- 34 to 36	- 18 to 23	+ 4 to 9
80mg ER	- 25	- 33 to 38	- 19 to 25	+ 7 to 11
Lovastatin IR				
10mg	- 16	- 21	- 10	+ 5
20mg	- 17 to 19	- 24 to 28	- 7 to 10	+ 6 to 8
40mg	- 22 to 27	- 30 to 34	- 6 to 21	+ 2 to 9
80mg	- 29 to 34	- 40 to 42	- 19 to 27	+ 8 to 10
Lovastatin ER				
10mg	- 18	- 24	- 17	+ 9
20mg	- 21	- 30	- 13	+ 12
40mg	- 25	- 35	- 10	+ 13
60mg	- 29	- 40	- 25	+ 12
Pravastatin				
10mg	- 16	- 22	- 15	+ 7
20mg	- 21 to 24	- 26 to 32	- 10 to 11	+ 1 to 2
40mg	- 13 to 33	- 21 to 41	- 12 to 24	+ 5 to 14
80mg	- 27	- 37	- 19	+3
Rosuvastatin				
5mg	- 24 to 33	- 28 to 45	- 21 to 35	+ 3 to 13
10mg	- 36 to 40	- 45 to 52	- 10 to 37	+ 8 to 14
20mg	- 34 to 40	- 31 to 55	- 23 to 37	+8 to 22
40mg	- 40 to 46	- 43 to 63	- 28 to 43	+ 10 to 17
Simvastatin				
5mg	- 19	- 26	- 12	+ 10
10mg	- 23	- 30	- 15	+ 12
20mg	- 28	- 38	- 19	+ 8
40mg	- 25 to 50	- 28 to 50	- 8 to 41	+ 7 to 13
80mg	- 31 to 52	- 35 to 51	- 24 to 38	+ 7 to 16
Ezetimibe/ Simvastatin				
10/10mg	- 31	- 45	- 23	+ 8
10/20mg	- 36	- 52	- 24	+ 10
10/40mg	- 39	- 55	- 23	+ 6
10/80mg	- 43	- 60	- 31	+ 6
Niacin ER/ Lovastatin				
1000/20mg	n/a	- 30	- 32	n/a
1000/40mg	n/a	- 36	- 39	n/a
1500/40mg	n/a	- 37	- 44	n/a
2000/40mg	n/a	- 42	- 44	+ 33 women/+ 24 men

IX. Clinical Effectiveness

Clinical studies evaluating the safety and effectiveness of the single and combination HMG-CoA reductase inhibitors are summarized in Table 9.

Literature search

To identify articles relevant to the HMG-CoA reductase inhibitors, these sources were used: Medline, Ovid, Cochrane Database of Systematic Reviews, and reference lists of review articles in The Pharmacist's Letter and The Medical Letter. Search parameters included the following terms: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, atorvastatin/amlodipine, lovastatin/niacin ER, ezetimibe/simvastatin, hyperlipidemia, LDL-C, dyslipidemia, triglycerides, and cholesterol. Pharmaceutical manufacturers were also invited to submit dossiers.

Study selection

Abstracts of all citations were assessed for patients with primary hyperlipidemia; history of stroke, MI, or TIA; diabetes with CV risk factors; and CHD. Interventions included: an HMG-CoA reductase inhibitor compared to placebo, an HMG-CoA reductase inhibitor compared to another HMG-CoA reductase inhibitor, and an HMG-CoA reductase inhibitor evaluated at different dosages and in different patient populations. Included medications were atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, atorvastatin/amlodipine, lovastatin/niacin ER, and ezetimibe/simvastatin. Outcomes were reduction in LDL-C compared to baseline, increase in HDL-C, reduction/prevention of major cardiovascular and cerebrovascular events, and evaluation of serious adverse reactions. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy. Clinical trials that are not randomized or blinded, and those that have other methodological flaws, are less reliable, but are also included in this review.

Table 9. Clinical Effectiveness Studies for the Single-entity and Combination HMG-CoA Reductase Inhibitors.

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
Atorvastatin				
SPARCL[30,31,32] Atorvastatin 80mg/day versus placebo	Prospective, randomized, double-blind, multicenter study n = 4,731 mean age = 62.5 patients with previously documented stroke or TIA (1-6 months	5 years	**Primary endpoint:** Time from randomization to first occurrence of fatal or nonfatal stroke.	Compared atorvastatin 80mg/day with placebo. Resulted in: • The incidence of fatal or nonfatal stroke was significantly reduced (16%) in the atorvastatin group. • Time to stroke or TIA was significantly reduced (23%) in the atorvastatin group, and time to TIA reduced by 26%. • Atorvastatin group also showed a 35% reduction in major coronary

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
	prior to randomization), LDL-C ≥ 100mg/dL and ≤ 190mg/dL			events. • There was no statistically significant difference in all-cause mortality between the 2 groups. • Atorvastatin was associated with a slight increase in liver enzymes when compared with placebo.
IDEAL[17,18.19] Atorvastatin 80mg/day versus simvastatin 20mg/day	Randomized, blinded, open label, prospective study n = 8,888 mean age = 62 patients with previous history of MI age < 80 years	5.5 years	**Primary endpoint:** Occurrence of a major coronary event, defined as coronary death, confirmed non-fatal acute MI, or cardiac arrest with resuscitation.	Compared intensive atorvastatin therapy (80mg/day) with traditional simvastatin therapy (20mg/day). Resulted in: • Primary endpoint reached in 10.4% of simvastatin patients and 9.3 % of atorvastatin patients (nonsignificant 11% relative risk reduction with atorvastatin). • Non-fatal MI - 6% with atorvastatin and 7.2% with simvastatin. • Major CV events – 12% with atorvastatin and 13.7% with simvastatin. • Occurrence of any coronary event – 20.2% with atorvastatin and 23.8% with simvastatin. • All cause mortality as well as death from CV and non-CV causes did not differ between groups. • There was a higher rate of discontinuation with atorvastatin (1%) than with simvastatin (0.1%) due to transaminase elevation.
TNT[17,19] Atorvastatin 10mg/day versus atorvastatin 80mg/day	Randomized, double-blind, placebo-controlled, multicenter, parallel study n = 10,001 patients with stable CHD LDL-C ≤ 130mg/dL	4.9 years	**Primary endpoint:** Defined as time to CHD death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke. **Secondary endpoint:** Any occurrence of a major coronary event, cerebrovascular event, and all cause mortality.	Compared intensive atorvastatin therapy (80mg/day) with standard atorvastatin therapy (10mg/day). Resulted in: • High dose group shows 22% relative risk reduction in primary endpoints. • Nonsignificant trend toward non-CV death in patients in the high dose group. • Higher doses well tolerated – only 1% of patients showed increased LFT's.
CARDS[20] Atorvastatin 10mg/day versus	Randomized, double-blind, placebo-controlled, multicenter study	Planned 4 years, study terminated	**Primary endpoint:** Any acute coronary heart event,	Compared atorvastatin 10mg/day with placebo. Resulted in: • 40% decrease in LDL-C with atorvastatin therapy

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
placebo	n = 2,838 mean age = 61 patients with type II diabetes LDL-C ≤ 160mg/dL TG ≤ 600mg/dL and one additional risk factor	2 years early	revascularizations, and stroke. **Secondary endpoint:** Included total mortality and any acute hospital verified CV endpoint.	• 37% risk reduction of major cardiovascular event. • 48% relative risk reduction of stroke. 27% risk reduction in all cause mortality.
PROVE-IT[17,19,21] Atorvastatin 80mg/day versus pravastatin 40mg/day	Randomized, double-blind, double-dummy, multicenter study n = 4,162 mean age = 58 patients hospitalized with ACS in the previous 10 days	2 years	**Primary endpoint:** Composite death from any cause, myocardial infarction, documented unstable angina requiring hospitalization, revascularization and stroke.	Compared pravastatin 40mg/day (LDL-C goal 100mg/dL) vs. atorvastatin 80mg/day (LDL-C goal 70mg/dL). Resulted in: • No statistically significant difference in reduction of LDL-C, although primary endpoint events occurred in 26.3 of pravastatin patients and 22.4% of atorvastatin patients (which is a significant 16% risk reduction for atorvastatin patients).
REVERSAL[22] Atorvastatin 80mg/day versus pravastatin 40mg/day	Randomized, double-blind, active control, multicenter study n = 654 mean age = 56 patients with angiographically demonstrated CHD LDL-C between 125-210mg/dL	18 months	**Primary endpoint:** The percentage change in atheroma volume (follow up minus baseline).	Compared atorvastatin 80mg/day with pravastatin 40mg/day. Resulted in: • LDL-C reduced by 46% in atorvastatin group and by 25% in pravastatin group. • Significantly lower progression rate seen in atorvastatin group. • Similar differences were seen between groups, including change in total atheroma volume, change in percentage in atheroma volume, and change in atheroma volume in the most severely diseased 10-mm vessel sub-segment. • Progression of coronary atherosclerosis occurred in 2.7% of the pravastatin group. • Progression did not occur in the atorvastatin group compared with baseline.
ASCOT-LLA[25] Atorvastatin 10mg/day versus placebo	Randomized, double-blind, placebo-controlled, multicenter study n =10,305 mean = 63 years baseline TC ≤ 251mg/dL and at least 3 risk factors for CHD	3.3 years	**Primary endpoint:** Nonfatal MI and fatal CHD. **Secondary endpoint:** All-cause mortality, cardiovascular death, total	Compared atorvastatin 10mg/day with placebo. Resulted in: • 36% reduction in risk of a composite nonfatal MI and fatal CHD. • 21% reduction in risk in total CV events. • 29% reduction in risk for total coronary events. • 13% nonsignificant reduction in risk in all-cause mortality

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
			cardiovascular events, revascularization and fatal/non-fatal stroke.	• 27% reduction in risk in fatal or nonfatal stroke.
MIRACL[28,29] Atorvastatin 80mg/day versus placebo	Randomized, double-blind, placebo-controlled, multicenter study n = 3,086	16 weeks	**Primary endpoint:** Death, non-fatal acute MI, cardiac arrest with resuscitation and recurrent symptomatic myocardial ischemia requiring hospitalization.	Compared atorvastatin 80mg/day to placebo in patients with acute coronary syndrome. Resulted in: • Atorvastatin group showed a 16% reduction of risk of a composite of death, nonfatal acute MI, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia requiring hospitalization. • Atorvastatin group showed a 50% reduction of risk of fatal/nonfatal stroke. • No statistically significant differences were found in the individual components of the primary outcome with the exception of recurrent ischemia requiring hospitalization.
AVERT[35,36] Atorvastatin 80mg/day versus percutaneous coronary transluminal angioplasty	Randomized, multicenter study n = 341	1.5 years	**Primary endpoint:** Number of ischemic events and/or need for revascularization.	Compared atorvastatin 80mg to percutaneous coronary transluminal angioplasty. Resulted in: • 13% of patients receiving atorvastatin compared to 21% of patients receiving revascularization experienced an ischemic event.
Fluvastatin				
LIPS[37] Fluvastatin 80mg/day versus placebo	Randomized, double-blind, placebo-controlled, multicenter study n = 1,677 mean = 60 years	3.9 years	**Primary endpoint:** Survival time free of cardiac death, non-fatal MI or reinterventional procedures.	Compared fluvastatin 40mg BID to placebo. Resulted in: • After the first 1.5 years, there was a 22% reduction of risk of a composite of cardiac death, nonfatal MI, or reinterventional procedure. • Nonsignificant trend towards reduction of cardiac death and combined cardiac death and nonfatal MI. • Diabetics in the fluvastatin group had a 21.7% rate of major adverse CV events vs. a 37.8% rate among placebo patients.
LCAS[51] Fluvastatin 40mg/day versus placebo	Randomized, double-blind, placebo-controlled trial. n = 429 patients with CHD	2.5 years	**Primary endpoint:** Change in LDL-C from baseline.	Compared fluvastatin 40mg/day to placebo. ¼ of patients also received open-label cholestyramine up to 12g/day. Resulted in: • LDL-C was reduced by 23.9% in all FV patients and by 22.5% in

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
	and mild-to-moderate hypercholesterolemia			FV-only patients. • FV patients showed significantly less lesion progression versus placebo.
Lovastatin				
AFCAPS/TexCAPS[40] Lovastatin 20-40mg/day vs placebo	Randomized, double-blind, placebo-controlled study. n = 6,605	5.2 years	**Primary endpoint:** First acute major coronary event (fatal or nonfatal MI, unstable angina, and sudden cardiac death).	Compared lovastatin 20-40mg/day to placebo. Lovastatin group resulted in: • 37% reduction in risk of first acute major coronary event. • 40% reduction in risk of fatal or nonfatal MI. • 33% reduction in risk of coronary revascularization procedures. • 32% reduction in risk of unstable angina. • 25% reduction in risk of CV events. • 25% reduction in risk for coronary events.
Pravastatin				
ALLHAT-LLT[26,27] Pravastatin 40mg/day versus placebo	Randomized, non-blinded, multicenter study n = 10,355 mean = 66 years age > 55 years hypertensive has at least 1 additional risk factor for CHD baseline LDL-C of 120-189mg/dL	4.8 years	**Primary endpoint:** All-cause mortality, with follow-up for up to 8 years. **Secondary endpoint:** Nonfatal MI or fatal CHD combined cause-specific mortality, and cancer.	Compared 'usual care' to pravastatin 40mg/day. Resulted in: • TC reduced by 17% in pravastatin group and by 8% in the usual care group. • No statistically significant difference was found between groups in all-cause mortality, CV disease deaths, or in fatal/nonfatal strokes.
PROSPER[38] Pravastatin 40mg/day versus placebo	Randomized, single-blind, placebo-controlled, multicenter study n = 5,804 Patients aged 70-82 years, with TC 155-350mg/dL, good cognitive function.	3.2 years	**Primary endpoint:** The combined endpoint of definite or suspected death from coronary heart disease, nonfatal MI and fatal or nonfatal stroke. **Secondary endpoint:** Examination of the coronary and cerebrovascular components.	Compared pravastatin 40mg/day to placebo. Pravastatin group showed:: • 16% reduction of risk for the combined endpoint of death from CHD, nonfatal MI, and fatal or nonfatal stroke. • 19% reduction of risk for CHD or nonfatal MI. • 24% risk reduction for CHD death. • No difference was found in the incidence of fatal or nonfatal stroke. • No difference was seen in all-cause death.

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
LIPID[39] Pravastatin 40mg/day versus placebo	Randomized, double-blind, placebo-controlled, multicenter study n = 9,014 aged 31 to 75 years with a history of MI or unstable angina and an initial cholesterol level of 155 to 271 mg/dl	6.1 years	**Primary endpoint:** Death from CHD (fatal MI, sudden death, death in the hospital after possible MI, or death due to heart failure or another coronary cause. **Secondary endpoint:** Death from any cause, death from cardiovascular causes, CHD, nonfatal MI, MI, hemorrhagic and non-hemorrhagic stroke, coronary revascularization.	Compared pravastatin 40mg/day to placebo. Pravastatin group showed: • 24% reduction of risk of death due to CHD. • 25% reduction of risk of death due to CV disease. • 22% reduction of risk of death from any cause. • 24% reduction of risk of death due to CHD or nonfatal MI. • 29% reduction of risk for any MI. • 19% reduction of risk for any stroke.
Rosuvastatin				
ASTEROID[33,34] Rosuvastatin 40mg/day	Prospective, open-label, blinded end-points, multicenter trial. n = 507 (end = 349) Patients were ≥ 18 years, statin-naive, and required to have coronary angiography for a clinical indication. Patients had to have ≥ 1 obstruction with > 20% stenosis in any major coronary artery. Any baseline level of LDL-cholesterol was permitted.	24 months	**Primary endpoint:** Change in PAV and in nominal atheroma volume in the 10-mm sub segment with the greatest disease severity at baseline. **Secondary endpoint:** Change in normalized total atheroma volume for the entire artery.	All patients were given rosuvastatin 40mg/day. Resulted in: • Both of the prespecified primary efficacy parameters -- the change in percent atheroma volume (PAV) and the change in atheroma volume in the 10-mm sub segment with the greatest disease severity -- were significantly reduced. For PAV, 63.6% of patients showed regression and 36.4% progression, and for the most diseased 10-mm sub segment, 78.1% and 21.9% showed regression and progression, respectively. • The secondary efficacy parameter, normalized total atheroma volume (TAV), was significantly reduced compared to baseline. • There was no placebo-control group in this study.
MERCURY II[47] Rosuvastatin 20mg, atorvastatin 10mg, atorvastatin 20mg, simvastatin 20mg, and simvastatin 40mg	Randomized, open-label, multicenter trial. n = 1,993 Patients were ≥ 18 years who had high risk of CHD events, fasting LDL-C level	16 weeks	**Primary endpoint:** Change in LDL-C	Patients randomized to one of the five groups and at week 8, either remained on starting treatment or switched to lower or milligram-equivalent rosuvastatin for an additional 8 weeks. Resulted in: • More patients achieved their LDL-C target by switching to 10mg RO than staying on 10mg AT (66% vs

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
	≥ 130 to < 250mg/dL, and TG < 400.			42%) or 20mg SV (73% vs 32%). • Changing to 20mg RO allowed more patients to reach their LDL-C goal than staying on 20mg AT (79% vs 64%) or 40mg SV (84% vs 56%) • There were no differences among treatment groups in skeletal muscle, hepatic, or renal toxicity.
STELLAR[48, 49] Rosuvastatin versus atorvastatin, pravastatin, and simvastatin	Randomized, parallel-group, open-label, comparator controlled trial. n = 2,431	6 weeks	**Primary endpoint:** Change in LDL-C from baseline.	Resulted in: • Mean increase in HDL-C in RO 10-40mg was 7.7-9.6% compared with 2.1-6.8% in other groups. • NCEP ATP III LDL-C goals were achieved by 82-89% of patients treated with RO 10-40mg compared with 69-85% treated with AT 10-80mg, 51% with SV 10-80mg, and 44-55% with PV 10-40mg.
ARIES[50] Rosuvastatin 10-20mg versus atorvastatin 10-20mg	Randomized, open-label trial n = 774 Adult African American patients with LDL-C ≥ 160 and ≤ 200mg/dL and TG < 400mg/dL	6 weeks	**Primary endpoint:** Change in LDL-C from baseline.	Resulted in: • At week 6, significantly greater reductions in LDL-C, TC, non-HDL-C, and apo B were seen with RO vs milligram-equivalent AT doses. • Both treatments were well-tolerated.
JUPITER[57] Rosuvastatin 20mg versus placebo	Randomized, double-blind, placebo-controlled trial n=15,000 males aged 50 years and older and females aged 60 years and older with no history of MI, stroke, or arterial revascularization and LDL-C levels <130 mg/dL. Patients had elevated C-reactive-protein (CRP) levels.	Study start date February 2003 Final data collection date for primary outcome measure July 2009	**Primary endpoint:** Reduction of major cardiovascular events.	Resulted in: • Study stopped early. • Evidence of reduction in CV morbidity and mortality when compared to placebo.
Simvastatin				
HPS[23,24] Simvastatin 40mg/day versus placebo	Randomized, double-blind, placebo-controlled, multicenter study n = 20,536 (including 5,963 with diabetes) age 40-80 years	5 years	**Primary endpoint:** First major coronary event (non-fatal MI or coronary death) and first major vascular event	Compared simvastatin 40mg/day with placebo. Resulted in: • 13% decrease in risk of all-cause mortality in simvastatin group. • 17% decrease in risk of death from any vascular cause. • 27% reduction in first nonfatal MI or coronary death.

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
	Patients considered to be high risk for experiencing a major coronary event due to existing CHD, history of stroke or other CV disease, PVD, diabetes, or HTN in males > 65 years of age.		(major coronary event, stroke or revascularization)	• 24% decrease in composite major coronary events, strokes, and revascularizations. • 25% reduction in first nonfatal or fatal stroke. • 24% reduction in first revascularization procedure. In patients with diabetes: • 27% reduction in first nonfatal MI or coronary death. • 22% reduction in composite major coronary events, strokes, and revascularizations. • 24% reduction in first nonfatal or fatal stroke. • 17% reduction in first revascularization procedure.
A to Z[17] Simvastatin 80mg/day versus simvastatin 20mg/day	Randomized, double-blind, placebo-controlled, multicenter study. n = 4,497	2 years	**Primary outcome:** Cardiovascular death, nonfatal myocardial infarction, readmission for ACS, and stroke.	Compared simvastatin 80mg/day to simvastatin 20mg/day. Results in: • Nonsignificant 11% reduction in primary endpoint in high dose group. • High dose therapy had a higher incidence of myopathy than standard therapy.
Atorvastatin/Amlodipine				
CAPABLE[41]	Open-label, comparative, multicenter study **n = 494** African American patients 18-80 years with hypertension and dyslipidemia, not at goal for BP and LDL-C at goal with medication or not at goal with or without medication Group I: hypertension and dyslipidemia with no other CV risk factors. Group II and III: hypertension and dyslipidemia plus ≥ 1 other CV risk factor. Group III also had CHD or risk equivalent.	20 weeks	**Primary endpoint:** Treatment to BP goal based on the JNC-7 guidelines and treatment to LDL-C goal based on the NCEP ATP III recommendations.	Results: • Overall, about 48% of patients achieved both BP and LDL-C goals at week 20. • Groups I and II had the highest of patients achieving BP and LDL-C goals compared to Group III.

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
Lovastatin/Niacin				
ADVOCATE[42] Lovastatin/niacin ER 40/1000mg versus simvastatin 40mg and atorvastatin 40mg	Randomized, open-label, multicenter study n = 315 patients had elevated LDL-C (≥ 160mg/dL without CAD or ≥ 130mg/dL with CAD) and decreased HDL-C (< 45mg/dL in men and < 50mg/dL in women)	16 weeks	**Primary endpoint:** Change from baseline in LDL-C and HDL-C. **Secondary endpoint:** Change from baseline in TC, apolipoprotein B, apolipoprotein A-1, HDL sub fractions, HDL_2 and HDL_3 and median percent change in triglycerides and lipoprotein (a).	Results: • LDL-C: LN -39% vs SV -9% vs AT -49%. • HDL-C: LN +17% vs SV +7% vs AT +6%. • TG: LN -29% vs SV -19% vs AT -31%. • A total of 6% of study subjects receiving LN withdrew because of flushing. • No significant differences were seen among study groups in discontinuance due to elevated liver enzymes.
Simvastatin/Ezetimibe				
VYVA[43] Simvastatin/ezetimibe 10-80/10mg versus atorvastatin 10-80mg	Randomized, double-blind, active controlled multicenter, eight-arm parallel group study n = 1,640 Patients not currently at NCEP ATP III goal.	10 weeks	**Primary endpoint:** LDL-C change from baseline. **Secondary endpoint:** Change from baseline in LDL-C at each mg-equivalent statin dose comparison, change from baseline in HDL-C, and percentage of subjects that reached NCEP ATP III goal.	Results: • LDL-C: 20/10mg SE -50.6% vs 10mg AT -43.7% vs 20mg AT -43.7%. • LDL-C: 40/10mg SE -57.4% vs 40mg AT -48.3%. • LDL-C: 80/10mg SE -58.6% vs 80mg AT -52.9%. • HDL-C: 10/10 SE +7.7% vs 10mg AT +6.9%. • HDL-C: 20/10mg SE +7.2% vs 20mg AT +5.1%. • HDL-C: 40/10mg SE +3.8% vs 40mg AT +3.8%. • HDL-C: 80/10mg SE +7.5% vs 80mg AT +1.4%. • When averaged across dose ranges, the percentage of patients that reached the NCEP ATP III LDL-C goal was significantly greater with the combination product; 89.7% vs 81.1%.
VYTAL[52] Ezetimibe/simvastatin versus atorvastatin	Randomized, double-blind, multicenter study n = 1,229 patients with type 2 diabetes and hypercholesterolemia	6 months	**Primary endpoint:** Change in LDL-C from baseline. **Secondary endpoint:** Number of patients attaining LDL-C levels less than 70mg/dL.	Patients randomized to 10/20mg/day SE vs 10-20mg/day AT or 10/40mg/day SE vs 40mg/day AT. Resulted in: • Significantly greater mean reductions in LDL-C were seen with 10/20mg SE (-53.6%) vs 10mg AT (-38.3%) or 20mg AT (-44.6%). • With 10/40mg SE (-57.6%) vs 40mg AT (-50.9%) similar results

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
				were seen. • LDL-C levels < 70mg/dL: SE patients were superior to AT group.
Bays[46] Ezetimibe 10mg, simvastatin 10, 20, 40, or 80mg or simvastatin/ezetimibe 10/10, 10/20, 10/40, or 10/80mg	Randomized, double-blind, placebo-controlled, multicenter study n = 1,528	12 weeks	**Primary endpoint:** Change in LDL-C from baseline to the end of the treatment period for pooled ezetimibe/simvastatin vs simvastatin alone.	Results: • The combination SE significantly lowered TC, LDL-C, Apo B, TG and non-HDL-C when compared to all doses of simvastatin alone. • SE also showed significantly greater reductions in LDL-C compared to all doses of simvastatin monotherapy. • The effects of SE and simvastatin on HDL-C were similar. • Overall safety was similar across all treatment groups.
Ballantyne[49] Atorvastatin 10, 20, 40, or 80mg versus simvastatin/ezetimibe 10/10, 10/20, 10/40, or 10/80mg	Randomized, double-blind, multicenter study After 4 weeks of diet/placebo, patients who had not reached NCEP LDL-C goal were randomized to treatment groups. n = 788	24 weeks	**Primary endpoint:** Change in LDL-C and HDL-C from baseline to end of treatment.	Results: • At the end of Period 1, the mean LDL-C reduction was significantly greater with SE 10/10mg/day (46%) and SE 10/20mg/day (50%) than with AT 10mg/day (37%) and the mean HDL-C increase was greater (8% and 10% vs 5%, respectively) • At the end of week 4, when the maximum doses of the drugs were administered, SE 10/80mg/day reduced LDL-C more than AT 80mg/day (59% vs 53%) and showed a greater increase in HDL-C (12% vs 6%, respectively). • Safety profiles were similar with both groups.
Goldberg[48] Ezetimibe and simvastatin versus simvastatin	Randomized, double-blind, placebo-controlled, multicenter study. n = 788 patients with primary hyperlipidemia	12 weeks	**Primary endpoint:** Change in LDL-C from baseline.	Results: • LDL-C: SE -53% vs SV -38%. • The mean percent reduction from baseline in LDL-C levels at study endpoint showed that SE 10/10mg was similar to SV 80mg monotherapy. • More patients in the SE group reached LDL-C goal than with SV monotherapy group (82% vs 43%, respectively.) • Administration of SE resulted in significant improvements in TC, non-HDL-C, TC, Apo B, LDL-C:HDL-C, and TC:HDL-C.

Study	Inclusion Criteria and Study Design	Duration	Endpoints	Outcome
Enhance[55] Simvastatin versus ezetimibe and simvastatin	Randomized n=720 patients with heterozygous familial hypercholesterolemia	2 year	**Primary endpoint:** Change in the intima-media thickness (IMT) of the carotid artery	Results: • IMT increased by 0.0111mm with ezetimibe plus simvastatin and 0.0058mm with simvastatin 80mg alone. • The ezetimibe plus simvastatin combination lowered LDL-C by 58% compared to 41% lowering with simvastatin alone.
SEAS[56] Simvastatin and ezetimibe versus placebo in patients with aortic stenosis	Randomized, multicenter, placebo-controlled study n~1800		**Primary endpoint:** Reducing aortic valve and cardiovascular events	Interim Results: • Simvastatin/ezetimibe no better than placebo in reducing aortic-valve and cardiovascular events. • Combination significantly more effective than placebo in reducing the risk of ischemic events, a secondary composite end point of nonfatal MI, coronary artery bypass graft (CABG) surgery, PCI, hospitalization for unstable angina, nonhemorrhagic stroke, and cardiovascular death. • Combination failed to meet a secondary goal of improving aortic-valve disease events, which included valve-replacement surgery, hospitalization because of heart failure, and cardiovascular mortality. • Significantly higher incidence of cancer (102 patients taking ezetimibe/simvastatin compared with 67 taking placebo) and more patients died of cancer with the combination, a finding of borderline significance.

X. Summary of Evidence

- ❖ For patients who require LDL-C reductions of up to 35% to meet their goal, any of the statins are effective.
- ❖ Neither Zetia nor Vytorin is recommended for initial treatment of hypercholesterolemia.
- ❖ In patients requiring an LDL-C reduction of 35% to 50% to meet the NCEP goal, atorvastatin 20mg or more, lovastatin 80mg, rosuvastatin 10mg or more, and simvastatin 20mg or more daily are likely to meet the goal.

- ❖ Among high potency statins,
  - o Atorvastatin 80mg daily and rosuvastatin 20mg or more reduced LDL-C by 50% or more.
  - o Atorvastatin 80mg had a higher rate of some adverse effects (GI disturbances and transaminase elevation) than simvastatin 80mg daily in a trial in which the LDL lowering of atorvastatin was greater than that of simvastatin.
  - o Adverse event rates in patients using rosuvastatin 40mg were similar to rates in patients using atorvastatin 80mg in short term trials.

XI. Conclusion

When clinically evaluating the HMG CoA reductase inhibitor class, it is important to look closely at safety and patient outcomes data. However, because the NCEP ATP III guidelines recommend such strict control of LDL-C, the efficacy and LDL-C lowering capacity must also be considered.

As demonstrated in the clinical studies, no clear differences seem to exist between the statins in terms of safety. All of the drugs in this class are effective for lowering cholesterol (including LDL-C), although differences do exist in terms of their lipid-lowering capacity. Whether patient specific outcomes including morbidity and mortality are class- or patient-specific is controversial. Each statin has demonstrated a reduction in cardiovascular morbidity and mortality. In addition, atorvastatin, lovastatin, pravastatin, and simvastatin have demonstrated reduction in all-cause mortality. The statins that have demonstrated the greatest LDL-C lowering capacity include atorvastatin, rosuvastatin, and simvastatin. Studies have demonstrated that combination products are safe, effective and show therapeutic benefit but offer no clinical advantage over the concurrent administration of the individual components.

References

1. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110:227.
2. Talbert RL. Hyperlipidemia. In: Pharmacotherapy. A Pathophysiologic Approach. Diprio JT, Talbert RL, Yee GC, et al. eds. McGraw Hill. New York. 2002; 395-417.
3. American Heart Association. CVD and Cholesterol Statistics. Available at www.americanheart.org. Accessed December 2007.
4. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Available at www.nhlbi.nih.gov/guidelines/cholesterol/index. Accessed December 2007.
5. Smith Jr MD SC, ScD JAR, PED, SNB. AHA/ACC Guidelines for the Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2006 Update. JACC. 2006;47:2130-2139.
6. Lipitor® [prescribing information]. New York, NY: Pfizer Pharmaceuticals; September 2005.
7. Lescol®, Lescol XL® [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; May 2003.
8. Altoprev® [prescribing information]. Fort Lauderdale, FL: Andrx Laboratories; May 2005.
9. Mevacor® [prescribing information]. Kirkland, Quebec, Canada: Merck Frosst; April 2005.
10. Pravachol® [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; December 2004.
11. Zocor® [prescribing information]. Whitehouse Station, NJ: Merck & Co.; August 2005.
12. Wolters Kluwer Health, Inc, ed. Drug Facts & Comparisons. St. Louis, MO. 2005.
13. Bellosta S, Paoletti R, Corsini A. Safety of Statins: Focus on Clinical Pharmacokinetics and Drug Interactions. Circulation 2004; 109:50.
14. Wolters Kluwer Health, Inc, ed. Drug Interaction Facts. Facts & Comparisons. St. Louis, MO. 2005.
15. Weitzel K. Current and future trends in the treatment of hyperlipidemia. Drug Topics 2003. Available at www.drugtopics.com.
16. Pasternak RC, Smith SC, Bairey-Merz CN, et al. ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. Journal of the American College of Cardiology 2002; 40(3):567-72
17. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. Ann Pharmacother 2001; 35:1096-1107.
18. Intensive versus standard lipid lowering therapy. Pharmacist's Letter/Prescriber's Letter 2006;22(1):220104.
19. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction. The IDEAL Study: A Randomized Controlled Trial. JAMA. 2005;294:2437-2445.
20. Grundy S. The Clinical Implications of IDEAL: In the Context of Recent Intensive Statin Therapy Trials. Medscape Cardiology. 2006;10(1)
21. Colhoun HM, Betteridge DJ, Durrington PN, et al, on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetics in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomized placebo-controlled trial. Lancet 2004;364:685-696.
22. Cannon CP, Braunwald E, McCabe CH, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy – Intensive versus Moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350:1495-1504.
23. Nissen SE, Tuzcu EM, Schoenhagen P, et al, for the REVERSAL Investigators. Effects of intensive compared with moderate lipid lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291:1071-1080.
24. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360:7-22.
25. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomized placebo-controlled trial. Lancet 2003. 361:2005-16.

26. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the anglo-scandinavian cardiac outcomes trial-lipid lowering arm (ASCOT-LLA): a multicenter randomized controlled trial. Lancet 2003; 361:1149-58.
27. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in the moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care. The antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA 2002; 288(23):2998-3007.
28. Curry C, Clark L, Watkins, L, et al. Clinical Implications of ALLHAT for African-Americans. ABC Working Group. Accessed January 2006. Available at www.abcmeetings.org.
29. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL study: a randomized controlled trial. JAMA. 2001;285:1711-18.
30. Helfand, Mark, Carson, Susan, Kelley, Cathy. Drug Class Review on HMG-CoA Reductase Inhibitors (Statins). 2006. Accessed December 2007. http://www.ohsu.edu/drugeffectiveness/reports/final.cfm
31. Kinlay S, Schwartz GG, Olsson AG, et al. Inflammation, Statin Therapy, and Risk of Stroke After an Acute Coronary Syndrome in the MIRACL Study. Arterioscler Thromb Vasc Biol. 2007 Nov 8.
32. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-59.
33. The SPARCL Investigators. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study. Cerebrovasc Dis. 200\6;21(suppl4):1. Abstract 1.
34. Armani A, Toth PP. SPARCL: the glimmer of statins for stroke risk reduction. Curr Atheroscler Rep. 2007 Nove;9(5):347-51.
35. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID Trial. JAMA. 2006;295:1556-65.
36. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA. 2004;291:1071-1080.
37. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. NEJM. 1999;341:70-6.
38. Waters DD. Medical therapy versus revascularization: the atorvastatin versus revascularization treatment AVERT trial. Can J Cardiol. 2000 Jan;16 Suppl A:11A-3A.
39. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. Lescol Intervention Prevention Study (LIPS). JAMA. 2002;287(24):3215-22.
40. Shepherd J, Blauw GJ, Murphy MB et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet. 2002;360:1623-30.
41. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. NEJM. 1998;339(19):1349-57.
42. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA. 1998;279(20)1615-22.
43. Flack JM, Victor R, Watson K, et al. Amlodipine/atorvastatin single pill improves goal attainment in the Treatment of Hypertension and Dyslipidemia in African-Americans: The CAPABLE trial. Program and abstracts from the American Society of Hypertension 21st Annual Scientific Meeting and Exposition; May 16-20; New York, NY. Recent and Late Breaking Clinical Trials.
44. Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). Am J Cardiol. 2003 Mar 15;91(6):667-72.
45. Ballantyne C, Abate N, Yuan Z, et al. Dose comparison study of the combination of ezetimibe and simvastatin vs atorvastatin in patients with hypercholesterolemia. The VYtorin Versus Atorvastatin (VYVA) Study. Am Heart J. 2005;149:464-73.

46. Bays HE, Ose L, Fraser N, et al. Ezetimibe/simvastatin therapy is more effective than simvastatin alone at reducing remnant-like particle cholesterol. J Am Col Cardiol 2004;43(5 Suppl A):481A.
47. Ballantyne CM, Blazine MA, King TA, et al. Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. Am J Cardiol 2004;93:1487-1494.
48. Goldberg AC, Sapre A, Liu J, et al. Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: A randomized, double-blind, placebo-controlled trial. Mayo Clinic Proceedings. May 2004;79(5):620-9.
49. Ballantyne CM, Bertolami M, Hernandez Garcia HR, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy (MERCURY) II. Am Heart J. 2006 May;151(5):975.e1-9.
50. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol. 2003 Jul 15;92(2):152-60.
51. McKenney JM, Jones PH, Adamczyk MA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial. Curr Med Res Opin. 2003;19(8)689-98.
52. Ferdinand KC, Clark LT, Watson KE, et al. Comparison of efficacy and safety of rosuvastatin versus atorvastatin in African-American patients in a six-week trial. Am J Cardiol. 2006 Jan 15;97(2):229-35.
53. Herd JA, Ballantyne CM, Farmer JA, et al. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). Am J Cardiol. 1997;80:278-86.
54. Goldberg RB, Guyton JR, Mazzone T, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study.
55. The Medical Letter on Drugs and Therapeutics. Zetia and Vytorin: The ENHANCE Study. Med Letter. 2008 Jan 28;50(1278):5.
56. O'Riordan M. Vytorin Misses Primary End Point in SEAS Study. Heartwire 2008. Available online www.medscape.com/viewarticle/577850. Accessed Sep 2008.
57. Hsia J, Ridker P. A Randomized, Double-Blind, Placebo Controlled, Multicenter, Phase 3 Study of Rosuvastatin 20mg in the Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL Cholesterol and Elevated Levels of C-Reactive Protein. Available online www.clinicaltrials.gov. Accessed Sep 2008.

Statin Utilization 08/01/2007 - 07/31/2008

Label Name	Rx Num	Total Reimb Amt	Avg Cost per Script
CADUET 5 MG-40 MG TABLET	3	$466.62	$155.54
PRAVACHOL 80 MG TABLET	1	$154.78	$154.78
CADUET 5 MG-20 MG TABLET	14	$2,133.58	$152.40
CADUET 10 MG-20 MG TABLET	23	$3,014.77	$131.08
CADUET 2.5 MG-10 MG TABLET	12	$1,342.69	$111.89
CADUET 5 MG-10 MG TABLET	26	$2,902.92	$111.65
LIPITOR 40 MG TABLET	396	$43,687.54	$110.32
PRAVASTATIN SODIUM 80 MG TAB	13	$1,382.19	$106.32
LIPITOR 20 MG TABLET	1054	$110,775.11	$105.10
CADUET 10 MG-10 MG TABLET	10	$1,023.35	$102.34
LIPITOR 80 MG TABLET	178	$17,676.28	$99.30
VYTORIN 10-80 MG TABLET	23	$2,167.29	$94.23
CRESTOR 5 MG TABLET	193	$17,286.15	$89.57
VYTORIN 10-40 MG TABLET	226	$20,165.05	$89.23
CRESTOR 10 MG TABLET	457	$40,195.81	$87.96
CRESTOR 40 MG TABLET	80	$7,005.28	$87.57
VYTORIN 10-20 MG TABLET	297	$25,630.18	$86.30
CRESTOR 20 MG TABLET	177	$15,024.89	$84.89
LIPITOR 10 MG TABLET	1250	$94,613.13	$75.69
LESCOL XL 80 MG TABLET SA	7	$514.48	$73.50
LESCOL 40 MG CAPSULE	1	$71.76	$71.76
SIMCOR 500-20 MG TABLET	3	$203.31	$67.77
LOVASTATIN 40 MG TABLET	106	$2,883.86	$27.21
PRAVASTATIN SODIUM 40 MG TAB	92	$2,081.90	$22.63
LOVASTATIN 20 MG TABLET	84	$1,469.75	$17.50
PRAVASTATIN SODIUM 20 MG TAB	66	$1,053.25	$15.96
LOVASTATIN 10 MG TABLET	8	$116.68	$14.59
SIMVASTATIN 80 MG TABLET	279	$3,832.93	$13.74
SIMVASTATIN 20 MG TABLET	646	$8,809.98	$13.64
SIMVASTATIN 40 MG TABLET	539	$7,165.22	$13.29
SIMVASTATIN 10 MG TABLET	79	$964.55	$12.21
935 Recipients	**6344**	**$435,815.28**	

Lipitor Utilization
08/01/2007 - 07/31/2008

Label Name	Rx Num	Total Reimb Amt	Avg Cost per Script
LIPITOR 10 MG TABLET	1250	$94,613.13	$75.69
LIPITOR 20 MG TABLET	1054	$110,775.11	$105.10

Simvastatin Utilization
08/01/2007 - 07/31/2008

Label Name	Rx Num	Total Reimb Amt	Avg Cost per Script
SIMVASTATIN 20 MG TABLET	646	$8,809.98	$13.64
SIMVASTATIN 40 MG TABLET	539	$7,165.22	$13.29
SIMVASTATIN 80 MG TABLET	279	$3,832.93	$13.74

Potential Statin Prior Authorization
Cost Savings

Lipitor 10mg	$77,112.50 savings if switched to any strength of Simvastatin
Lipitor 20mg	$96,019.40 savings if switched to any strength of Simvastatin

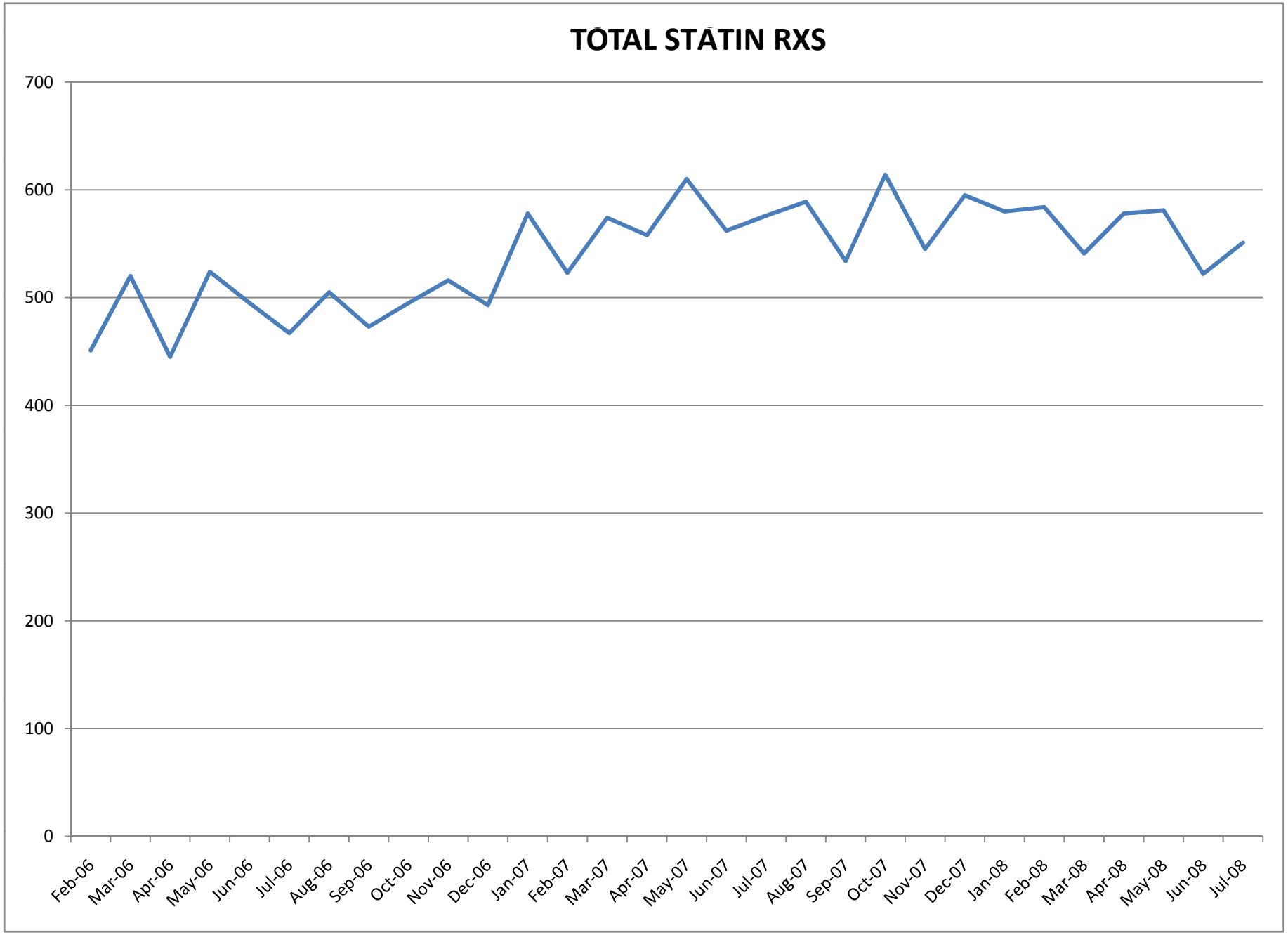
Statin % Market Share

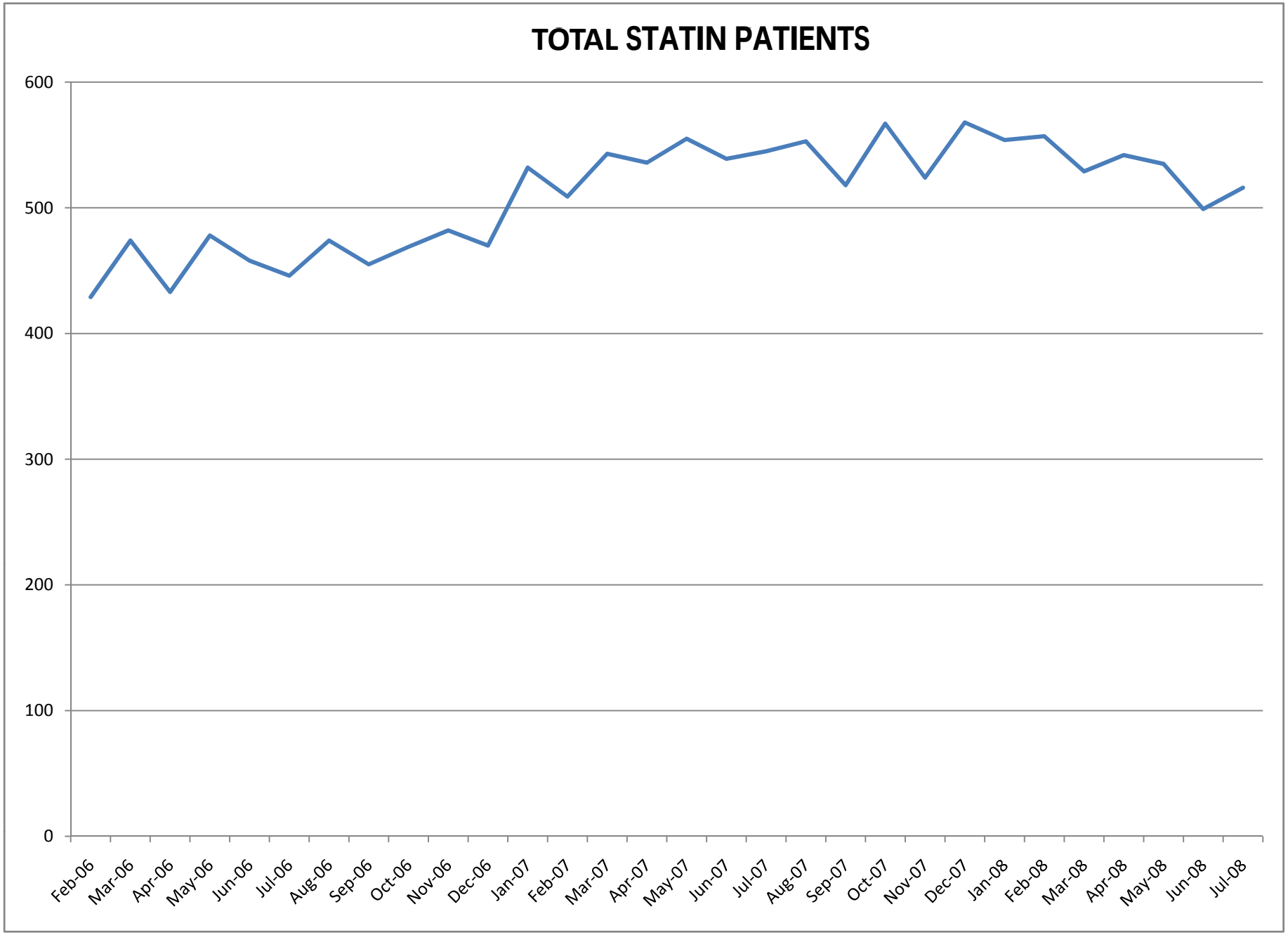
	Jul 06	Jul 07	Jul 08
Caduet	1.29	1.52	1.47
Lipitor	56.44	47.15	44.57
Vytorin	5.58	8.94	7.73
Lescol	0.64	0.19	0.00
Mevacor	1.93	2.47	2.95
Advicor	0.21	0.00	0.37
Pravachol	3.43	2.47	2.58
Crestor	15.67	16.35	12.15
Simvastatin	14.81	20.91	28.18

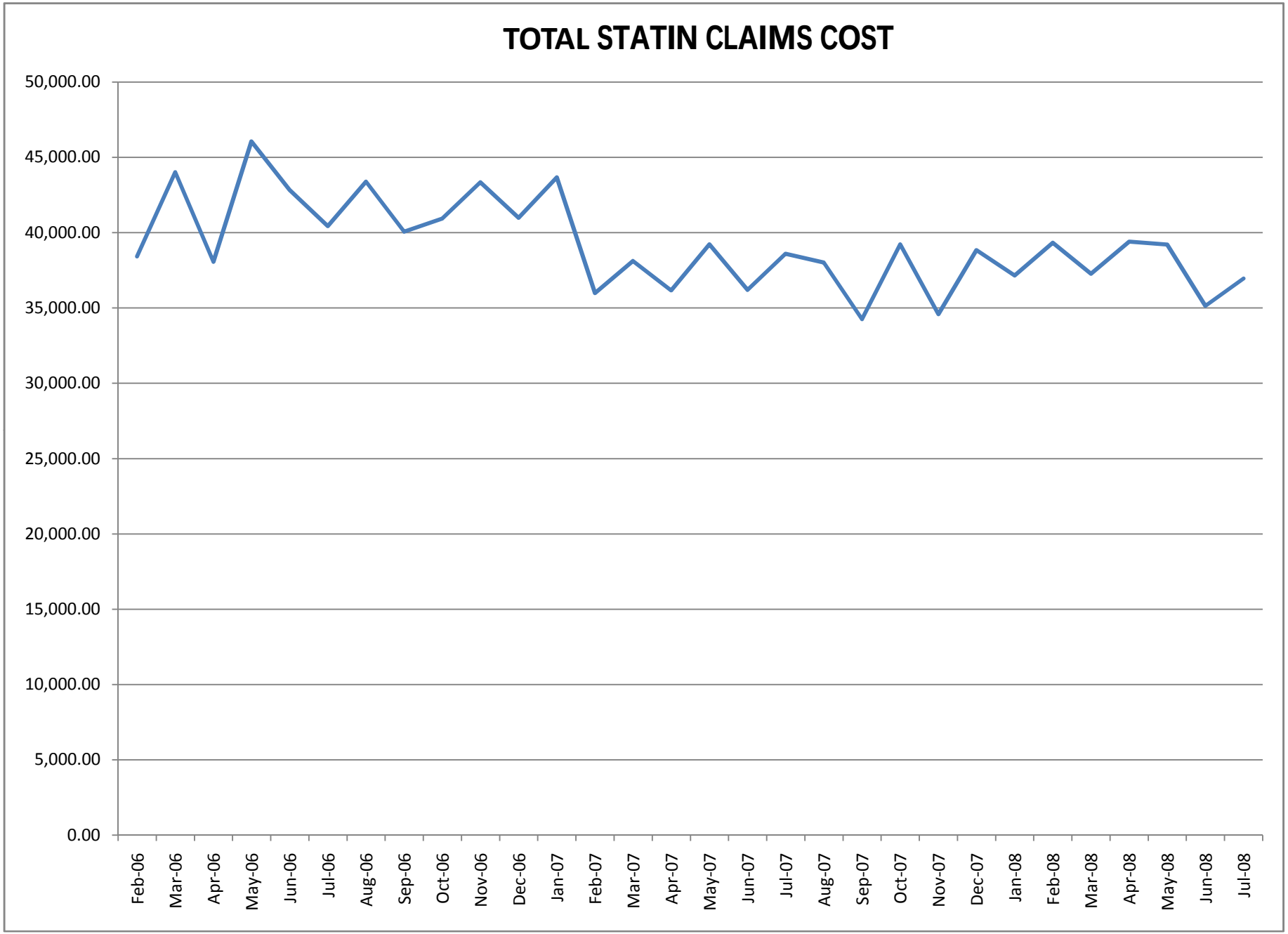
Statins Summary by Age
08/01/2007 - 07/31/2008

Age	Recip Count	Rx Count
15	1	10
16	1	10
18	2	12
19	1	12
21	2	14
22	2	21
24	5	27
25	3	24
26	7	38
27	2	4
28	7	50
29	1	5
30	5	37
31	8	47
32	8	41
33	9	56
34	5	37
35	14	65
36	13	69
37	8	51
38	14	94
39	18	95
40	18	134
41	16	66
42	19	120
43	29	193
44	23	108
45	17	107
46	24	126
47	31	202
48	32	224
49	35	249

Age	Recip Count	Rx Count
50	33	200
51	36	222
52	25	176
53	32	244
54	36	283
55	40	261
56	27	197
57	32	192
58	38	264
59	35	303
60	38	317
61	49	383
62	25	209
63	36	281
64	21	157
65	27	141
66	4	12
68	3	16
69	1	12
71	1	6
73	3	26
74	1	13
75	2	15
76	1	4
77	3	15
80	1	6
81	1	3
83	1	10
84	1	10
85	1	11
86	1	7


TOTAL STATIN RXS
700
600
500
400
300
200
100
0
Feb-06
Mar-06
Apr-06
May-06
Jun-06
Jul-06
Aug-06
Sep-06
Oct-06
Nov-06
Dec-06
Jan-07
Feb-07
Mar-07
Apr-07
May-07
Jun-07
Jul-07
Aug-07
Sep-07
Oct-07
Nov-07
Dec-07
Jan-08
Feb-08
Mar-08
Apr-08
May-08
Jun-08
Jul-08


TOTAL STATIN PATIENTS
600
500
400
300
200
100
0
Feb-06
Mar-06
Apr-06
May-06
Jun-06
Jul-06
Aug-06
Sep-06
Oct-06
Nov-06
Dec-06
Jan-07
Feb-07
Mar-07
Apr-07
May-07
Jun-07
Jul-07
Aug-07
Sep-07
Oct-07
Nov-07
Dec-07
Jan-08
Feb-08
Mar-08
Apr-08
May-08
Jun-08
Jul-08


TOTAL STATIN CLAIMS COST
50,000.00
45,000.00
40,000.00
35,000.00
30,000.00
25,000.00
20,000.00
15,000.00
10,000.00
5,000.00
0.00
Feb-06
Mar-06
Apr-06
May-06
Jun-06
Jul-06
Aug-06
Sep-06
Oct-06
Nov-06
Dec-06
Jan-07
Feb-07
Mar-07
Apr-07
May-07
Jun-07
Jul-07
Aug-07
Sep-07
Oct-07
Nov-07
Dec-07
Jan-08
Feb-08
Mar-08
Apr-08
May-08
Jun-08
Jul-08

B, G, or O	COM	P, N, R, or NR	Therapeutic Category
PDL Categories Iowa			
CHOLESTEROL - HMG COA + ABSORB INHIBITORS: High Potency Drugs/Combinations			
B		P	LIPITOR
B		P	CRESTOR
G		P	Simvastatin
B		N	ZOCOR
B		P	VYTORIN
CHOLESTEROL - HMG COA + ABSORB INHIBITORS: Low Potency Drugs/Combinations			
B		P	ZETIA
B		P	LESCOL
B		P	LESCOL XL
B		N	MEVACOR
G		P	lovastatin
B		N	ALTOPREV
G		P	PRAVASTATIN TAB 10MG
G		N	PRAVASTATIN TAB 20MG
G		N	PRAVASTATIN TAB 40MG
B		N	PRAVACHOL
G		N	PRAVASTATIN TAB 80MG
B		N	PRAVIGARD PAC
B		P	ADVICOR
B		N	LOVAZA
CHOLINERGIC			
B		N	URECHOLINE
G		P	bethanechol chloride
CONTRACEPTIVES - BI-PHASIC COMBINATIONS			
B		P	ORTHO-NOVUM 10/11-28
G		N	norethindrone-eth estradiol tab 0.5-35/1-35 mg-mcg (10/11)
CONTRACEPTIVES - EMERGENCY CONTRACEPTIVE			
B		P	PLAN B
CONTRACEPTIVES - INJECTABLE			
B		P	DEPO-PROVERA CONTRACEPTIV
G		N	medroxyprogesterone acetate im susp 150 mg/ml
B		P	DEPO-SUBQ PROVERA 104
B		N	LUNELLE

B, G, or O	COM	P, N, R, or NR	Therapeutic Category
CONTRACEPTIVES - MONOPHASIC COMBINATION O/C'S			
B		N	DESOGEN
B		P	ORTHO-CEPT-28
G		N	desogestrel & ethinyl estradiol tab 0.15 mg-30 mcg
B		P	MIRCETTE
G		N	desogest-eth estrad & eth estrad tab 0.15-0.02/0.01 mg(21/5)
B		N	YAZ TAB 3-0.02MG
B		N	YASMIN 28
B		P	DEMULEN 1/35-28
G		P	ethynodiol diacetate & ethinyl estradiol tab 1 mg-35mcg
B		P	DEMULEN 1/50-28
G		P	ethynodiol diacetate & ethinyl estradiol tab 1 mg-50 mcg
B		P	LEVLITE-28
G		P	levonorgestrel & ethinyl estradiol tab 0.10 mg-20 mcg
B		N	LEVLEN CONTRACT PACK
B		N	LEVLEN-28
B		N	NORDETTE-21
B		N	NORDETTE-28
G		P	levonorgestrel & ethinyl estradiol tab 0.15 mg-30mcg
B		N	FEMCOM FE
B		P	OVCON-35/28
B		N	BREVICON-28
B		P	MODICON-28
G		N	norethindrone & ethinyl estradiol tab 0.5 mg-35 mcg
B		N	NORINYL 1+35
B		P	ORTHO-NOVUM 1/35-28
G		N	norethindrone & ethinyl estradiol tab 1 mg-35 mcg
B		P	OVCON-50 28
B		N	LOESTRIN 1/20-21
G		N	norethindrone ace & ethinyl estradiol tab 1 mg-20 mcg
B		N	LOESTRIN 1.5/30-21
G		N	norethindrone ace & ethinyl estradiol tab 1.5 mg-30 mcg
B		P	NORINYL 1+50
B		P	ORTHO-NOVUM 1/50-28
G		N	norethindrone & mestranol tab 1 mg-50 mcg
B		N	LO/OVRAL 28
G		P	norgestrel & ethinyl estradiol tab 0.3 mg-30 mcg
G		N	norgestrel & ethinyl estradiol tab 0.5 mg-50 mcg
B		N	ORTHO-CYCLEN-28
G		P	norgestimate & ethinyl estradiol tab 0.25 mg-35 mcg
B		N	LOESTRIN FE 1/20
G		N	norethindrone ace & ethinyl estradiol-fe tab 1 mg-20 mcg
B		N	LOESTRIN 24 FE
B		N	LOESTRIN FE
G		N	norethindrone ace & ethinyl estradiol-fe tab 1.5 mg-30 mcg
B		N	SEASONALE
B		N	SEASONIQUE

State of Idaho, Division of Medicaid
STATIN PRIOR AUTHORIZATION FORM
CONFIDENTIAL INFORMATION

Phone: 1-208-364-1829 *One drug per form ONLY – Use black or blue ink* **Fax: 1-208-364-1864**

Patient Name: _____	Medicaid ID#: _____	Date of Birth: _____
Prescriber Name: _____	State License #: _____	Specialty: _____
Prescriber Phone: _____	Prescriber Fax: _____	
	Pharmacy Phone:	Pharmacy Fax: Pharmacy/Sto

Lescol®, Lescol® XL, Lipitor®, Pravastatin, Simvastatin, and Lovastatin are approved for payment without prior authorization for eligible participants over 8 years old within the approved dosage quantities.

Advicor®, Altoprev®, Crestor ®,Pravigard®, and Simcor® will be approved for payment only after documented failure of two preferred agents listed above for a total ≥ 150 days in the last 6 months or failure of two different doses of a single preferred agent for a total of ≥ 150 days in the last 6 months.

Brand name medications: please use the Brand Name prior authorization request form located on our website.

Prescriptions will only be approved for payment for quantities of one dosage unit per day for the following agents and respective strengths:

Atorvastatin (Lipitor®) – 10mg, 20mg, 40mg
Lovastatin (Mevacor®) – 10mg, 20mg
Fluvastatin (Lescol®) – 20mg, 40mg
Pravastatin (Pravachol®) – 10mg, 20mg, 40mg
Simvastatin (Zocor®) – 5mg, 10mg, 20mg, 40mg
Rosuvastatin (Crestor®) 5mg, 10mg, 20mg, 40mg

Statin Drug Requested

Lescol®	**NO PA REQUIRED**
Lescol® XL	**NO PA REQUIRED**
Lipitor®	**NO PA REQUIRED**
Lovastatin	**NO PA REQUIRED**
Pravastatin	**NO PA REQUIRED**
Simvastatin	**NO PA REQUIRED**

	Drug	Strength	Instructions
❑	Advicor®	_____	_____
❑	Altoprev®	_____	_____
❑	Crestor®	_____	_____
❑	Pravigard®	_____	_____
❑	Simcor®	_____	_____

History of Other Statin Trials

Drug	Dates of Trial	Reason for Failure

Prescriber Signature: _____ **Date**:_____
By signing, the prescriber agrees that documentation of above indication and medical necessity is available for review by Idaho Medicaid in patient's current medical chart.

For Medicaid Office Use Only

Date:	RPh:	Tech:	PA#:
Approved	Denied	Comments:	

All current PA forms and criteria for use are available at: http://www.medicaidpharmacy.idaho.gov (PA Criteria & Forms)

Fee-for Service PA Criteria for Non-Preferred Drugs

Drug Class **Statins**
Therapeutic Area Cardiovascular

Preferred	Non preferred
High Potency	
simvastatin - generic Crestor (rosuvastatin)	Lipitor (atorvastatin) Zocor (simvastatin)
Low Potency	
Lescol, Lescol XL lovastatin - generic pravastatin - generic	Mevacor* Pravachol*

*mac and DAW criteria apply

Drugs and Equivalent Statin Dosing[1]

Preferred					Non Preferred
simvastatin (Zocor)	fluvastatin Lescol Lescol XL	pravastatin (Pravachol)	lovastatin (Mevacor)	Crestor (rosuvastatin)	Lipitor (atorvastatin)
10 mg	40 mg	20 mg	20 mg		
20 mg	80 mg (Lescol XL)	40 mg	40 or 80 mg	5 or 10 mg	10 mg
40 mg		80 mg	80 mg		20 mg
80 mg					40 mg
				20 mg	80 mg^
				40 mg	

^Lipitor 80mg is not under PA restrictions

Criteria

Lipitor or branded Zocor

1. Patient is intolerant to simvastatin and rosuvastatin or receives inadequate response to simvastatin and rosuvastatin for a minimum of 6 weeks in the absence of adverse events.

2. Patient is on an antiretroviral therapy regimen for which atorvastatin is the preferred statin.

3. Lipitor 20, 40, and 80 mg tablets should be split whenever possible for cost effectiveness.

1. Adapted from the OHSU Drug Effectiveness Review Project. June 2004, Final Report Drug Class Review on HMG Co A Reductase Inhibitors. Accessed at http://www.ohsu.edu/drugeffectiveness/reports/final.cfm

CARDIOVASCULAR – ANTI-HYPER-LIPIDEMIC AGENTS & COMBOS

Preferred			Non-Preferred	
Advicor®	Lovastatin	Simvastatin	Caduet®	Pravachol® *
Altoprev®	(generic Mevacor®)	(generic Zocor®)	Lipitor®	Pravigard PAC®
Crestor®	Pravastatin	Vytorin®	Mevacor®*	Zocor®*
Lescol®	(generic Pravachol®)	Zetia®		
Lescol XL®	Simcor®			

CARDIOVASCULAR – TRIGLYCERIDE LOWERING AGENTS

Preferred			Non-Preferred		
Gemfibrozil (generic Lopid®)			Antara®	Lofibra®	Lovaza®
Tricor®			Fenofibrate	Lopid®*	Triglide®
			Fenoglide®	Lipofen®	

CARDIOVASCULAR – HEMATOPOIETIC AGENTS

Preferred			Non-Preferred
Aranesp®	Epogen®	Procrit®	

CARDIOVASCULAR – LOW MOLECULAR WEIGHT HEPARINS

Preferred		Non-Preferred
Arixtra®	Innohep®	
Fragmin®	Lovenox®	

ENDOCRINOLOGY – GROWTH HORMONES

**PA is required to use preferred products.

Preferred			Non-Preferred
Genotropin®**	Norditropin®**	Saizen®**	
Humatrope®**	Nutropin®**	Serostim®**	

ENDOCRINOLOGY - BISPHOSPHONATES

Preferred		Non-Preferred	
Alendronate	Fosamax® Solution	Actonel®	Boniva®
(generic Fosamax®)	Fosamax Plus D®	Actonel® with Calcium	Fosamax® Tablets*

ENDOCRINOLOGY – NASAL CALCITONINS

Preferred	Non-Preferred
Miacalcin®	Fortical®

ENDOCRINOLOGY – ALPHA-GLUCOSIDASE INHIBITORS

Preferred		Non-Preferred
Glyset®	Precose®	

ENDOCRINOLOGY - MEGLITINIDES

Preferred	Non-Preferred
Starlix®	Prandin®

For Prior Authorization please call or fax:
Mountain Pacific Quality Health Foundation Clinical Call Center
Telephone: 800-395-7961/406-443-6002
Fax: 800-294-1350/406-443-7014

Wyoming Medicaid Pharmacy Program
Preferred Drug List
Effective 04/01/2008

Drugs listed are preferred or do not require prior authorization. All other medications within the following classes are non-preferred and require prior authorization.

Long Acting Opioids
Morphine Sulfate

Preferred Statins
Lovastatin
Pravastatin
Statins Not Requiring PA
Lipitor 40 mg & 80 mg
Crestor 20 mg & 40 mg
Simvastatin 80 mg

Calcium Channel Blockers
Verapamil
Felodipine
Diltiazem

Overactive Bladder Agents
Oxybutynin
Detrol (tolterodine)
Ditropan XL (oxybutynin)

Skeletal Muscle Relaxants
Cyclobenzaprine

ACE Inhibitors
Captopril and Captopril/HCTZ
Enalapril and Enalapril/HCTZ
Lisinopril and Lisinopril/HCTZ

Preferred Proton Pump Inhibitors
Prilosec OTC (omeprazole)
Protonix Tablets
PPI Not Requiring PA
Prevacid for children 8 & under

NSAIDs
Ibuprofen
Naproxen

2nd Generation Antihistamines
Loratadine
Loratadine-D

For comparative cost information, please visit our website at http://uwyo.edu/PDL.

HMG-CoA REDUCTASE INHIBITORS - STATIN PA FORM

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

Prior Authorization Vendor for ND

ND Medicaid requires that patients receiving a new prescription for a statin follow these guidelines:

- **Patients requiring LDL-C reduction of up to 35% to meet the NCEP (National Cholesterol Education Program) guidelines; any of the statins are effective.**
- **Patients requiring LDL-C reduction of 35% to 50% to meet the NCEP guidelines should use Lipitor® 20mg or more, Lovastatin 80mg, Crestor® 10mg or more, and Simvastatin 20mg or more to meet this goal.**
- **Patients requiring LDL-C reduction of 50% or greater to meet the NCEP guidelines should use Lipitor® 80mg and Crestor® 20mg or more to meet this goal.**
- **Lipitor® 40mg, Lipitor® 80mg, Lescol XL®, Fluvastatin, Pravastatin, Simvastatin, and Lovastatin are approved without prior authorization.**
- **Advicor®, Altoprev®, Crestor®, Lipitor® 10mg, Lipitor® 20mg, Pravigard®, and Simcor® will be approved after documented failure of an agent listed above.**
- **Neither Zetia nor Vytorin is recommended as initial therapy for hypercholesterolemia.**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage:	**LDL-C reduction needed:**		
Qualifications for coverage:			
LDL-C level _____	Failed therapy: Start Date: End Date:	Dose	Frequency
□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*			
Physician Signature		Date	

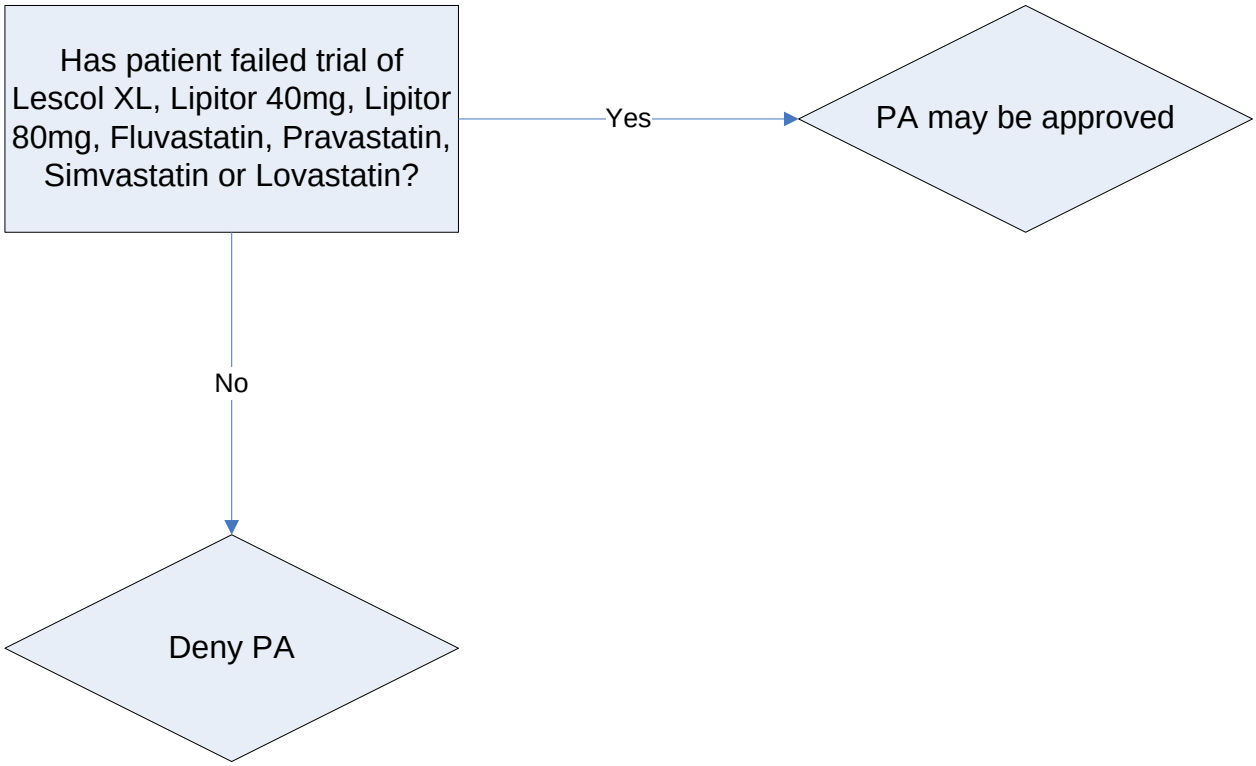
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
HMG-CoA REDUCTASE INHIBITORS
Statin Prior Authorization Algorithm



HEALTH INFORMATION DESIGNS

Ketek PA Form

Clear Fields

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

Prior Authorization Vendor for ND Medicaid

ND Medicaid will cover Ketek with a diagnosis of community-acquired pneumonia (of mild to moderate severity) due to Streptococcus pneumoniae for patients 18 years and older.

ND Medicaid will cover Ketek for patients with an allergy to fluoroquinolones or tetracyclines.

Part I: TO BE COMPLETED BY PHYSICIAN

RECIPIENT NAME:	
RECIPIENT DATE OF BIRTH:	RECIPIENT MEDICAID ID #:
PHYSICIAN NAME:	PHYSICIAN MEDICAID ID NUMBER:
Address:	Phone:
City:	FAX:
State: Zip:	

REQUESTED DRUG: KETEK	**Requested Dosage:** (must be completed)

Qualifications for coverage:

☐ Community acquired pneumonia (of mild to moderate severity) due to Streptococcus pneumoniae, (including multi-drug resistant isolates, Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae, or Mycoplasma pneumoniae) for patients 18 years and older.

*Please list fluoroquinolone or tetracycline that patient is allergic to:*_____

Physician Signature: Date:

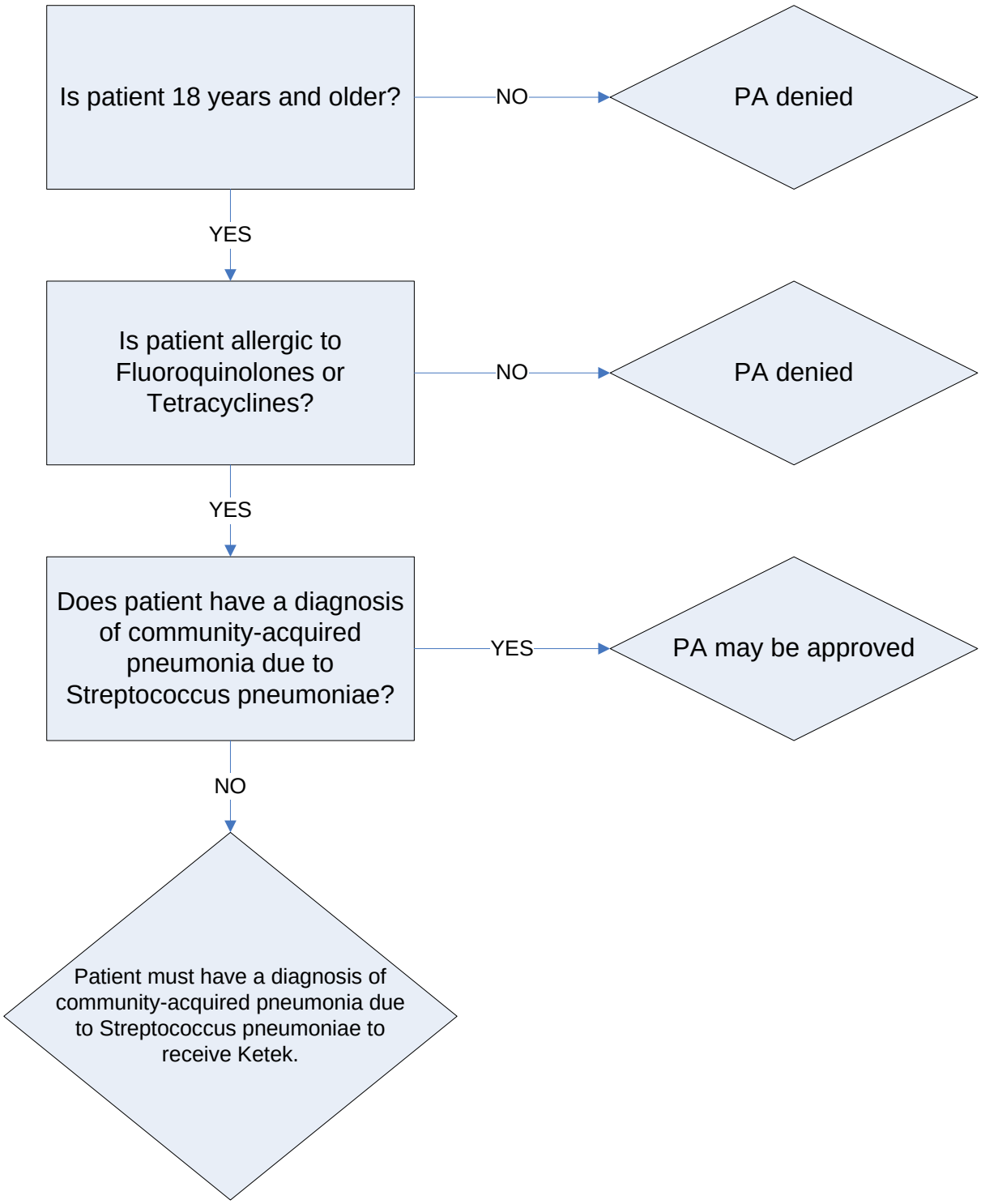
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	FAX:
Drug:	NDC#:

Part III: FOR OFFICIAL USE ONLY

Date: / /	Initials: _____
Approved - Effective dates of PA: From: / /	To: / /
Denied: (Reasons)	

North Dakota Department of Human Services
Ketek Criteria Algorithm



HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

ORACEA PRIOR AUTHORIZATION

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

Note: ND Medicaid will not pay for Oracea without documented failure of a first line tetracycline agent.

- First line agents include: doxycycline, minocycline, and tetracycline.

Part I: TO BE COMPLETED BY PHYSICIAN

RECIPIENT NAME:	RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth:	
PHYSICIAN NAME:	PHYSICIAN MEDICAID ID NUMBER:
Address:	Phone:
City:	FAX:
State: Zip:	

REQUESTED DRUG:	**Indication:**
☐ Oracea	

☐ *Patient has failed a 90 day trial of which first line agent* _____

Physician Signature:	Date:

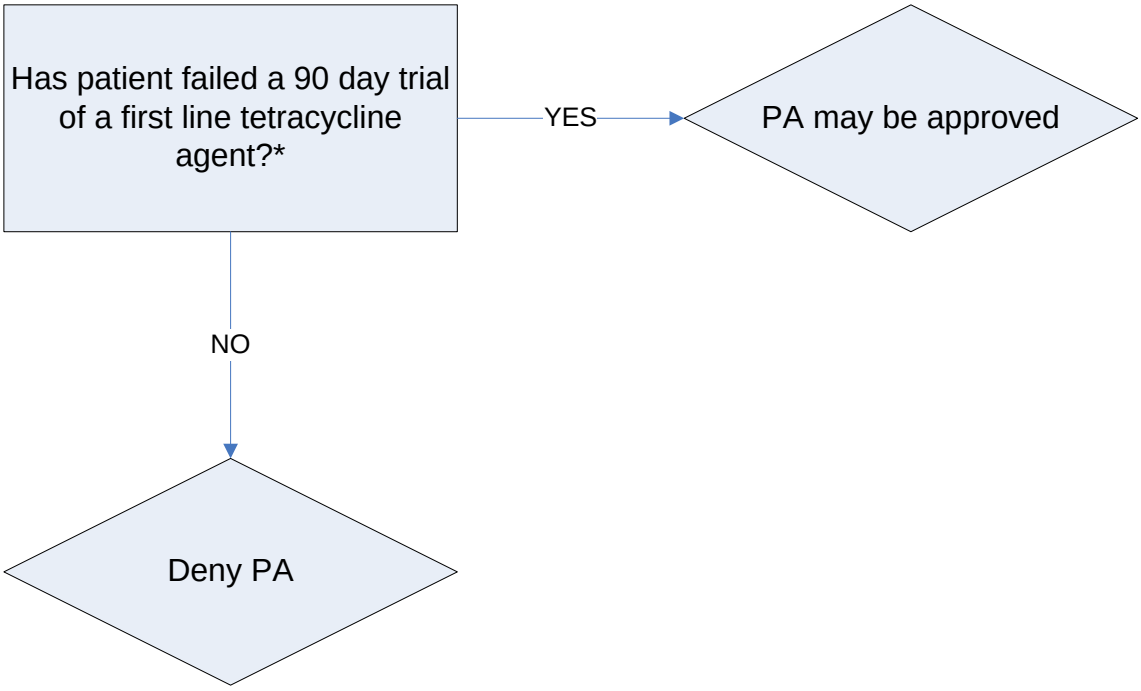
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	FAX:
Drug:	NDC#:

Part III: FOR OFFICIAL USE ONLY

Date: / /	Initials: _____
Approved - Effective dates of PA: From: / /	To: / /
Denied: (Reasons)	

North Dakota Department of Human Service
Oracea Authorization Algorithm



*First line agents include: doxycycline, minocycline, and tetracycline.

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

OXYCODONE CR PA Form

Clear Fields

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

**Note: The PA may be approved if all of the following criteria are met:*

-Patient has a chronic pain indication (includes cancer).
-Patient has taken an immediate release narcotic for the past 90 days or is switching from another sustained release opioid analgesic.

Part I: TO BE COMPLETED BY PHYSICIAN

RECIPIENT NAME:	RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth:	
PHYSICIAN NAME:	PHYSICIAN MEDICAID ID NUMBER:
Address:	Phone:
City:	FAX:
State: Zip:	

REQUESTED DRUG:	**Requested Dosage:**	**Diagnosis for this request:**
☐ OXYCODONE CR		

Qualifications for coverage:

☐ Chronic malignant pain indication	List IR Medication taken:
☐ Chronic non-malignant pain indication	List IR Medication taken:

List other sustained release opioid analgesic patient is switching from_____

Physician Signature:		Date:

Part II: TO BE COMPLETED BY PHARMACY

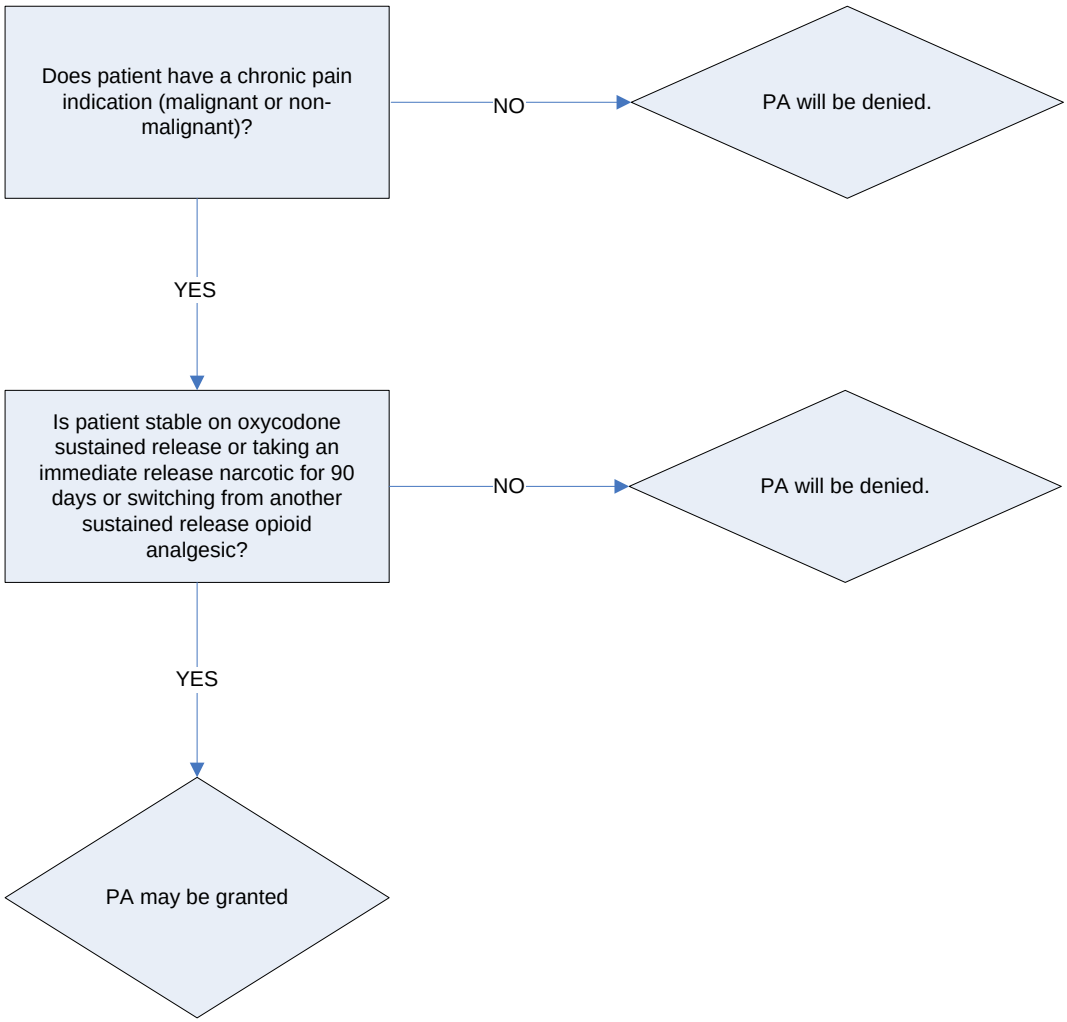
PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	FAX:
Drug:	NDC#:

Part III: FOR OFFICIAL USE ONLY

Date: / /	Initials: _____
Approved - Effective dates of PA: From: / /	To: / /
Denied: (Reasons)	

North Dakota Department of Human Services

Oxycodone CR Prior Authorization Criteria Algorithm



NORTH DAKOTA MEDICAID
Utilization and Percentage Market Share
Oxycontin®
August 1, 2007 – July 31, 2008

Label Name	Rx Num	Total Reimb Amt	% Market Share
OXYCODONE HCL 10 MG ER TABLET	280	$14,007.84	19.50
OXYCODONE HCL 20 MG ER TABLET	454	$56,539.36	31.62
OXYCODONE HCL 40 MG ER TABLET	350	$71,310.71	24.37
OXYCODONE HCL CR 80 MG TABLET	114	$36,985.12	7.94
OXYCONTIN 10 MG TABLET SA	66	$5,551.26	4.60
OXYCONTIN 15 MG TABLET SA	2	$308.54	0.14
OXYCONTIN 20 MG TABLET SA	104	$17,762.34	7.24
OXYCONTIN 30 MG TABLET SA	6	$1,058.81	0.42
OXYCONTIN 40 MG TABLET SA	41	$12,852.77	2.86
OXYCONTIN 60 MG TABLET SA	2	$1,013.60	0.14
OXYCONTIN 80 MG TABLET SA	17	$11,467.97	1.18
211 Recipients	**1436**	**$228,858.32**	

Trend Summary

2005	Label Name	Rx Num	Total Reimb Amt	Patients
January	Oxycodone	97	$20,208.42	66
February	Oxycodone	94	$18,877.17	68
March	Oxycodone	99	$19,463.27	73
April	Oxycodone	92	$17,194.69	66
May	Oxycodone	103	$20,048.05	70
June	Oxycodone	105	$20,279.93	77
July	Oxycodone	109	$20,858.45	82
August	Oxycodone	95	$18,928.73	74
September	Oxycodone	100	$19,318.99	74
October	Oxycodone	83	$16,864.02	68
November	Oxycodone	80	$15,479.73	68
December	Oxycodone	79	$14,636.74	61

Drug added to PA Dec 2007

Trend Summary (cont'd)

2006	Label Name	Rx Num	Total Reimb Amt	Patients
January	Oxycodone	151	$32,811.07	103
February	Oxycodone	114	$18,029.02	83
March	Oxycodone	119	$15,880.06	83
April	Oxycodone	121	$16,109.55	86
May	Oxycodone	146	$17,981.40	94
June	Oxycodone	127	$18,905.85	79
July	Oxycodone	110	$15,291.53	79
August	Oxycodone	113	$14,783.26	85
September	Oxycodone	131	$14,016.81	92
October	Oxycodone	141	$14,839.66	93
November	Oxycodone	134	$15,382.04	84
December	Oxycodone	126	$13,305.09	82

2007	Label Name	Rx Num	Total Reimb Amt	Patients
January	Oxycodone	148	$15,750.44	97
February	Oxycodone	136	$13,479.59	99
March (**generic mandate began)**	Oxycodone	138	$13,787.80	99
April	Oxycodone	135	$16,355.09	98
May	Oxycodone	115	$14,687.81	90
June	Oxycodone	124	$18,056.36	89
July	Oxycodone	103	$13,742.06	78
August	Oxycodone	130	$19,153.04	85
September	Oxycodone	109	$16,432.33	77
October	Oxycodone	107	$15,954.15	79
November	Oxycodone	121	$18,102.72	86
December	Oxycodone	119	$16,878.96	86

2008	Label Name	Rx Num	Total Reimb Amt	Patients
January	Oxycodone	123	$16,343.99	85
February	Oxycodone	121	$17,078.00	84
March	Oxycodone	138	$21,795.18	89
April	Oxycodone	132	$20,304.15	93
May	Oxycodone	121	$21,067.19	89
June	Oxycodone	105	$22,004.38	79
July	Oxycodone	110	$23,744.23	81

Drug added to PA Dec 2007

Short-Acting HFA Beta$_2$ Agonist PA FORM

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving a new prescription for ProAir HFA, Ventolin HFA, or Xopenex HFA must use Proventil HFA as first line therapy.

***Note: Proventil HFA does not require a prior authorization.**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage: □ XOPENEX HFA □ VENTOLIN HFA □ PROAIR HFA	**Diagnosis for this request:**		

Qualifications for coverage:

□ Failed Proventil HFA therapy	Start Date	End Date	Dose	Frequency

□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*

Physician Signature	Date

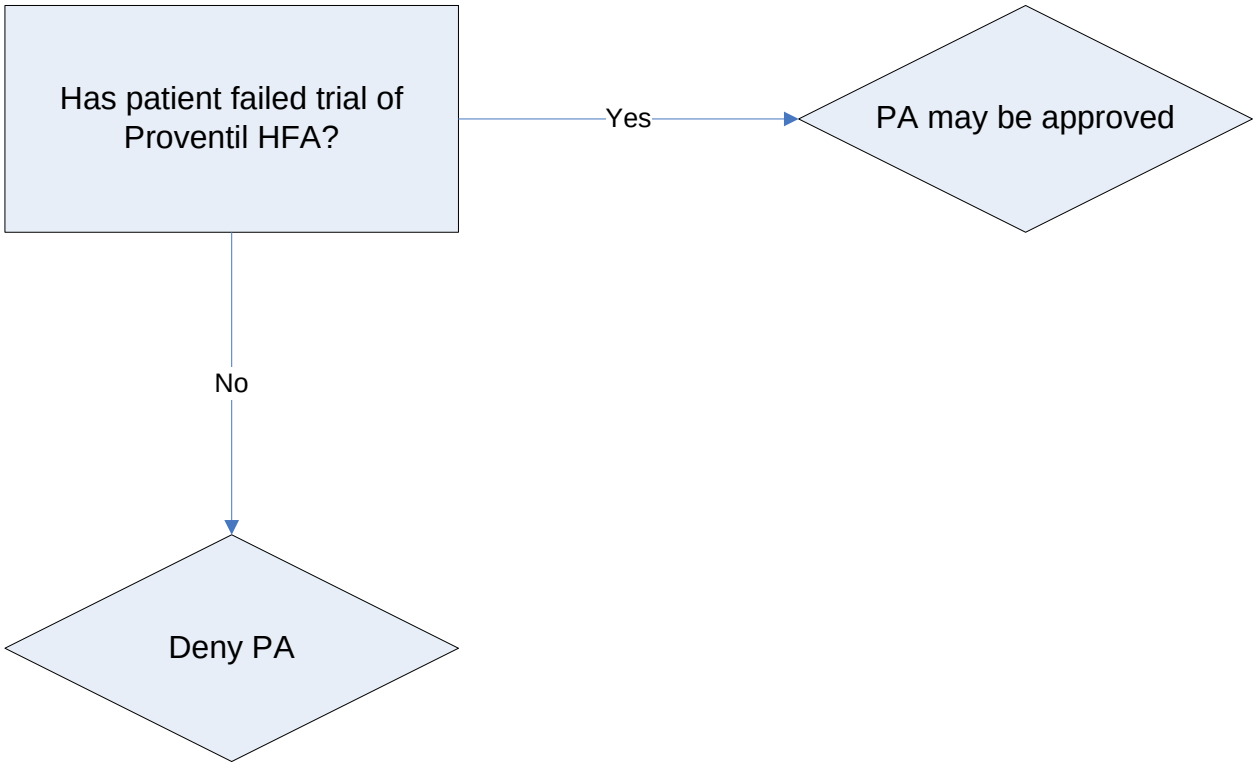
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
TELEPHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services Short-Acting Beta$_2$ Agonist Authorization Algorithm



NORTH DAKOTA MEDICAID
Percentage Market Share Within Sub-Classes
Short-Acting Beta-2 HFA Agonists

	FEB 04	SEP 07	JUN 08
All Short-Acting Beta-2 HFA Agonists(No Subclass)			
PROAIR HFA	0.00	4.63	0.98
PROVENTIL HFA	87.50	86.57	94.79
VENTOLIN HFA	12.50	0.00	0.00
XOPENEX HFA	0.00	8.80	4.23

Class added to PDL Oct 2007

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

SOLODYN PRIOR AUTHORIZATION

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

Note: ND Medicaid will not pay for Solodyn without documented failure of a first line tetracycline agent.

- First line agents include: doxycycline, minocycline, and tetracycline.

Part I: TO BE COMPLETED BY PHYSICIAN

RECIPIENT NAME:	RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth:	
PHYSICIAN NAME:	PHYSICIAN MEDICAID ID NUMBER:
Address:	Phone:
City:	FAX:
State: Zip:	

REQUESTED DRUG:	**Indication:**
☐ Solodyn	
☐ *Patient has failed a 90 day trial of which first line agent* _____	
Physician Signature:	Date:

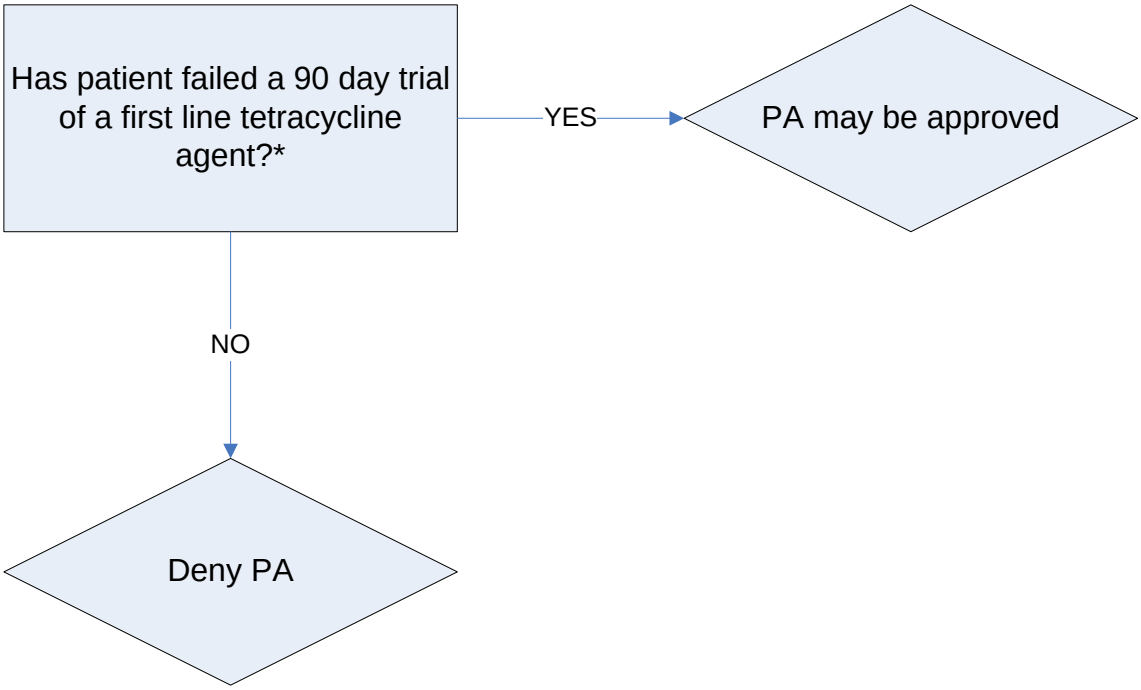
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:	ND MEDICAID PROVIDER NUMBER:
Phone:	FAX:
Drug:	NDC#:

Part III: FOR OFFICIAL USE ONLY

Date: / /	Initials: _____
Approved - Effective dates of PA: From: / /	To: / /
Denied: (Reasons)	

North Dakota Department of Human Service
Solodyn Authorization Algorithm



*First line agents include: doxycycline, minocycline, and tetracycline.

HEALTH INFORMATION DESIGNS

Prior Authorization Vendor for ND Medicaid

Zanaflex Capsule PA Form

Fax Completed Form to:
866-254-0761
For questions regarding this Prior authorization, call
866-773-0695

ND Medicaid requires that patients receiving Zanaflex capsules must use tizanidine tablets first line.
Note:

- **Tizanidine tablets do not require a PA.**
- **Patient must fail therapy on tizanidine tablets before a PA may be granted.**

Part I: TO BE COMPLETED BY PHYSICIAN

Recipient Name	Recipient Date of Birth	Recipient Medicaid ID Number	
Physician Name			
Physician Medicaid Provider Number	Telephone Number	Fax Number	
Address	City	State	Zip Code
Requested Drug and Dosage:	**Diagnosis for this request:**		
Qualifications for coverage:			
□ Failed generic drug	Start Date: End Date:	Dose: Frequency:	
□ *I confirm that I have considered a generic or other alternative and that the requested drug is expected to result in the successful medical management of the recipient.*			
Physician Signature		Date	

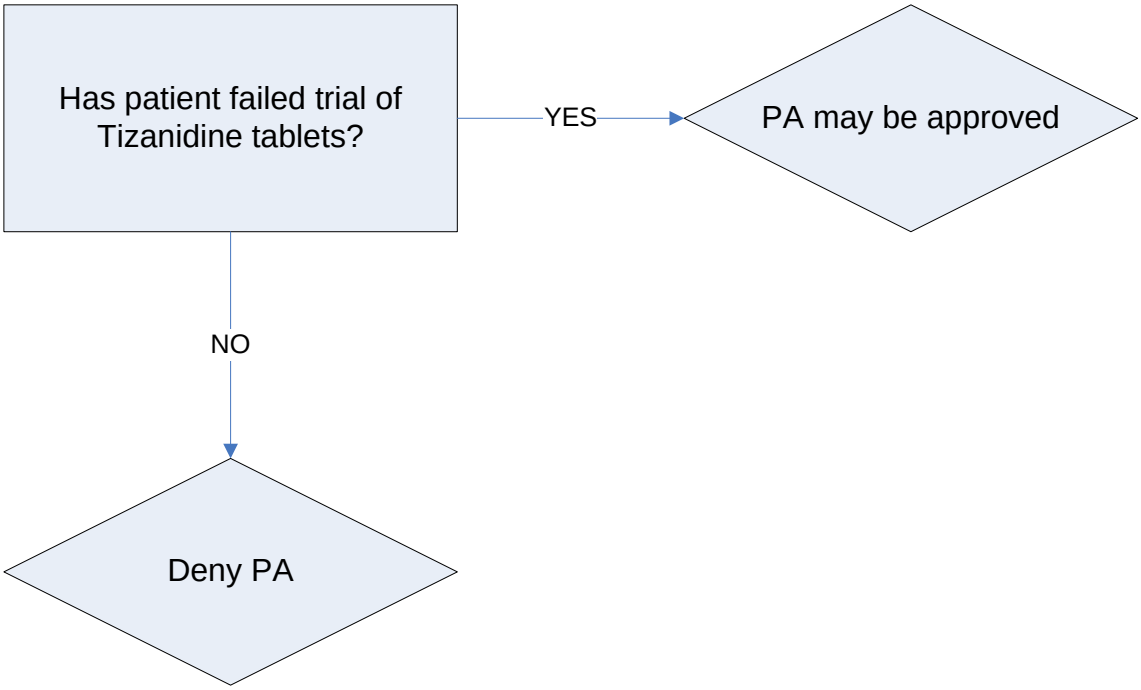
Part II: TO BE COMPLETED BY PHARMACY

PHARMACY NAME:			ND MEDICAID PROVIDER NUMBER:
PHONE NUMBER	FAX NUMBER	DRUG	NDC #

Part III: FOR OFFICIAL USE ONLY

Date Received	Initials:
Approved - Effective dates of PA: From: / / To: / /	Approved by:
Denied: (Reasons)	

North Dakota Department of Human Services
Zanaflex Authorization Algorithm



NORTH DAKOTA MEDICAID
RETROSPECTIVE DRUG UTILIZATION REVIEW
CRITERIA RECOMMENDATIONS
OCTOBER 2008

Recommendations	*Approved*	*Rejected*

1. Fluoroquinolones / Black Box Warning _____ _____

Alert Message: Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in those over 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy. Patients should be advised to stop the fluoroquinolone at the first sign of tendon pain, swelling, or inflammation, to avoid exercise and use of the affected area, and to promptly contact the prescriber about changing to a non-fluoroquinolone antimicrobial drug.
Conflict Code: TA – Therapeutic Appropriateness (Black Box Warning)
Drug/Disease:

Util A	Util B	Util C
Ciprofloxacin		
Gemifloxacin		
Levofloxacin		
Moxifloxacin		
Norfloxacin		
Ofloxacin		

References:
MedWatch: The FDA Safety Information and Adverse Reporting Program, 2008.

2. Conventional Antipsychotics / Black Box Warning _____ _____

Alert Message: Conventional antipsychotics are not approved for the treatment of dementia-related psychosis. The FDA has determined through epidemiological studies that elderly patients with dementia-related psychosis treated with conventional antipsychotics are at an increased risk of death compared to placebo.
Conflict Code: TA – Therapeutic Appropriateness (Black Box Warning)
Drug/Disease:

Util A	Util B	Util C (Negating)
Prochlorperazine		Schizophrenia
Haloperidol		Bipolar Disorder
Loxapine		
Thioridazine		
Molindone		
Thiothixene		
Pimozide		
Fluphenazine		
Trifluoperazine		
Chlorpromazine		
Perphenazine		

Age Range: 65 year of age or older
References:
MedWatch: The FDA Safety Information and Adverse Reporting Program, 2008.

3. Lidoderm Patches / Therapeutic Appropriateness _____ _____

Alert Message: Lidoderm (transdermal lidocaine) is indicated for relief of pain associated with postherpetic neuralgia. A review of the patient's recent diagnostic history did not reveal a FDA approved indication for the use of transdermal lidocaine. The safe and effective use of this agent for indications other than postherpetic neuralgia has not been evaluated.
Conflict Code: TA – Therapeutic Appropriateness
Drug/Disease:

Util A	Util B	Util C (Negating)
Lidoderm Patches		Post Herpetic Neuralgia

References:
Facts & Comparisons, 2008 Updates.
Lidoderm Prescribing Information, Feb. 2008, Endo Pharmaceuticals.

4. Exenatide / Therapeutic Appropriateness _____ _____

Alert Message: Postmarketing cases of acute pancreatitis have been reported in patients treated with Byetta (exenatide). Patients receiving exenatide should be informed that persistent severe abdominal pain, with or without vomiting, is the hallmark symptom of acute pancreatitis. If pancreatitis is suspected all suspect drugs should be discontinued, diagnosis confirmed and appropriate treatment initiated. Exenatide should not be restarted unless an alternative etiology is identified.
Conflict Code: TA – Therapeutic Appropriateness
Drug/Disease:

Util A	Util B	Util C
Exenatide		

References:
Facts & Comparisons, 2008 Updates.
MedWatch: The FDA Safety Information and Adverse Reporting Program, 2008.

5. Becaplermin / Therapeutic Appropriateness _____ _____

Alert Message: An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of Regranex (topical becaplermin gel) in a postmarketing retrospective cohort study. Use becaplermin only when the benefits can be expected to outweigh the risks. Use becaplermin with caution in patients with known malignancy.
Conflict Code: TA – Therapeutic Appropriateness (Black Box Warning)
Drug/Disease:

Util A	Util B	Util C
Becaplermin		

References:
Facts & Comparisons, 2008 Updates.
MedWatch: The FDA Safety Information and Adverse Reporting Program, 2008.
Regranex Prescribing information, 2008, Ortho-McNeil