THE PACKAGE INSERT SERIES

Statins — Five Labels, One Drug Class

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Every statin sold in the United States comes with an FDA-approved prescribing document — the package insert. It runs between 20 and 35 pages of small type. It lists what the drug does, what it doesn't do, what it might do to you, and what no one has bothered to find out.

> *Most patients have never seen it. Most doctors don't walk through it. But it exists, it's publicly available, and it says what it says. Among the things it says: one of these drugs produced liver carcinomas in 90% of male mice at high doses. Another increases the risk of haemorrhagic stroke. All five raise blood sugar — in some cases past the diagnostic threshold for diabetes. The effects on male fertility have not been adequately studied. The effects on female hormones are unknown. These are not allegations from the margins. They are statements from the FDA-approved label, written by the manufacturers, reviewed by the regulators, and filed with the agency.*

This is the first installment of The Package Insert — a series that reads the documents your prescriber should have discussed with you. We're starting with the five best-selling statins in the United States: Lipitor (atorvastatin), Crestor (rosuvastatin), Zocor (simvastatin), Pravachol (pravastatin), and Mevacor (lovastatin). Between them, these drugs have been prescribed to tens of millions of Americans. The oldest has been on the market since 1987. The newest since 2003. Their labels have been revised dozens of times — warnings added, sections removed, language quietly changed.

What follows comes directly from the FDA-approved prescribing information — the same documents filed with the agency and available on its website. Every claim below can be verified by reading the label.

The Package Insert reads the FDA-approved prescribing information for a major drug class in each installment — the document that comes with every prescription but that most patients never see. If you're currently taking a statin, considering one, or have a family member on one, this is the installment to start with.

What the Labels Say They Can Do

Not all five statins carry the same approved indications, and the differences matter.

Only two — Zocor and Pravachol — are approved to reduce total mortality. Zocor's label states it reduced the risk of mortality by 30% in the Scandinavian Simvastatin Survival Study, with 182 deaths in the Zocor group versus 256 in the placebo group. Pravachol's label reports a 23% reduction in total mortality in its long-term trial.

Lipitor, despite being the highest-selling pharmaceutical drug in history, is not approved to reduce total mortality. Its own label reports the result plainly: “There was no significant difference between the treatment groups for all-cause mortality.” In the TNT trial — which compared Lipitor 80 mg to Lipitor 10 mg in patients with existing heart disease — all-cause mortality was virtually identical: 282 deaths on the lower dose, 284 on the higher dose, hazard ratio 1.01. The higher dose did not save more lives. It did, however, produce more non-cardiovascular deaths: 158 in the 80 mg group versus 127 in the 10 mg group (HR 1.25). Cancer deaths were numerically higher on the 80 mg dose (85 versus 75). Deaths from suicide, homicide and other traumatic causes were also higher (15 versus 9, HR 1.67 — though the confidence interval was wide).

Crestor's JUPITER trial — the study that expanded statin prescribing to millions of people without heart disease — showed no significant difference between Crestor and placebo for death due to cardiovascular causes. The trial was stopped early by the Data Safety Monitoring Board, which means the long-term mortality picture was never completed.

Lovastatin's label reports a small mortality signal in one subgroup analysis (1 death versus 8 in placebo) but its primary indication is lipid reduction, not mortality reduction.

> ASK YOUR DOCTOR
> *Is this specific statin approved to reduce my risk of death from all causes — or only to change my cholesterol numbers? What's the absolute risk reduction in the trial that supports my prescription?*

Muscle Damage: From Pain to Organ Failure

Every statin label warns about myopathy and rhabdomyolysis. But the language varies in ways that reveal how the risk profile differs across the class.

Myopathy — muscle pain, tenderness or weakness with elevated creatine kinase — is the most commonly reported serious adverse reaction. Rhabdomyolysis is its severe form: muscle tissue breaks down, floods the kidneys with myoglobin, and can cause acute kidney injury. The labels note that rare fatalities have occurred.

Zocor's label provides the most specific incidence data. In a clinical study of over 12,000 patients, the incidence of myopathy on Zocor 20 mg was approximately 0.02%. On 80 mg, it was 0.9% — a 45-fold increase. Rhabdomyolysis at the 80 mg dose occurred at approximately 0.4%. These numbers led to the restriction: the 80 mg dose is now limited to patients who have been taking it chronically without muscle problems, and Zocor is no longer marketed in the 80 mg strength.

Zocor's label also includes a specific warning for Chinese patients. In one study, the incidence of myopathy on simvastatin 40 mg was 0.24% in Chinese patients compared with 0.05% in non-Chinese patients — roughly five times the rate. When combined with niacin, the rate in Chinese patients reached 1.24%. Crestor's label carries a parallel warning for Asian patients more broadly, noting an approximate 2-fold increase in rosuvastatin exposure compared with White controls. The recommended starting dose for Asian patients is 5 mg — half the standard dose.

Four of the five labels — all except Mevacor, which carries the oldest label format — warn about immune-mediated necrotising myopathy (IMNM), an autoimmune condition where the body's immune system attacks muscle tissue even after the statin is stopped. The labels note that IMNM has recurred when patients were switched to a different statin — meaning the immune response is not drug-specific but class-specific. It is characterised by proximal muscle weakness, elevated CK, positive anti-HMG-CoA reductase antibody, muscle biopsy showing necrotising myopathy, and improvement with immunosuppressive agents. A patient who develops IMNM may require immunosuppressive treatment and cannot safely switch to a different statin.

The risk factors for myopathy are the same on every label: age 65 or older, uncontrolled hypothyroidism, renal impairment, and concomitant use of certain medications. The labels instruct patients to promptly report unexplained muscle pain, tenderness or weakness — particularly if accompanied by malaise or fever. They also note that periodic CK monitoring will not reliably prevent myopathy.

> ASK YOUR DOCTOR
> *What is my baseline CK level before starting this drug? If I develop muscle pain, how will you distinguish statin myopathy from normal aches? Have you checked my thyroid and kidney function — both of which increase my myopathy risk?*

Liver Damage

Every label in the class warns about hepatic dysfunction. Increases in serum transaminases have occurred, some persistent. Rare cases of fatal and non-fatal hepatic failure have been reported.

Lipitor's trial data showed liver enzyme elevations (greater than 3 times the upper limit of normal) in 1.3% of patients on the 80 mg dose versus 0.2% on the 10 mg dose. Crestor's pooled analysis showed 1.1% on the drug versus 0.5% on placebo. The labels recommend considering liver enzyme testing before starting therapy and when clinically indicated thereafter — but they no longer mandate routine periodic monitoring, a change from earlier labelling.

Active liver disease or decompensated cirrhosis is a contraindication for all five drugs. Patients who consume substantial quantities of alcohol or have a history of liver disease may be at increased risk.

> ASK YOUR DOCTOR
> *What are my liver enzyme levels before starting this drug? How will you monitor for hepatic injury, and what symptoms should prompt me to contact you immediately?*

Diabetes: The Warning They Added Later

All five labels now carry a warning about increases in HbA1c and fasting serum glucose levels. This warning was not present in the original approvals — it was added after years of post-market surveillance. Lovastatin was approved in 1987. Zocor and Pravachol in 1991. Lipitor in 1996. Crestor in 2003. The diabetes warning came decades later. Millions of patients were prescribed these drugs before the risk was formally acknowledged in the labelling.

Crestor's label is the most explicit. It states that glucose increases "may exceed the threshold for the diagnosis of diabetes mellitus." In the JUPITER trial — the study conducted in people without heart disease — 2.8% of patients on Crestor developed diabetes compared with 2.3% on placebo. Mean HbA1c increased by 0.1% in the Crestor group. The number of patients with HbA1c above 6.5% — the diagnostic threshold for diabetes — was significantly higher in Crestor-treated patients. JUPITER enrolled 17,802 patients and was stopped early for efficacy after a mean of only 2 years. The diabetes signal emerged in that short window.

The labels' recommended response is identical for every drug in the class: "Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices." The label does not discuss whether the drug should be reconsidered. It does not address whether the cardiovascular benefit persists in a patient who develops drug-induced diabetes — a condition that independently increases cardiovascular risk.

The Mevacor label adds a mechanistic admission that the other labels omit. Under "Endocrine Function", it states: "HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production." It then notes that clinical trial results "have been inconsistent with regard to drug effects on basal and reserve steroid levels". That word — theoretically — acknowledges a mechanism that has never been fully investigated for the class.

> ASK YOUR DOCTOR
> *What is my current HbA1c and fasting glucose? How often will you recheck these values while I'm on this drug? If my blood sugar rises, will you reconsider the prescription or add a diabetes medication?*

Cognitive Effects

Every label in the class reports cognitive impairment in its post-marketing section. The language is nearly identical: rare reports of memory loss, forgetfulness, amnesia, memory impairment and confusion associated with statin use. The labels state these cognitive issues were “generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).”

The framing — “generally nonserious” — deserves scrutiny. The onset can range from one day to years. The resolution time is measured in weeks. And the word “generally” does real work: it means some cases were serious.

Lovastatin's label goes further than the others in documenting neurological findings. In its animal toxicology section, it reports that lovastatin produced optic nerve degeneration in dogs, along with CNS vascular lesions characterised by perivascular haemorrhage, oedema, mononuclear cell infiltration, fibrin deposits and necrosis of small vessels. It states: “Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.” Cataracts were also seen in dogs at higher doses. A three-year human study on lovastatin and the lens found no significant differences in cataract incidence — but the label notes there are “no controlled clinical data assessing the lens available for treatment beyond three years”. The label also states that lovastatin crosses the blood-brain barrier.

Lipitor's label notes that the CNS Toxicity warning section was removed in December 2022 — the label records the removal in its “Recent Major Changes” section but no longer contains the warning itself. The label does not explain why it was removed.

In addition to cognitive effects, the post-marketing sections across the five labels report depression (all five), peripheral neuropathy (all five), sleep disorders including insomnia and nightmares (Crestor, Lipitor, Pravachol and Lovastatin), and dizziness (Zocor, Crestor, Lipitor). Lovastatin's post-marketing section also lists dysfunction of cranial nerves — including altered taste, impaired eye movement and facial paresis — along with tremor and peripheral nerve palsy. Pravachol lists interstitial lung disease. These are not theoretical risks. They are adverse reactions reported after the drugs reached the general population — a population far larger and more varied than the clinical trial cohorts.

> ASK YOUR DOCTOR
> *If I notice changes in memory, concentration or mood after starting this drug, what is your protocol? Will you consider a drug holiday to determine whether the statin is the cause?*

Reproductive and Endocrine Effects

The Mevacor label contains the most detailed endocrine section in the class. It states that the effects of HMG-CoA reductase inhibitors on male fertility "have not been studied in adequate numbers of male patients". It reports that the effects on the pituitary-gonadal axis in pre-menopausal women "are unknown". It notes that another statin in the class reduced testosterone response to HCG stimulation, and that lovastatin's own effect was "slightly but not significantly reduced" in a 16-week study of 21 men.

The animal toxicology data tells a more alarming story than the clinical data, and it is consistent from drug to drug. Lovastatin's label reports drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation with "a similar drug in this class". Zocor's label reports the same findings in dogs: testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation. Decreased fertility was observed in male rats treated with simvastatin for 34 weeks. Crestor's label reports spermatidic giant cells in dog testes and in monkeys. Lipitor's label reports testis weight decreases, aspermia, decreased sperm motility and increased abnormal sperm in rats.

The post-marketing sections add more: Lovastatin lists gynaecomastia, loss of libido and erectile dysfunction. Zocor and Pravachol list erectile dysfunction and gynaecomastia respectively. Crestor lists gynaecomastia.

Lipitor's label carries a unique drug interaction: it increases plasma levels of the oral contraceptive hormones norethindrone and ethinyl estradiol. The label instructs prescribers to "consider this when selecting an oral contraceptive for patients taking LIPITOR". Whether most prescribers or patients know about this interaction is another matter.

> ASK YOUR DOCTOR
> *If I'm planning to conceive — as either parent — what is the evidence that this drug does not affect fertility? Has anyone studied the effects of long-term statin use on hormone levels in someone my age and sex?*

What the Labels Admit Has Not Been Studied

The labels also contain a pattern of admissions about what was never investigated — or what was investigated inadequately.

Long-term effects in children are unknown. Children as young as 8 (Crestor, Zocor) or 10 (Lipitor, Pravachol, Lovastatin) can be prescribed statins for familial hypercholesterolaemia. But Lovastatin's label states: “The long-term efficacy of lovastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.” Zocor's label contains identical language. These drugs are prescribed to children on the theory that early cholesterol reduction will prevent adult heart disease — but the labels acknowledge that this has never been demonstrated. The safety and effectiveness sections add that no statin has been studied in pre-pubertal children, and Lovastatin's label specifically notes it “has not been studied in pre-pubertal patients or patients younger than 10 years”. Meanwhile, the animal data showing testicular effects, liver tumours and CNS toxicity applies to developing organisms across every species tested.

Male fertility is understudied in humans. The Mevacor label's admission that fertility effects “have not been studied in adequate numbers of male patients” stands against the extensive animal data showing testicular and spermatogenic damage in every statin tested. Adequate human fertility studies have not been conducted for any of the five drugs, despite their use by millions of men for decades.

Endocrine effects in pre-menopausal women are unknown. The Mevacor label states this directly. Since HMG-CoA reductase inhibitors interfere with cholesterol synthesis — the precursor pathway for all steroid hormones — and since clinical trial results on steroid levels have been “inconsistent”, this gap affects every woman of reproductive age taking a statin.

The Crestor proteinuria finding has unknown clinical significance. Crestor's label notes that dipstick-positive proteinuria and microscopic haematuria were observed in clinical trials, more frequently at the 40 mg dose. The label then states: “the clinical significance of this finding is unknown.” Proteinuria is typically a marker of kidney stress.

Women's mortality response is inadequately assessed. Zocor's landmark 4S survival study — the trial that established mortality reduction — enrolled a population that was only 19% female. The label states: “the effect of ZOCOR on mortality in women could not be adequately assessed.”

The effect of statin-induced blood sugar rises is unaddressed. Every label warns that statins increase HbA1c and fasting glucose. The Crestor label acknowledges these increases can cross the diabetes diagnostic threshold. But no label addresses the long-term consequences of this drug-induced metabolic shift, nor whether the cardiovascular benefits persist in

patients who develop statin-induced diabetes. A drug prescribed to reduce cardiovascular risk is creating a condition — diabetes — that independently increases cardiovascular risk. The labels do not examine whether the net effect is positive or negative in this subgroup.

Post-marketing surveillance has uncertain reach. Every label notes that post-marketing adverse reactions "are reported voluntarily from a population of uncertain size" and that "it is not always possible to reliably estimate their frequency". This standard disclaimer means that the adverse reaction rates in the post-marketing sections — cognitive impairment, depression, peripheral neuropathy, interstitial lung disease, tendon rupture, pancreatitis — cannot be quantified from the available data. The denominator is unknown. The reported cases represent an unknown fraction of the actual incidence.

Animal carcinogenesis signals have limited human follow-up. Lovastatin produced hepatocellular carcinomas in mice at higher exposures, along with pulmonary adenomas and stomach papillomas. In rats, there was a positive dose-response relationship for liver cancer. Simvastatin produced liver carcinomas in mice with a maximum incidence of 90% in high-dose males — and also significantly increased lung adenomas and Harderian gland adenomas. Pravachol showed hepatocellular carcinomas in both rats and mice, along with lung adenomas in female mice. Lipitor produced liver adenomas and carcinomas in mice, and two rare muscle tumours (a rhabdomyosarcoma and a fibrosarcoma) in high-dose rats. Crestor produced uterine stromal polyps in rats and hepatocellular adenomas/carcinomas in mice at the highest dose. An increased incidence of thyroid neoplasms — noted in the Lovastatin label — "appears to be a response that has been seen with other HMG-CoA reductase inhibitors".

The labels note that these findings occurred at multiples of human exposure. That qualifier does real work: it allows the drugs to remain on the market. But the long-term carcinogenicity data in humans taking these drugs for 20 or 30 years does not exist in the labels. The animal findings show a consistent pattern across the entire drug class — liver tumours in particular — and the absence of long-term human data is a choice, not an impossibility. These drugs have been on the market since 1987. The cohorts exist. The studies could be done.

Drug Interactions: The Combinations That Amplify Risk

The drug interaction profiles differ substantially across the five statins, and the differences have practical consequences for patients on multiple medications.

Every label warns against concomitant use with cyclosporine and gemfibrozil. Every label warns about fibrates, niacin at lipid-modifying doses, and colchicine increasing myopathy risk. But the specific contraindications and dose restrictions differ.

Lovastatin and Zocor are metabolised through CYP3A4, which means they interact with a long list of drugs that inhibit this enzyme: azole antifungals (ketoconazole, itraconazole, voriconazole), macrolide antibiotics (erythromycin, clarithromycin), HIV protease inhibitors, and nefazodone. These combinations are contraindicated for Lovastatin and restricted for Zocor. Grapefruit juice — which inhibits the same enzyme — significantly increases lovastatin exposure. The label reports that double-strength grapefruit juice increased lovastatin blood levels by 15-fold, and even single-strength grapefruit juice nearly doubled them. Pravachol's label includes specific dose ceilings with erythromycin and clarithromycin — do not exceed 40 mg daily with either antibiotic.

Zocor carries unique dose-ceiling restrictions when used with amiodarone (a common heart rhythm drug), amlodipine (a common blood pressure drug), ranolazine and dronedarone. Patients on these combinations must not exceed Zocor 20 mg daily. Given that hypertension and arrhythmias are common in the same population being prescribed statins, these restrictions apply to a large number of patients. The label does not estimate how many patients are on these combinations.

Lipitor increases plasma levels of oral contraceptive hormones — specifically norethindrone and ethinyl estradiol. It also increases digoxin levels, requiring monitoring. Crestor affects warfarin anticoagulation. These interactions are documented but easily missed when multiple prescribers are managing different conditions — a cardiologist prescribing the statin, a gynaecologist prescribing the contraceptive, and neither checking the other's work.

> ASK YOUR DOCTOR
> *Given everything else I take — including over-the-counter medications and supplements — are there dose restrictions or contraindications I should know about? Can you check the interaction profile for my complete medication list?*

Two Warnings Worth Isolating

Two findings from the labels illustrate how easily critical information gets buried in 30 pages of dense text.

Crestor and kidney markers. Crestor is the only statin whose label warns about proteinuria and haematuria — protein and blood in the urine. These were observed more frequently at the 40 mg dose compared with lower doses or other statins. The label describes the findings as “generally transient” but acknowledges the clinical significance is unknown. It recommends considering a dose reduction for patients with unexplained persistent proteinuria. Proteinuria is a standard clinical marker of kidney stress, and Crestor already carries a lower starting dose recommendation for patients with severe renal impairment. The finding is disclosed; whether prescribers routinely check urine protein in their statin

patients is another matter.

Lipitor and haemorrhagic stroke. Lipitor 80 mg carries a unique warning based on the SPARCL trial: a significantly higher incidence of haemorrhagic stroke compared with placebo (2.3% versus 1.4%, hazard ratio 1.68, p=0.0168). Patients who entered the trial with a prior haemorrhagic stroke appeared to be at particularly elevated risk — 16% on Lipitor versus 4% on placebo. The label advises prescribers to "consider the risk/benefit of use of LIPITOR 80 mg in patients with recent hemorrhagic stroke". The mechanism is not established in the label. The question of whether aggressive cholesterol lowering itself affects haemorrhagic stroke risk — relevant to the entire drug class — remains unaddressed.

Questions to Take to Your Doctor

These questions are drawn directly from what the labels say and what they don't. Print this list.

1. Is this specific statin approved to reduce my risk of dying — or only to change my cholesterol numbers? What is the absolute risk reduction?
2. What are my baseline CK, liver enzyme, HbA1c and fasting glucose levels before starting?
3. How often will you recheck my blood sugar and liver function while I'm on this drug?
4. What is your protocol if I develop muscle pain, cognitive changes or mood disturbance?
5. Am I taking any other medications — including blood pressure drugs, antifungals, antibiotics or oral contraceptives — that interact with this statin?
6. Am I in a population (Asian descent, over 65, hypothyroid, renal impairment) that the label identifies as higher risk?
7. If I'm planning to conceive, what is the evidence regarding this drug and fertility?
8. What is your threshold for discontinuing this drug if I experience side effects?
9. Has the long-term benefit of this drug been demonstrated in someone with my specific risk profile — or are we extrapolating from a different population?
10. Can I see the package insert?

> Disclaimer
> Nothing in this series constitutes medical advice. The purpose is to help you read what's already written about the drugs you're taking, and to ask better questions of the people prescribing them.

Sources

- Lipitor (atorvastatin) — NDA 020702, FDA-approved prescribing information, FDA.gov/drugsatfda
- Crestor (rosuvastatin) — NDA 021366, FDA-approved prescribing information, FDA.gov/drugsatfda
- Zocor (simvastatin) — NDA 019766, FDA-approved prescribing information, FDA.gov/drugsatfda
- Pravachol (pravastatin) — NDA 019898, FDA-approved prescribing information, FDA.gov/drugsatfda
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