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By Lynne Peterson

SUMMARY

Sales of AstraZeneca's new statin, Crestor, are expected to grow very slowly. Cardiologists are likely to use it much as they would any other statin, but there may be little initial use by family practice doctors, who may approach it cautiously. Doctors do not appear worried about proteinuria or hematuria with Crestor, and they do not believe they are class effects. Crestor use is likely to cut into sales of Pfizer's Lipitor but not Schering Plough's Zetia. Canadian pharmacists report extremely slow sales of Crestor, even in Saskatchewan where government coverage started July 1, 2003.

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ASTRAZENECA'S CRESTOR

The FDA Endocrinologic and Metabolic Drugs Advisory Committee met on July 9, 2003, to consider AstraZeneca's Crestor (rosuvastatin calcium, ZD-4522). AstraZeneca had previously withdrawn its application for the 80 mg dose due to unacceptably high adverse event rates, and the panel voted to recommend approval of Crestor at all other requested doses – 5 mg, 10 mg, 20 mg and 40 mg. However, the Advisory Committee also recommended the FDA require blood and urine monitoring at the 40 mg dose. On August 12, 2003, the FDA approved Crestor, and did not require renal monitoring. This report reviews the outlook for sales of Crestor and the advisory panel's concerns.

USAGE OUTLOOK

Fourteen doctors – 10 cardiologists, three family practice doctors and a geriatric specialist – were questioned about the outlook for Crestor if the FDA follows the Advisory Committee's recommendation and approves 5-40 mg. Doctors were also asked about the impact that periodic creatinine and urinalysis monitoring would have on Crestor usage.

Sources generally expect Crestor sales to grow slowly, with most of the usage by cardiologists, and very little initial use by family doctors. A Kansas family doctor said, "Use will ramp up slowly after Baycol (Bayer, cerivastatin). We've seen some new products come out, and then they're withdrawn." An Oregon cardiologist said, "I anticipate that Crestor at all doses will be used in perhaps 10% of my patients six months after approval, 15% one year after approval, and 20% at peak. I would not anticipate changing patients to Crestor who are doing well on other statins unless they are not adequately controlled for their hypercholesterolemia." A Utah cardiologist said, "I'll probably be using 5% in six months, 10% in a year, but peak usage depends on how the drugs works in the real world." A New York cardiologist said, "In six months, I'll be using less than 5% Crestor, and by a year from 5%-10%. Peak usage will be 5%-10% unless Crestor proves to be a really superior product – or it proves toxic."

Crestor Market Share Outlook in the U.S. *

Time point	U.S. market share among expected users	U.S. market share among all sources
6 months	6%	2%
12 months	10%	5%
Peak usage	14%	Unable to predict

*based on average estimates by sources.

Six of the 10 cardiologists interviewed plan to use Crestor as soon as it is available, and they will use it much as they would any other statin. One said, "I'll use Crestor for any patient needing a statin." A Utah cardiologist said, "I'll use Crestor for patients whom I can't get to goal." A New York cardiologist said, "I'll use Crestor pretty much in any patient with hyper-cholesterolemia." An Oregon doctor said, "I anticipate using Crestor in patients with severe familial hypercholesterolemia who will ultimately require high does of a statin and usually combination therapy." A North Carolina doctor said, "There may be a place for Crestor. The majority of patients with atherosclerotic vascular disease tend to have cholesterols not too far apart from the normal distribution of the average population, and the real problem for these patients has been taking the drugs that are prescribed. So, if a new statin is available ***at a lower cost***, that could be helpful. But the side effects with existing statins have been so small that it will be hard to think that that's going to be an area where there could be major improvement. So, the two areas where there is room for improvement is with lower cost and potentially in patients refractory or very hard to control with high levels of cholesterol." A Connecticut cardiologist said, "I expect to use Crestor for the same patients for whom I use Lipitor (Pfizer, atorvastatin)…It's been studied extensively. It's really been through the hoops."

One cardiologist and two family practice doctors said they plan to wait until there is more clinical experience with Crestor before trying it. The cardiologist said, "Given all the safety concerns and the availability of so many other statins, I will most likely not be one of the first doctors to use it. I will wait until more safety and efficacy data becomes available." A family doctor said, "I would wait quite a while before I prescribe this myself…apparently, it isn't safer (than other statins) if there could be renal involvement at higher doses." The other family doctor predicted his colleagues would be slow to start using Crestor, "You don't want to be the first on the block with a new toy or the last kid either, and that will be true of this also. I'll let other physicians try it first. I don't want to talk down Crestor, but my physicians will see what the national data is and see what happens and not be rapid adopters."

Three cardiologists, one family doctor, and the geriatric specialist said they didn't know enough about Crestor yet to make a decision about usage. A Maryland cardiologist said, "I'm unfamiliar with Crestor; indeed, I haven't heard of it." A family doctor said, "I don't know anything about Crestor. I generally use Lipitor."

Doctors predicted that Crestor sales would be helped if it were priced lower than other statins. However, AstraZeneca has priced 10 mg Crestor at a slight premium to 10 mg Lipitor, but Crestor will be the same price at all doses. One source said, "Cost of therapy has been a concern for many doctors, and that's a consideration. If there's something with a competitive pricing edge, that would be important." Another doctor said, "If it is more expensive…then I would not use it." A third doctor said, "Cost is an incredibly important factor. Price is very important to physicians – and to patients. The companies negotiate with the HMOs, so even though Crestor may be priced under Lipitor on the open market for someone who has to pay for it, patients in drug plans may use something else because the HMO got it cheaper."

Most sources agreed that the early clinical experience with Crestor will determine how well the drug ultimately will sell. A cardiologist said, "I think time will tell if there is a benefit with Crestor in terms of efficacy in treating some of the more resistant hyperlipidemia. No doubt patients who have difficulty with the highest doses of existing statins may be given a trial with Crestor. I don't know whether Crestor will be significantly better, but it's always nice to have an alternative and think there may be a chance (of something working)." A geriatric specialist said, "The safety of such a new agent will only be determined sufficiently after it has been used by the masses on a large scale. As with all new drugs, caution is warranted after the initial release."

Most doctors preferred the 10 mg starting dose, but two preferred a 5 mg starting dose, and one preferred 20 mg. An Oregon cardiologist said, "I would start patients on 10 mg and titrate them up based on their response. The starting dose would not limit my use of Crestor." Another cardiologist said, "I'd go with the FDA recommendation. I think that the experience recently with Baycol would suggest that people should be careful and monitor patients." A Utah cardiologist said, "I'd start with 20 mg, even if the FDA approved a 10 mg starting dose, because I would only use it for high potency – or I'd use another statin with which I had more experience." A family doctor added, "If 10 mg is the recommended starting dose, that would be the logical place to start."

If the FDA had mandated periodic serum creatinine monitoring and/or urinalysis with the 40 mg Crestor dose, most cardiologists agreed that the monitoring would ***not*** have raised concerns, and they would have still used that dose. However, one cardiologist and several family doctors predicted monitoring would have discouraged their use. A Utah cardiologist said, "I would still use it if it gets patients to goal and nothing else does." Another cardiologist said, "We do not normally do urinanalysis unless the patient has some complaints, and the need to do urine testing would potentially limit my use of Crestor since this is not required for other statins." A third cardiologist said, "Monitoring at 40 mg would not make me uncomfortable." An Illinois family doctor said, "The need to monitor extra parameters adds more cost and inconvenience to any drug, not to mention increased liability to the physician if one of the measurements is inadvertently overlooked." A Kansas family doctor said, "An FDA requirement for monitoring would affect use because so many medications are available that don't require that monitoring…Because of the memory of Baycol, a monitoring requirement will have a psychological effect on Crestor use." A New England cardiologist said, "Having to do testing at 40 would have been an impediment to using it."

Most sources do not believe the proteinuria reported with Crestor is a class effect. A Utah doctor said, "I've never looked for proteinuria with other statins. It certainly is not something that I have been worried about. If it does happen, it appears to be irrelevant to anything serious, such as development of renal failure, etc., because these things just don't happen, even in very large studies like HPS." An Oregon doctor said, "This has not been shown to be a risk factor with other statin, and I disagree that other statins also carry the risk of proteinuria. I don't believe that is true. Statins have been used in patients with nephritic syndrome who concurrently have hypercholesterolemia, and my conceptual view has been that lowering LDL has beneficial effects on vascular reactivity." A Kansas doctor commented, "The proteinuria is one reason a lot of doctors won't go right out and transfer patients to Crestor, even if it works better." The exception was a Connecticut cardiologist who said, "I tend to believe most of these things are a class effect."

Doctors were divided as to whether they would use Crestor in diabetic patients with proteinuria.

- **Would use:** A cardiologist said, "If other statins seem inefficient, I'd still use it." Another cardiologist said, "I don't think that proteinuria will affect my decision." Another cardiologist
- **Would not use:** A doctor said, "I wouldn't do that without more information." Another said, "In view of the potential of Crestor to cause proteinuria, I wouldn't use it in patients with diabetes who concurrently have proteinuria." A family doctor said, "If one of the side effects is proteinuria, it would be unadvisable to start this medication in anyone with diabetes or renal problems."

Crestor use is likely to have the greatest impact on Lipitor, doctors predicted. A cardiologist said, "Crestor approval may reduce my use of Lipitor because Crestor has similar efficacies at the higher doses but tends to raise HDL at all doses, where high dose Lipitor lowers HDL." Another cardiologist said, "Lipitor and simvastatin (Merck's Zocor), at the highest doses, are used for patients with more severe hypercholesterolemia, so one would expect competition in that area." A third cardiologist said, "Crestor will reduce my Lipitor use slightly." A fourth cardiologist said, "If things go fine with Crestor – if it is equal to or more powerful than Lipitor, it has a better effect on HDL, is priced right, and the side effects are all right – then it will give Lipitor a run for its money…At high doses, Lipitor seems to lower HDL, and here's a drug that doesn't seem to do that." A family doctor said, "I use mostly Zocor, Pravachol (Bristol-Myers Squibb, pravastatin), and some lovastatin. Those are the three statins with outcome data. I don't see Crestor having a big impact on those until it has outcomes data. That piece of data has to come along."

Crestor approval is unlikely to affect use of Schering Plough's Zetia (ezitimibe), which doctors are using both as monotherapy and in combination with different statins. A cardiologist said, "Crestor will not impact my use of Zetia." Another cardiologist said, "Most of my patients who are taking Zetia are taking it in combination with a statin, but I have four or five patients who are on monotherapy because they had previous side effects with statin. I tend to use Zetia with all the statins." A family doctor said, "I usually use Zetia in combination first, adding it to whatever statin a patient is on, but a statin is still first-line."

CANADIAN SALES

Cost of 30-Day Supply of Crestor in Canada *

Dose	Average Price
10 mg Crestor	$ 36.74
20 mg Crestor	$45.23
40 mg Crestor	$51.71

*** Average at four pharmacies in May 2003**

AstraZeneca claimed in May 2003 to have 23.5% of new prescriptions in the private payor market, which is estimated at 40% of the total market. That would have given Crestor 9.4% of the total market. However, pharmacies across the country were surveyed, and they reported much slower sales. All estimated sales at only a "handful" and certainly less than 2% of total statin sales. One pharmacy had not yet filled a single Crestor prescription, and only two had filled any 40 mg prescriptions. An Ontario pharmacist said, "Crestor sales have been slow. It takes a while for a new drug to pick up – and the government isn't paying for it yet." A Toronto pharmacist said, "I've filled perhaps six prescriptions for Crestor in the past month." A Vancouver pharmacist said, "I've filled five prescriptions. There isn't huge demand for it yet, and I don't expect it to be huge." A Saskatchewan pharmacist said, "I've only filled one prescription. It isn't moving very well." Another pharmacist said, "A lot of doctors are still hesitant to prescribe it, but the feedback is good so far. The problem is it is not covered by any drug plans and not by the government."

Another survey of 10 Canadian pharmacies in July 2003 found similar results. Pharmacists estimated Crestor sales at significantly below 5% of total statin prescriptions, and three had only filled one prescription so far. None of these sources had seen any substantial use of Crestor yet, but the Saskatchewan government began covering Crestor on July 1, 2003, and pharmacists there said they expected sales to pick up soon as a result.

Despite the approval of Crestor by the Saskatchewan government, sales continue to be slow in that province. In early August 2003, six pharmacists in Saskatchewan were interviewed again. Only one had seen any increase in Crestor prescriptions so far. The others all continued to report very minimal or no demand for Crestor.

FDA ADVISORY COMMITTEE

Currently, Crestor is approved in 24 countries other than the U.S. – all with the 10 mg to 40 mg doses. AstraZeneca submitted an NDA for Crestor in 2001. Initially, it requested approval for 5 mg, 10 mg, 20 mg, 40 mg and 80 mg, but when safety concerns were raised about the 80 mg, the company withdrew that dosage.

AstraZeneca requested approval to market Crestor for:

- Primary hypercholesterolemia and mixed dyslipidemia – with a starting dose of 10 mg daily.
- Hypertriglyceridemia – with a starting dose of 10 mg daily.
- Homozygous familial hypercholesterolemia – with a starting dose of 20 mg QD.
- A 5 mg dose for patients taking cyclosporine.

The FDA appeared satisfied with the efficacy of Crestor at all the proposed doses. FDA reviewers concluded, "Crestor is marginally more effective, the HDL effects are variable. There is a small increase with 2 mg over 10 mg, consistent with the statin class." Another said, "I think there is compelling evidence today – and more to come – that lower LDL is better. So, it is reasonable to assume on the benefit side, on balance, having an improved ability to lower LDL additionally, beyond what can be done with the current armamentarium, will benefit at least some patients."

An FDA official offered comments on several issues.

a. On LDL mean change from baseline: "I conclude the responses are very similar across these (Crestor) studies. There is a dose response at 5 mg in every study but at 40 mg and 80 mg, we see a small difference of 2%-3%, suggesting a leveling off of effect…The 5 mg dose provides about 2/3 of the lowering seen for the 40 mg dose (42% vs. 60%)."

b. On the comparison of Crestor to Lipitor: "Looking at the highest dose of each…~23% of Lipitor 80 mg patients had a decrease of 60% or more and twice as many Crestor 40 mg patients had that decrease…there were no differences between Crestor 20 mg and Lipitor 80 mg."

c. On HDL lowering with Crestor: "There is a lack of dose effect."

d. On the appropriate starting dose (AstraZeneca asked for a 10 mg starting dose): "For many patients, 5 mg may be an adequate starting dose."

The FDA also appeared comfortable with the myopathy, myalgia and rhabdomyolysis incidence with Crestor at doses of 40 mg or less. An official said, "There is no question the 80 mg dose raises serious safety questions in terms of myopathy, proteinuria, hematuria, rhabdomyolysis, CK elevation, ALT elevation, etc. However, CK elevation and myopathy at 40 mg and lower is similar to other statins." Dr. David Orloff, Director of the FDA's Division of Metabolic and Endocrine Drug Products, said, "There is a small risk of myopathy and a reduced risk of cardiovascular events (with Crestor)…We talk a lot about the risk of myopathy with this class (statins)…but there is absolutely no expectation that we can obviate all myopathy with statins…Even if we reduced the maximum doses across the board with the marketed statins, we would still see cases (of myopathy)…In five-year placebo-controlled trials -- and most recently with up to 40 mg simvastatin -- there have been vanishingly few cases of rhabdomyolysis and to my knowledge no deaths attributable to drug-induced myopathy."

An AstraZeneca official defended the 40 mg dose, noting it: (a) adds benefits, (b) is well-tolerated, and (c) is not the recommended starting dose but is an "important dose for patients who do not achieve lipid modification at a lower dose." Company officials insisted that all the safety problems with Crestor were at the 80 mg dose. They also claimed the 40 mg and lower doses were safe and similar to other marketed statins. However, AstraZeneca is only seeking a maximum dose of 20 mg in Japan.

The big safety question for Crestor – and it became public for the first time just two days before the Advisory Committee meeting – was proteinuria and hematuria. The FDA seemed to accept AstraZeneca's claim that the proteinuria is reversible when Crestor is stopped, but the agency had several unanswered questions about the renal findings:

1. Have the renal effects of Crestor been adequately characterized?
2. Is monitoring necessary? At higher doses? (how -- CR, urinalysis?)
3. What investigations are needed to better describe the "natural history" of this drug effect?
4. Is this a class effect of statins?

Among the key points relating to proteinuria and hematuria were:

- Proteinuria usually occurs as soon as two weeks, but it can occur later. However, patients didn't drop out of the trials because of either of these events.
- The FDA reported a higher incidence of proteinuria and hematuria than AstraZeneca. The FDA counted any incident of elevated proteinuria/hematuria, but AstraZeneca only counted these problems in patients at 96 weeks, at which time point there was a lower incidence. Panel members suggested the FDA measuring system was better.
- AstraZeneca scored points with the example of a patient who took Crestor, developed proteinuria, and stopped Crestor. The patient was re-challenged with Crestor, developed proteinuria again and stopped a second time. Then, the patient was tried on Lipitor and got proteinuria a third time.

- An AstraZeneca official said, "We are seeing a signal potentially at the 40 mg dose…but at the end of the day, is the proteinuria causing any detrimental effect in renal function? We just are not seeing that."

Among the company's claims for Crestor were:

a. **Liver**: *Almost* no liver failure.

b. **Muscle**: All cases of myopathy associated with symptoms. The 20 mg case had a Coxsackie-type virus, and the 40 mg patient was a weight-lifter who stopped and then safely restarted Crestor. Seven cases of rhabdomyolyis at 80 mg and 5 of these were women.

c. **Kidney**: All proteinuria is tubular, similar in frequency to other statins at doses of 40 mg or less. Proteinuria does not lead to excessive renal complications except at 80 mg and was always reversible.

d. **Drug-drug interactions**: More (7.1x) increase in concentration when given with cyclosporine, so the recommended dose would be 5 mg – but still this is less a problem than with lovastatin. No interaction with fenofibrate.

e. **Ethnicity**: Exposure increase is double in Japanese patients living in Japan, but AstraZeneca doesn't know if this is environmental or genetic.

Dr. Sid Wolfe of Public Citizen argued against approval of any dose. He cited "two strikes against this (Crestor) in terms of safety"-- renal toxicity and rhabdomyolyis. He asked, "Why approve the drug, which has negative risks compared to the other statins?"

The final panel votes were:

- **Efficacy**: Unanimous that Crestor is efficacious at all doses, including the 40 mg dose.
- **Myotoxicity**: Unanimous that there is sufficient evidence that the myotoxic potential is similar to other marketed statins.
- **Renal effects**: Majority felt the renal risk was defined and adequately evaluated, but the mechanism is not as well defined, and further studies are needed (animal and post-marketing).
- **Renal class effect**: Suggested but not proven.
- **Monitoring**: Clearly recommended for 40 mg, with a minimum of baseline creatinine and urinalysis and a plea for a creatinine/protein ratio – plus periodic evaluations with creatinine and at least dipstick but preferably a full urinalysis.
- **Dosing**: 5-10 and 20 mg are all safe starting doses in appropriate populations. Fixed starting dose of 10 mg is reasonable, but many members would like to see doctors have a notation on the label of the option of starting with 5 mg.
- **Overall**: Recommended approval.

Following are the actual questions put to the Advisory Committee by the FDA, and some panel member comments:

Efficacy

1. Has the sponsor provided sufficient rationale for the addition of a new statin to the therapeutic armamentarium for the treatment of dyslipidemia to prevent or delay cardiovascular disease?

YES

- "Without the 40 mg there is really little advantage to this drug over what is out there already."
- "Why not go down to 2.5 mg?"

2. Do the efficacy data support a dose-response sufficient to justify use of the 40 mg dose?

YES

- "How many low risk patients would have reached goal without the 40 mg? If the upper limit were 20 mg, you still get 91% of low risk patients achieving target instead of 96% (with 40 mg)…so still above 90% but there is an additional modest benefit to 40 mg, but it is a diminishing benefit."

Safety

Myotoxicity

1. Has the sponsor provided sufficient evidence that the myotoxic potential per LDL-lowering efficacy of rosuvastatin is similar to that of currently marketed statins?

YES

- "There is no significant difference from other statins...I would say the evidence to date indicates that, up to 40 mg, we are at levels comparable to other statins, but with some reservations about the 40 mg dose. At present there is no difference from the other statins, but ***we may see a difference with the 40 mg dose in time with more data.***"

2. Has the risk of muscle toxicity associated with rosuvastatin therapy been adequately evaluated in the clinical development program with respect to:

a. number of patients studied and duration of trials?

YES

- "The myopathy has been studied enough. The concern would be if we see additional toxicity between 5 mg and 40 mg, but it is similar to other statins in that."

- "I was favorably impressed with the long follow-up…Drug-drug interactions are not a problem other than what was mentioned."

b. special populations (e.g., elderly, drug-drug interactions, renal impairment, co-morbid medical conditions)?
YES

- "I am concerned about certain populations, and we may find that Asian Americans or Asians in general may have a problem….I would also like to see more evaluation of drug-drug interactions. The common ones have been looked at, and Crestor is in the range of other statins, but I think this needs to bear watching, especially at 40 mg."
- "The sponsor has done as well as can be expected."

Renal Toxicity

1. Has the risk of renal functional impairment been adequately investigated over proposed dose range?
YES

- "Yes, but we need to find if there are medications, herbs, or subgroups – and what is the hematuria due to? There are further investigations that should be done prospectively now that we know that there is this potential effect."
- "Yes, but I now believe there is a risk at the 40 mg dose…The 20 mg dose has a low rate but far higher than other marketed statins, and when it is increased to 40 mg, it is up to 1.2%. I'm concerned about what happens when millions of people take this drug for five to 10 yrs. I'm not sure this will be a reversible tubular effect. The data I saw showed a diminution, not complete reversibility. I would like to see more basic research."
- "The studies were adequate but could be improved…I'm not sure it is only functional and not structural also…And is it progressive out three to five years?"

2. What further investigations are needed?

- "More basic research."
- "Human studies need to be carried further."
- "I'm intrigued by the sponsor's hypothesis on the mechanism for tubular handling of protein, but it is a struggle to make that answer all the renal questions, especially the hematuria – so I encourage the company to do more looks at the possibility of tubular epithelial levels and other parts of the kidney to see if there is an increased turnover or inflammatory process."
- "I'd like to see more biopsies on proteinuria patients."

3. Is proteinuria a statin class effect? Is the potential for rosuvastatin to induce proteinuria similar to that of other statins?
MIXED

- "It very likely may be. I'm impressed with the data on: (a) A lipophilic study showing this is more likely to get into renal tubules than most of other statins except pravastatin, which is a weaker drug, so this is more likely to get to and into tubules. And this is a very potent drug. (b) The melavolate acid study, which showed this drug is taken up by tubules more easily than other drugs, so I think it will turn out to be a class effect."
- "No matter how you slice and dice it, the 40 mg has a greater issue than other doses and other statins."
- "I think it is not necessarily peculiar to this drug but to 40 mg and above with this drug."
- "I don't know, but it doesn't matter because we don't see this with other statins. Whether it is a class effect doesn't matter to me. We see it here at 40 mg to some extent and certainly at 80 mg."
- "My gut feeling tells me, yes, but there is not enough data here to warrant stating that…I do think it is important to understand this because use of all these agents will be broadly applied and will increase over time."
- "Possibly, but this may have additional action and it is hard to sort that out."
- "The class effect is only a suggestion at this point."

4. Is monitoring in clinical use recommended for this drug and possibly for all statins?
YES

- "I don't think we need monitoring for all the statins on the market…We don't have to go back to the others…(but) monitoring should be recommended for Crestor doses of 40 mg because we don't know the long-long term problems associated with the proteinuria. Many of these patients will have co-morbid conditions requiring renal monitoring. Individuals on 40 mg should have periodic monitoring -- at least urinalysis."
- "Clearly, monitoring is needed at 40 mg with more than a dipstick...I think a full urinalysis and urine protein measurements, Cr at least…For sure, there has to be mandatory monitoring in clinical trials, and I would like to see urinalysis and formal protein measurements or Cr on patients at 40 mg at some interval…These are people likely to have co-morbid processes and may be difficult to sort."
- "Monitoring may be too much, but it may be too little…I'm still not getting my hands around both the mechanism and the magnitude of the issue."
- "Yes, it is needed if you are going to approve this -- at least for now."

- "If I were starting this in the clinic, I would want a baseline urinalysis and serum creatinine. That's a modest and acceptable start for this."
- "Yes for the 40 mg but maybe for other patients, too. I think the package should say patients at high risk of toxicity should be monitored…with at a minimum a creatinine, urinalysis and creatinine/protein radio every six to 12 months."
- "Yes, at 40 mg and I still have some reservations about eliminating monitoring at 20 mg."

Dosing Recommendations

1. Are the data adequate to support the 5, 10, or 20 mg doses as safe starting doses?

YES

2. Is data sufficient to support a 40 mg maximum dose?

YES

- "40 mg is a very valuable addition…In this population I'd rather have some unexplained proteinuria than cardiovascular disease."

3. If yes, does the committee recommend a range of start doses (e.g., 5 to 20 mg) in which an individual may be initiated on therapy based on CHD risks, baseline LDL-C levels, and targeted goals OR should there be a fixed start dose of 10 mg recommended for the general population with 5 and 20 mg reserved for special circumstances, as proposed by the sponsor?

10 mg fixed starting dose

- "I'd start with a fixed dose but offer options as to why a doctor might want to do something differently."
- "I'd like to start at 1 but offer other options."
- "I like titrating based on risk factors and target levels, especially in the primary prevention population, but to do the greatest good for the greatest population, a fixed starting dose of 10 mg is reasonable – but 5 mg is also reasonable. I'd like to give clinicians the ability to go either way."

♦