Trends-in-Medicine

March 2002
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SUMMARY

Niaspan has increased with the increased attention on HDL levels, but the outlook is for that growth to slow. Doctors are starting to prescribe Advicor, but most are taking a cautious approach to it, and it is likely to cannibalize Niaspan sales rather than expand the market – unless it helps make primary care doctors more comfortable with niacin.

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Niacin

Fourteen doctors – seven clinical cardiologists and seven primary care physicians (PCPs) – were interviewed to determine the outlook for Kos Pharmaceuticals' two niacin products, Niaspan (extended release niacin) and Advicor (extended release niacin/lovastatin) There was little enthusiasm for niacins in general or for either of these products in particular.

Niaspan

Doctors have known for years that niacin raises HDL, making it a potential agent for cholesterol control. However, side effects, primarily flushing, are so common with niacin that many doctors refused to prescribe it, and patients would not take it. In 1997, Kos Pharmaceuticals' introduced Niaspan, a hydrogel formulation of sustained-release niacin administered once-a-day at bedtime. Data indicated that Niaspan did not have the liver toxicity associated with other sustained-release niacins and that the flushing, though still common, was manageable with Niaspan, but doctors were dubious and the drug caught on very slowly.

Now, five years later, these sources estimated that fewer than 4% of their hypercholesterolemic patients are on Niaspan. A New England PCP said, "Less than 5% of my patients are on Niaspan. I had one patient on Niaspan who developed a full-blown diabetes that disappeared when we discontinued the drug." An Ohio cardiologist said, "I don't use Niaspan because it is not on the VA formulary here." A Georgia cardiologist said, "Even though niacin is an excellent compound and safe, the side effects related to histamine release are quite significant and cause a significant reduction in overall compliance." A Louisiana family practice doctor said, "A large number of people don't tolerate Niaspan very well and won't take it." The one exception was a doctor in Maine who said, "I'm one of the larger Niaspan users in the East. Patients call back with niacins but not with Niaspan that is properly dosed and given with aspirin."

Most doctors (11 of 14) predicted Niaspan use would remain relatively flat for the next six months. A Midwest family practice doctor said, "My use is unlikely to increase. The titration hassles and adverse events make niacin much less attractive than the statins." A New England PCP said, "My usage probably won't increase. I've been using more Omega 3 fish oil because it has fewer side effects."

However, three sources – two PCPs and one cardiologist – are prescribing more Niaspan now than six months ago, and all of these expect usage to

increase over the next six to 12 months. They cited the New National Cholesterol Education Program (NCEP) guidelines issued in May 2001 as a key reason for the increased used of Niaspan. Those guidelines call for more aggressive cholesterol-lowering treatment and an increased focus on targeting patients with low HDL.

- A California cardiologist said, "I was using no Niaspan six month ago, but about 5% of my patients are on it today, and I expect my use to increase to a peak of 10% over the next six months."

- A Texas family practice doctor said 5% of his patients are on Niaspan today, an increase from 2% six months ago, "Prior to the latest NCEP guidelines, I used Lopid (Pfizer, gemfibrozil) or, more recently, TriCor (Abbott, fenofibrate) when I only needed to lower triglycerides and raise HDL. I used Niaspan as an add-on to a statin when I needed to get trigylcerides lower. Now, I have to use more Niaspan because I have to get the trigylcerides lower and have to get the HDL higher than I did before to meet the guidelines. I've been led to believe that there is less rhabodmyolysis with a statin-Niaspan combination than with a statin-gemfibrozil combination. I use only Niaspan, and I don't use any of the short-acting niacins. Over the next six months, my usage will increase to 10%. In short, I and my colleagues here will be using more Niaspan."

- A Virginia cardiologist said, "My use of Niaspan may increase, given the new data from the HPS (Heart Protective Study) indicating that lower LDL is better."

Advicor

In December 2001, Kos gained FDA approval for Advicor (formerly known as Nicostatin), in three different niacin strengths (500 mg, 750 mg and 1000 mg), each combined with 20 mg lovastatin (Merck's Mevacor). Kos launched the drug at the end of January 2002. Kos augmented its own specialty sales force with 150 contract sales people through Quintiles Transnational's Innovex, for a total of 450 sales people, with plans to target both cardiologists and primary care doctors.

Data from the 316-patient, randomized, open-label ADVOCATE trial was presented at the American College of Cardiology meeting in March 2002, comparing combination extended-release niacin plus lovastatin (ERNL) to 10 mg atorvastatin and simvastatin (Merck's Zocor). Dosing was titrated up in all arms.

In this study, 6% of the Advicor patients withdrew because of flushing, two patients on atorvastatin and one on simvastatin discontinued for ALT elevation. A speaker said, "The most difficult thing about using niacin is time. Time is a valuable thing, and with niacin you can't just prescribe it and say, 'There you go.' With niacin you have to spend time with the patients, and educate them about flushing, avoiding hot drinks, alcohol, and spicy foods, etc. The ADVOCATE trial design was way too complicated, and it was a stacked deck because no one starts Lipitor (Pfizer, atorvastatin) at 10 mg any more. (But) more and more niacin is being used in diabetics to get their HDL up."

Sources generally were aware of Advicor, and most believe it will find a role. Five doctors said they already

Comparison of Combination Niacin/Statin to Statin Only therapy

(% Change From Baseline)

Measurement	extended-release niacin plus lovastatin (1000/40 mg)	Atorvastatin 10 mg	Simvastatin 10 mg	Extended-release niacin plus lovastatin (1000/40 mg)	Atorvastatin 20 mg	Simvastatin 20 mg
	Week 8			Week 12		
LDL	-38% *	-38%	-28%	-42% *	-45%	-39%
HDL	+20% **	+3%	+7%	+32% **	+6%	+7%
Triglycerides	-28% **	-15%	-10%	-38% **	-29%	-0%
Lp(a)	-16% **	+7%	0	-20% **	+3%	-2%

were prescribing Advicor or planned to start using it soon.

- A Texas family practice doctor said, "The HMO's will force us to use it. Patients will have to fail it before we will be allowed to use other drugs." Another family practice doctor said, "A lot of doctors ignore the importance of HDL. But usage will be affected by pricing and co-pays."
- A Maine PCP said, "I think it will have a role because it will lower LDL quite nicely but also raise HDL which statins don't do. Advicor could be primary therapy in some patients, even though it doesn't have FDA approval for that. But it will be a niche product here in Maine because a lot of my patients already have low HDL."
- A Georgia cardiologist said, "I believe Advicor can do rather well if the price is competitive (i.e., the same or less than the other statins). Otherwise, it is not too difficult for the patient to take a statin tablet plus a niacin tablet."
- A Virginia cardiologist said, "It may be a good option if you know that the LDL is high and can't be brought down with a statin alone. But I will use it infrequently because of the side effects of niacin and because most patients are able to reach goal on Lipitor (Pfizer, atorvastatin)."

Four doctors were considering use of Advicor, but they are taking a slow, cautious approach. Only three doctors have no plans to use Advicor. Two had no comment on future use.

- A New England PCP said, "I need more information before I can decide whether to use it. I haven't been detailed on it yet."
- A Pennsylvania physician's assistant said, "I'll wait and see how well it works and whether there are significant side effects before I try it."
- A North Carolina cardiologist said, "I've heard of Advicor, but I don't have any experience with it. I'm not excited to start this agent. It will be a second line therapy at best. Niacins take too much time. The more drugs you mix together, the more side effects, and you have to worry about liver elevations with niacins…If a patient doesn't tolerate a statin, then I give Niaspan. Almost no one currently is on the combination of Niaspan and a statin."
- A California cardiologist said, "Advicor has excellent potential. I'll use it after more safety data is accumulated. The combination of statins and niacin is potentially serious, with liver toxicity as a major factor. I would want to see clinical safety data prior to putting patients on it."

Most sources predicted that Advicor will be primarily a second-line therapy for patients who could not reach goal on a statin alone. A niacin expert said, "Personally, I would titrate up on (statin) monotherapy and add niacin as a second agent. If the patient does well on that, then I would go to a combination tablet (Advicor). If you start with a combination (Advicor), and the patients have side effects, they won't know which agent caused the side effects, and they might stop the statin. Usually, you don't titrate up the statin and then change to a niacin. Instead, you usually add niacin as a second drug. You could go from directly from the titrated statin to Advicor, but you also need to titrate the niacin. The significant side effect of niacin is flushing, so it is important to start with a low dose and titrate up. (Advicor) will be titrated."

Advicor also is expected to cannibalize Niaspan sales. A California cardiologist said, "I would use Advicor in place of Niaspan, when I need combination therapy with statin." A Maryland cardiologist said, "I use Niaspan all the time but usage is flat. I'm starting to use Advicor, which is wonderful. We are converting our Niaspan patients or adding Advicor instead of Niaspan. Our PCPs are intrigued with Advicor, and they may be willing to use niacin now, in Advicor."