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SUMMARY

Compared to six months ago, use of IDEC's Zevalin is relatively flat, and the outlook is for that to continue over the next three to six months. Nearly half the major medical centers questioned are not using any Zevalin at all yet. Distribution, compounding restrictions, cost, reimbursement, formularies, and referral patterns are all affecting use. When and if Corixa's Bexxar is approved, sources plan to use it, mostly by taking market share from Zevalin, though it may also expand the market somewhat.

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RADIOIMMUNOTHERAPEUTICS FOR NON-HODGKIN'S LYMPHOMA: IDEC'S ZEVALIN AND CORIXA'S BEXXAR

Fourteen oncologists and nuclear pharmacists at major medical centers were interviewed to determine the outlook for IDEC's Zevalin (ibritumomab tiuxetan) and Corixa's Bexxar (tositumomab), radioimmunotherapuetics for non-Hodgkin's lymphoma (NHL). IDEC recently reported Zevalin sales of $5.7 million in the first quarter of 2003, which is only slightly higher than the $5.5 million in the previous quarter. Sources predicted that Zevalin sales will remain sluggish for the rest of this year. When and if Bexxar gets FDA approval, it is likely to take market share from Zevalin, though it could also expand the market slightly.

BACKGROUND

Zevalin was approved on February 19, 2002, but not launched until April 2002. It is labeled for treatment of patients with relapsed or refractory low-grade follicular or transformed B-cell NHL. Shortly after it was approved, IDEC officials predicted that Zevalin sales would "come down to what payors will pay, duration of response and survival." They said Zevalin would be positioned for use in:

- **Rituxan refractory patients** -- non-responders (which is <50% tumor shrinking or time to progression <6 months), estimating that about 75% of these patients would respond to Zevalin. An IDEC official estimated that, at least at first, 99% of Zevalin patients would be Rituxan-refractory patients.
- **Chemotherapy refractory patients**, which were estimated to have a 73% chance of responding to Zevalin and 42% chance of responding to Rituxan. An IDEC official said, "So, from a payor perspective, it would probably be a good argument to try Zevalin first. The community based doctor will have a preference to hold on to patients. So, we see the decision to go to Rituxan or Zevalin being driven by economic considerations in the community-based practice. Doctors lose some revenue when they refer."

Because of the imaging dose, patients need to go to the nuclear medicine department for administration of Zevalin. Thus, IDEC officials said they would be selling to the radiopharmacy sector of the market. About 300,000 patients are being managed with NHL lymphoma today, and IDEC officials estimated the potential market for Zevalin as 75,000, initially, with little or no off-label use because of the cost of the drug.

The pricetag for Zevalin includes (1) drug, (2) isotope (about $500), and (3) compounding fee. An IDEC official predicted that Zevalin use would be: 45% -50% Medicare, 45% private insurance and 5%-10% others (VA, Medicaid), etc. Zevalin reimbursement by Medicare for hospitals is 78% of AWP (unless another contract price is negotiated). For free-standing centers, reimbursement is 95% of AWP.

Reimbursement problems delayed uptake of Zevalin. In May 2002, IDEC claimed that hospitals were not using Zevalin yet because of cash flow problems and that, for paperwork reasons, hospitals wouldn't submit claims until there was a Medicare C-code. IDEC officials insisted that a C-code would make processing easier but was not required for Medicare reimbursement/coverage. They said they expected a permanent and unique J code to be assigned to Zevalin in January 2003, and this would replace the C code. In December 2002 an IDEC official said, "Reimbursement is not like a light switch. We were focused on it, and CMS was, and we had a long, grinding road to garner clarity and get acceptable rates. That occurred in mid-October (2002), but the oncology community was not focused and waiting with baited breath. We are in process of getting the word out…but we are still working through those issues…Basically, we are back to selling the features of Zevalin, working on the trafficking of patients from the oncologist to nuclear medicine. That effort is coming along. It is not 100% greased as we would like to see it, but we've made significant progress in that area. Now, we are sitting down nose-to-nose with medical oncologists on why this is a great drug."

Recently, IDEC said that 24% of hospitals lose money on Zevalin, and 76% make money. The hospitals that make money reportedly are mostly in major metropolitan areas. The company said it is working on a plan that would allow rural treatment centers to at least break even on Zevalin.

As of December 2002, the company claimed 650 centers had the capability to give Zevalin, though only about half had administered even one dose, and an IDEC official said he doubted that the number of centers certified to give Zevalin would even exceed 1,000. Another IDEC official said, "There is a cash flow issue (for hospitals). I think that was a problem. Now, reimbursement is cleared up and hospitals know they won't lose money and will make a little on private pay patients, but there is still reluctance to get too many done. Hospitals who didn't treat anyone are treating a couple to see how reimbursement goes, and those that were doing one or two a month are now doing three or four a month."

IDEC officials denied that the imaging scan before administration of Zevalin was discouraging use of the drug. One commented, "The scans are normally done by nuclear medicine. The biggest challenge we've been facing is working out the logistics networking process to make sure that runs smoothly. Imaging is done not so much to diagnose a tumor but to determine if biodistribution is altered in any way due to other complicating issues, so it is more of a safety check than anything…That is not an issue. Will it go away? The FDA is concerned this is a new, first-in-class product…In our experience to date, we have detected a couple of cases altered by distribution, so as a result of those deliberations, perhaps the agency was correct (in requiring scans). Perhaps there are small, rare situations where they probably shouldn't go on to receive the rest of the treatment. It probably would take large database to convince FDA this should go away."

CURRENT FINDINGS

Compared to six months ago, Zevalin usage is unchanged, and the outlook is for usage to remain relatively flat. Eleven sources said usage over the next three to six months would remain flat, and three said use would increase slightly. A Wisconsin nuclear pharmacist said, "use will increase until Bexxar is approved because of the very good results using Zevalin." An Ohio pharmacist said, "Use will increase a little, would be my guess."

Six of the 14 sources said their hospitals are not using any Zevalin yet, and none of these plans to start. They explained:

- South Carolina. "We aren't using any Zevalin because the company has a business strategy of not allowing the hospitals to compound the product. This is in possible conflict with the Joint Commission standards and with our Medical Center policy in using therapeutic agents like this. This prevents the drug from being admitted to our formulary."
- Oklahoma. "We don't use Zevalin because IDEC will not sell to our pharmacy (directly). They have stonewalled our legal department."
- Texas #1. "I'm convinced it's an excellent product, (but) none of our doctors is interested in it at all. We were really excited about outcomes, and it seemed like a really good product, but I've talked to two friends whose patients really responded poorly as far as cell count, and so they quit referring patients for it…It's expensive, and we were set back on the price – most people are unless they are sure of reimbursement."
- Texas #2. "We're hesitant to try it because of the cost and logistics. I don't think anyone thinks it is worth it."
- New Mexico. "The IDEC sales rep says they are selling 112 units a month, but we aren't using any. The IDEC people made a distribution decision that they were only going to sell to commercial radiopharmacies. That disenfranchised all the trial sites – the people who worked the hardest to give IDEC data. And the model IDEC rolled out eliminated any incentive to use it. Nobody is going to buy something for $25,000 on the possibility that you're going to make $50 or even $100…We've met with all kinds of people to get some explanation (of the

distribution decision) and some easement of that capricious and arbitrary decision, but they were unwilling to bend in any way. They said, 'We have our reasons, and we are not going to change our policy.'"

The other eight centers are using Zevalin, but very sparingly, though three expect a slight increase in the future – at least until Bexxar is approved.

- A Kansas pharmacist said, "We treated 10-12 patients in the clinical trials. We've only treated one or two patients since then. We currently offer Zevalin as one of our radiopharmaceuticals, but in the last few months we haven't had any requests to use it. Use has dropped off considerably since FDA approval."
- An Illinois oncologist said, "We've used Zevalin for three years, but we've only treated two patients in the last two months."
- A Wisconsin nuclear pharmacist said, "We participated in the trials, and we've used it for several years. We've treated four patients in the last two months…We did not use Zevalin for eight months to protest IDEC's marketing of the drug. They will not sell the reagent kits directly to me and are forcing us to buy unit doses from commercial nuclear pharmacies at a cost that is several thousand dollars higher, even though we have an in-house nuclear pharmacy which prepared the unit doses during the clinical trials."
- An Ohio nuclear pharmacist said, "We use it once a month – the same as we did five months ago. If there were no reimbursement problems with Zevalin, we would use it at least once a week."
- A Massachusetts nuclear pharmacist said, "We were in the clinical trials, but we've only treated one patient since it was approved. We haven't had any other requests since then."

Six factors are affecting Zevalin usage, and they are all inextricably linked. They are distribution, compounding restrictions, cost, reimbursement, formularies, and referral patterns. Nuclear pharmacists are still up in arms over IDEC's requirement – which is not an FDA requirement – that the drug be compounded only at specified sites. In September 2002, the head of the American Pharmaceutical Association (APhA), the national professional society of pharmacists, wrote for the second time to IDEC about its distribution of Zevalin. The letter outlined the following concerns:

1. **Inconsistencies in the distribution plan.** "It appears that access is inconsistent, as some pharmacies are able to secure the product, but requests from other pharmacies have been denied."
2. **Patient care issues.** "We have concerns that the timing for the distribution of Zevalin could impact the ability of the patient to receive the medication, which could negatively affect drug therapy due to potential lost doses of the drug."
3. **Exclusion of "certified" medical facilities.** "It is our understanding that various medical facilities that were certified by IDEC to participate in clinical trials of Zevalin are now unable to procure Zevalin directly from IDEC."

Comments by sources indicate these issues will not go away any time soon:

- A Kansas nuclear pharmacist said, "The drug alone is extremely expensive. Reimbursement rates are a big factor. I believe that we are not reimbursed the amount that the drug costs us, but it is close. IDEC's decision not to sell the drug to anyone but Central Nuclear Pharmacies has hurt use of the drug. It has also, in my opinion, increased the cost considerably. If we could, we would buy the drug directly, and then we could and would pass the savings on to the patient."
- A California nuclear pharmacist said, "IDEC's decision to restrict the distribution of Zevalin to institutional sites is an unpopular and disturbing move."
- An Oklahoma pharmacist said, "IDEC is confusing the referring physicians who do want to order Zevalin, and they are jeopardizing patient care."
- An Ohio nuclear pharmacist said, "Zevalin is expensive, and there are reimbursement issues. As best we can tell, we're not even getting reimbursed for what we're paying for the drug. So, every time we use it, we're losing money. The reimbursement levels are not adequate – but that's not why our hospital isn't using more of it."
- A New Mexico pharmacy professor said, "The aggregate cost for Rituxan and Zevalin are similar, but the episodic costs are not the same, so there's a big price barrier. But the main issue is that there is a chasm between the oncologists and the nuclear medicine physicians who do the therapy. Zevalin ties up a therapeutic radiopharmacist for an hour, and there is just too much revenue they can generate in that one hour – e.g., 10 cardiac scans. They can't spend one hour with one patient for $1,000…If medical oncologists want to use Zevalin, they have to send the patient to a nuclear medicine physician, and they give up the revenue. So they lose money, and it is more complicated…(And) there was a tsunami-type shock wave in the industry when people found out the company wouldn't budge (on distribution)."
- A Wisconsin nuclear pharmacist said, "The high cost and competing agents and modalities have to be balanced against very good clinical results (with Zevalin)."

When and if Bexxar is approved, nine sources plan to use it as well as Zevalin.

- California. "We will use both Bexxar and Zevalin. When Bexxar becomes available on the market, the popularity of this intervention will move both agents to the forefront. Expect expansion of their indications in the future, but remember, these agents are of limited appeal."
- Wisconsin. "We will preferentially use Bexxar for two reasons: (1) We are very upset with IDEC because of its marketing, and (2) We also did the Bexxar trials, and we had similar results with less bone marrow toxicity compared to Zevalin. It makes a great a deal of sense to tailor the dose to the individual patient like Bexxar does. It allows the administration of the maximum dose to the tumor while controlling bone marrow exposure."
- Massachusetts. "If doctors request it, we will have it available, too."
- North Carolina. "We were involved in development, and I'm sure we'll use it, but it depends on physician orders."
- Texas. "We probably will try it, but the more difficult a drug is, the less likely our doctors are to use it."
- New Mexico. "Bexxar will have some of the same problems as Zevalin, but the Bexxar marketing people understand that, and they have been trying to work from a nuclear medicine perspective a little more than IDEC. IDEC just thought it could market Zevalin the way it did Rituxan. Corixa hasn't had a non-radioactive drug first, so they worked through nuclear medicine and have a lot more technical support people, so they'll be more successful…IDEC really made some marketing missteps that Corixa is not making. Bexxar will have some of those same issues, but Corixa is working a little harder to make Bexxar more attractive."

Four sources have not made a decision yet, and one source has no plans to use Bexxar.

- South Carolina. "We will evaluate the cost and efficacy and make a decision on its rational use."
- Kansas. "Bexxar would seem to be a reasonable alternative for those states that are NRC states. Those of us that are Agreement States, in most cases, are not allowed to release patients from the hospital if they receive more than 30 mCi's of 131-Iodine. In that case, even if Bexxar were considerably cheaper and we could buy the drug directly, the cost of doing the procedure might still be prohibitive because the patients would be hospitalized for several days as an inpatient. I would hope that the makers of Bexxar would not limit its sales like Zevalin, but that remains to be seen."
- Ohio. "It depends on reimbursement…***I wouldn't be surprised if we'll see more use of Bexxar than we do of Zevalin."***

How does Bexxar compare to Zevalin? A source explained, "Zevalin Y90 will be better for solid tumors, but NHL is not a classic solid tumor model, so you might find differences that make Bexxar better -- less toxic, better outcome. (But) Zevalin doesn't cause as much myelosuppresion…Bexxar is manufactured as a ready-to-use drug, compared to Zevalin which has to be compounded. There have been a lot of radiolabeling problems with Zevalin recently that the tech support people at IDEC can't seem to resolve. Those things won't happen with Bexxar. Bexxar also is manufactured by a commercial firm with reportedly high quality, but you'll have the same logistic issues." Another source said, "Bexxar is probably a bit easier, simpler, to use, so it would have advantages in that regard. Zevalin is a little more complicated, but not awful, to administer."

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