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Quick Pulse

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FDA's Dermatologic and Ophthalmic Drugs Advisory Committee Meeting on Allergan's Tazoral for Moderate-to-Severe Psoriasis

Gaithersburg, Maryland
July 12, 2004

Allergan is seeking FDA approval of Tazoral (oral tazarotene 4.5 mg) for the treatment of moderate-to-very severe psoriasis, and the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee agreed the drug is effective, but only in moderate-to-severe, not very severe, psoriasis. However, the panel did not believe the benefits of Tazoral outweigh the risks, particularly teratogenicity and bone loss. The panel strongly urged that Tazoral be a part of the same risk management program as other marketed retinoids. That program was recommended in February 2004, but patent issues have delayed implementation. Several panel members also want to see a concerted effort by Allergan to show it will discourage off-label use of Tazoral in acne.

Tazoral still may gain FDA approval, but the issues will be:

- Approval of Tazoral could be delayed until the patent issues with other retinoids – e.g., Roche's Accutane (isotretinoin) for acne and Connetics' Soriatane (acitretin) for psoriasis – are resolved, so a unified risk management program can be implemented for all retinoids. It is unclear whether Allergan is affected by the Celgene patent on its Thalmid (thalidomide) risk management program, S.T.E.P.S., that is holding up the new retinoid program, but it is likely that Tazoral will be affected.
- If Allergan is not affected by the patent dispute, it might be able to launch on approval with its own PACT risk management program, but Tazoral then would have a label that initially is worse than Soriatane. However, the playing field would even up when the unified risk management program is implemented.

The FDA Perspective

The FDA appeared to be asking the advisory committee for guidance on how restrictive the label for Tazoral should be more than whether or not it should be approved. The FDA's position was that the label should be fairly restrictive, especially as it relates to pregnancy, and the agency made this clear in its opening statements. An FDA official said, "We have a major focus on fetal exposure…but we are also looking at the benefit/risk on this product."

Among the points the FDA made about Tazoral:

- **Doses.** Allergan is asking for two doses: 1.5 mg and 4.5 mg, and the FDA said the request for the 1.5 mg dose was due, at least in part, to concern with compliance at the 4.5 mg dose.

- **Long-term safety.** Safety and efficacy beyond 52 weeks has not been established.
- **Half-life.** The half-lives of tazarotene (6.68-11.8 hours) and its metabolite (mean 63 hours) are much shorter than Roche's Accutane and Soriatane.
- **Male reproduction.** Tazarotenic acid can be found in semen in a 1:1 ratio with that of the plasma. There was no impairment of mating performance or fertility observed in male rats, but sperm count and density was reduced.
- **Teratogenicity.** In animal studies, tazarotene appears to be a more potent teratogen than other retinoids. Tazoral was a teratogen in rats and rabbits, and more teratogenic in rabbits than rats. It was described as a potent human teratogen. The maximum recommended human dose is 0.075 mg/kg/day for Tazoral, 0.83 mg/kg/day for Soriatane, and 2.0 mg/kg/day for Accutane. Four pregnancies have occurred in trials, one in a psoriasis trial (study 050P) and three in acne trials. The psoriasis pregnancy was electively terminated. In the acne trials, there was one elective termination, one spontaneous abortion, and one normal delivery of a healthy baby.
- **Carcinogenicity.** Cell and animal studies found no carcinogenicity risk.
- **Side effects.** Only cheilitis remained a statistically significant adverse event post-treatment. Overall decreases in bone mineral density (BMD) were seen in up to 17% of patients on Tazoral. In Study 048P, four patients on Tazoral and one on placebo had decreases in BMD of >5%. All were men aged 40-69. In addition, there was one patient who had a decrease of 50%. This is significant because men lose bone density at a rate of only 0.5%-0.75% per year and women lose bone density at a rate of 1.5%-2% per year. Thus, a loss of even 1%-3% over 36 weeks implies a greater than normal bone loss over a year. Over a period of five to 10 years of treatment, this could be significant.
- **Off-label use.** Potential off-label use in acne is a concern. Tazorac, gel and cream forms of tazarotene, currently are marketed by Allergan for acne as well as psoriasis. The FDA is concerned that presentations at scientific meetings and a journal article published this year on the use of Tazoral in acne could encourage off-label use for acne.
- **Efficacy.** Patients with moderate disease showed the most success over placebo. There was no efficacy in nail psoriasis, but a subgroup analysis showed efficacy in scalp psoriasis.
- **Gender effect.** There is a gender effect in the efficacy results. Even though there were more men in the studies, the response rates of males were lower than those of females.

Of all the issues raised about Tazoral, the FDA did ***not*** appear to be questioning Allergan's use of the Overall Lesion Assessment (OLA) scale, which was developed in 1997 through a collaboration between Allergan and the FDA when Allergan was seeking approval of Tazorac (tazarotene), a topical cream therapy for psoriasis.

FDA Review of Tazoral Efficacy in Trial 049P at Week 12

Measurement	Tazoral n=182	Placebo n=187	p-value
OLA Score			
Primary endpoint: 0 or 1 (by ITT)	18.7%	4.8%	<.001
0 or 1 in patients with moderate psoriasis	19.8%	5.6%	<.001
0 or 1 in patients with severe psoriasis	17.5%	3.6%	0.016
0 or 1 in patients with very severe psoriasis	0	0	N/A
0 or 1 in U.S. patients	21.3%	7.3%	0.003
0 or 1 in non-U.S. patients	14.9%	1.3%	0.002
0 (none)	3.8%	1.1%	---
1 (minimal)	14.8%	3.7%	---
2 (mild)	35.7%	11.2%	---
3 (moderate)	33.5%	54.5%	---
4 (severe)	12.1%	27.3%	---
5 (very severe)	0	2.1%	---

FDA Review of Tazoral Efficacy in Trial 048P at Week 12

Measurement	Tazoral n=166	Placebo n=171	p-value
OLA Score			
Primary endpoint: 0 or 1 (by ITT)	15.7%	3.5%	<.001
0 or 1 in patients with moderate psoriasis	19.0%	2.9%	<.001
0 or 1 in patients with severe psoriasis	10.9%	3.2%	0.164
0 or 1 in patients with very severe psoriasis	0	33.3%	1.0
0 or 1 in U.S. patients	16.2%	2.0%	<.001
0 or 1 in non-U.S. patients	14.9%	5.8%	0.078
0 (none)	2.4%	1.2%	---
1 (minimal)	13.3%	2.3%	---
2 (mild)	36.7%	11.7%	---
3 (moderate)	38.6%	55.0%	---
4 (severe)	8.4%	28.7%	---
5 (very severe)	0.6%	1.2%	---

FDA Review of Second Course of Tazoral

Measurement	First course of Tazoral	Second course of Tazoral
Discontinuations	3.2%	6.5%
Back pain	7.7%	17.4%
Arthralgia	14.1%	33.7%
Alopecia	0.9%	5.4%

FDA View of Long-Term Data on 4.5 mg Tazoral

Measurement	Week 52
Median duration of exposure	271.8 days
≥1 adverse event	98.9%

FDA Review of Tazoral Safety

Measurement	Tazoral 4.5 mg: n=831* 1.5 mg: n=156	Placebo n=383	p-value
Adverse events	90.2%	74.6%	<.001
Drug-related discontinuations	3.4%	2.5%	---
Decrease in BMD	17%	N/A	---
Adverse Events in Treatment Period			
Headache	18.7%	12.0%	<.05
Back pain	.6%	2.8%	<.05
Foot pain	2.9%	0.8%	<.05
Cheilitis	65.5%	16.8%	<.05
Arthralgia	17.5%	7.3%	<.05
Myalgia	14.7%	8.4%	<.05
Joint disorder	4.0%	1.1%	<.05
Nasal dryness	3.7%	1.1%	<.05
Dry skin	23.6%	14.8%	<.05
Rash	2.9%	0.6%	<.05
Dermatitis	1.4%	0	<.05

*From 2 pivotal Phase II trials and 2 open-label trials

FDA Examples of Drugs with Restricted Distribution

Manufacturer	Drug	Restriction
Actelion	Tracleer (bosentan)	Available through specialty pharmacy distribution
Corcept	Corlux (RU-486, mifepristone)	Available through specialty pharmacy distribution
Novartis	Clozaril (clozapine)	Available only through registered pharmacies
Celgene	Thalmid (thalidomide)	Available only through registered pharmacies

THE COMPANY PERSPECTIVE

Among the points Allergan officials and experts made in its presentation:

Disease. Psoriasis is a life-long disease, many patients are untreated or poorly treated, and more treatment options are needed.

Efficacy. Efficacy was shown in several ways.

- The primary efficacy endpoint of clear or almost clear: 15%-20% at 12 weeks. The two pivotal trials had very similar results. In fact, all the trials of Tazoral mimicked each other in efficacy.
- Decrease in body surface area ≥10% was 30%-40%, with a peak at 12 weeks that was sustained post-treatment.
- Physicians' Global Assessment of ≥50% was 54% at Week 12 and 43% in the post-treatment period.
- Physicians' Global Assessment of ≥75% was 30% at Week 12, which was sustained at that rate in the post-treatment period.

Safety.

- Four pregnancies occurred in the trials, none with fetal abnormalities. Only one went to term, and that resulted in a normal birth and fetus.
- The most common side effect is cheilitis, and it is mostly mild.
- There is some elevation of triglycerides, but those elevations are modest.
- On bone, DXA exams found no differences in the median percent change in spine or femur. In the hip there was a small but statistically significant ***increase*** in BMD, but this was not considered clinically meaningful and may or may not be due to normal variation in this population.
- There is some increase in arthralgia, myalgia, and possibly headache with continued treatment. Longer term, there is an increase in alopecia (<8%), which is less than with other retinoids but higher than in placebo trials.
- Alcohol is not an issue with Tazoral, as it is with methotrexate.

Tazoral Drop-Outs

Measurement	Drop-outs due to adverse events
In pivotal trials	<5%
In 6-month trials	6.5%
In open label, one-year study	15%

Risk management program

The PACT program that Allergan outlined to the panel was a slightly tougher program than it originally proposed and which members had in their briefing documents. Allergan proposed:

- A mandatory registry for ***all*** patients. Originally, this was just for women of child-bearing potential.
- Mandatory registration certification for doctors and pharmacies.
- Verification of all patients at the pharmacy (another change). Before, it was only for women of child-bearing potential.
- A lab-based pregnancy test.
- Managed access. This is the main change. Allergan is recommending women of child-bearing potential get a 1-month supply with no refills. Others would be allowed up to two refills.

- A pregnancy exposure registry designed with FDA guidance. This includes a pro-active study to follow each pregnancy through its duration.

An Allergan official said, "The acne (risk management) program is for six months. Psoriasis is a life-long disease. Requiring a patient to come in every month is burdensome to patients and to health economics. The majority of our patients are >age 40. You could have unintended consequences of the doctor not prescribing treatment or a patient not coming in or getting a drug that has a possibly less safe profile or getting no systemic therapy when it is needed…We want to protect the vulnerable population, but we want a practical program…We also wonder, propose, that there be **the same program for all retinoids to avoid confusion in the marketplace**."

ADVISORY COMMITTEE CONCERNS

Initially, the panel seemed positively inclined toward Tazoral, but as the day wore on, their attitude took a clear turn to the negative, with teratogenicity the huge concern. Panel questioning focused on:

Risk management program for teratogenicity. An FDA official said the generic and innovator firms have been working very well together on this, but patent issues over Celgene's S.T.E.P.S. risk management for Thalmid (thalidomide) program are delaying implementation of a new, uniform program for all retinoids, which this same FDA advisory committee recommended at a meeting in February 2004. S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety) was developed by Celgene in cooperation with the FDA as a way to allow use of thalidomide without exposing fetuses to that highly teratogenic drug. This mandatory program includes a restrictive distribution system for prescribing and dispensing Thalmid. Celgene has multiple issued patents that cover the S.T.E.P.S. program, and a Celgene SEC filing described the patent protection this way: "S.T.E.P.S. is protected by a business patent covering controlled distribution systems that register pharmacists, patients, and physicians who have agreed to follow the safety program. It includes systems that track compliance and authorize each prescription based on confirmation of compliance. S.T.E.P.S. is designed as a blueprint for pharmaceutical products that offer life-saving or other important therapeutic benefits but have potentially problematic side effects."

- An FDA official said the FDA Chief Counsel is trying to work out the patent problems, "The patent issue is potentially quite large…The patents cover both products where fetal toxicity is of concern as well as any potential adverse effects or contraindication…This is the first time we've encountered a situation like this…Our lawyers are studying this, but it appears it may pose some obstacles to implementation of the modified program as you recommended and as we have been pursuing."
- An Allergan official said their PACT program differs from the SMART program used with Soriatane in that it calls for "not just a pregnancy test but also a response to the pregnancy test." However, Allergan's PACT program also may be affected by the patent issues.
- A panel member said, "We are taking another step in teratogenicity (with Tazoral)…Soriatane has a spectacular effect, so very few doctors give it to women, and that is why we have been safe from much of the teratogenicity of that drug…On the other hand, we are talking of a drug (Tazoral) that would be given indefinitely to women of child bearing potential…I don't know how well we can expect (contraception to be perfect long term)…If this were wonderfully efficacious, maybe it would be worth it …but it is not…And teratogenicity is very serious."

Negative effects on bone. Two committee members expressed concern about the effect of Tazoral on bone mineral density.

- One panel member said, "What we are looking for is low frequency, idiosyncratic events…These data don't tell us this drug is not bad for bones or it is bad for bones. We have to live with that uncertainty. We can look at this data five ways from Sunday and come to opposite conclusions…These are one-year data for a chronic disease that has an average duration in severely affected patients of 40-60 years…So, we are looking for a little signal…If we had one patient who went from normal to osteoporosis, we probably wouldn't be meeting here today. We have to look for subtle signals…and I don't find this one-year data terribly reassuring."
- Another panel member said, "I agree…but this is a class of drugs we have 20 years of experience with, and we are not seeing anything outside of what we would expect from the class with them…We have a signal from the lab…From years of retinoid use, I've rarely seen alkaline phosphatase increase with other drugs (retinoids)…The sponsor didn't pursue more clarification...and as much as we want to dance around the data…We have another signal indicating a problem with bone metabolism…Far too few people are in your studies now…While we need alternatives (to treat psoriasis), we also, as clinicians, need to offer things we are sure are safe long-term."
- An Allergan official countered, "We aren't saying you don't detect a signal, but we are saying the risk is minimal, not certain."
- Dr. Mark Lebwohl, a dermatologist and Allergan psoriasis expert, said, "The amount of data on BMD here compares very favorably to other retinoids that are available on the market now. We have a long history of their use, with a large number of patients...In those patients…I don't doubt there is an amount of BMD loss that can be found, but it is not clinically significant…We are not seeing the fractures that we see with steroids."

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FDA Overview of Psoriasis Therapies

Type of drug	Example	Degree of psoriasis	Efficacy	Side effects	Comments
Topical Therapies					
Corticosteroid	Clobetasol propionate lotion	Moderate-to-severe	36.6% clear/almost clear at 4 weeks (placebo 0)	Skin atrophy, burning and stinging, suppression of hypothalamic-pituitary-adrenal axis	Mainstay of treatment since 1952; often first-line
Vitamin D analogue	Calcipotriene cream, ointment or scalp solution	Cream and ointment: plaque psoriasis Scalp solution: moderately severe	Marked improvement at 8 weeks: cream: 50% ointment: 49.6% solution: 31%	Cutaneous: burning, stinging, itching, skin irritation, tingling	---
Retinoid	Allergan's Tazorac (tazarotene gel)	Moderate	75% improvement from baseline at 12 weeks: 18%-28% at 0.05%; 25%-38% at 0.1% (placebo 10%-12%)	Cutaneous: pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, skin pain	Pregnancy category X product
Phototherapy (chemo)	Narrow and Broadband UVB (with psoralen)	Moderate-to-severe	Very effective in refractory psoriasis	Acute sunburn reaction, time consuming, increased risk of skin cancer	Narrow is now thought to be more optimal
Oral Therapies					
Folic acid antagonist	Methotrexate	Severe, recalcitrant psoriasis	Maximum benefit at 8-12 weeks: >75% improvement in 90% of patients	hepatotoxicity, leukopenia, anemia, thrombocytopenia, interstitial pneumonitis, stomatitis, alopecia, nausea/vomiting, photosensitivity, burning	Contraindicated in nursing mothers, alcoholics, liver disease, immunodeficiency syndromes, blood dyscrasias. Pregnancy category X product
Immuno-suppressant	Novartis's Neoral and Sandimmune (cyclosporine)	Severe, recalcitrant psoriasis	Clear/almost clear at 16 weeks: Neoral 58% Sandimmune 50%	Possibility of irreversible renal damage, hypertension, headache, hirsutism, hypertriglyceridemia, parathesia, flu-like symptoms, diarrhea, nausea/vomiting, lethargy, arthalgia	---
Retinoid	Connetics' Soriatane (acitretin)	Severe psoriasis (adults only)	N/A	cheilitis, alopecia, skin peeling, dry skin, pruritus, rhinitis, xeropthalmia, arthralgia, hypertriglyceridemia, decreased HDL, hypercholesterolemia, liver enzyme elevations, hepatitis, jaundice	Pregnancy category X product. Pregnancy contraindicated for 3 years after discontinuation. Alcohol contraindicated for 2 months after discontinuation.
Retinoid	Allergan's Tazoral (oral tazarotene)	Moderate-to-very severe psoriasis	15.7%-18.7%	TBA	TBA
Biologics					
Biologic	Biogen's Amevive (alefacept)	Moderate-to-severe psoriasis	Clear/almost clear at 12 weeks: 11% at 7.5 mg 14% at 15 mg	Dose-dependent reduction in CD4+ and CD8+ T lymphocytes, increased risk of malignancies, infection, lymphopenia, hypersensitivity reactions	CD4 cells must be monitored before and during therapy
Biologic	Genentech's Raptiva (efalizimab)	Moderate-to-severe psoriasis	N/A	N/A	---
Biologic	Amgen's Enbrel (etanercept)	Moderate-to-severe psoriasis	N/A	N/A	---

Likely off-label use of Tazoral for acne. An Allergan official said the company has done Phase II trials of Tazoral in acne but has no plans at this time to start Phase III trials or pursue that indication, "We did a Phase II dose-ranging study, and showed some efficacy…Whether that meets the criteria for approval is not known…We are currently not pursuing a Phase III program for acne…It is a leap of faith to believe 75% of the oral tazarotene would be used for acne without approval…(For Phase III) the FDA wants a head-to-head trial with isotretinoin (Accutane) for five-six months, followed for one year, and that would be an incredibly large study. That study would be so onerous that the company is not sure – given the results of the Phase II trial – that at this point we want to do that…The Phase III designs we've discussed with the FDA – and I'm not saying what they asked for is wrong – are not something that we are sure we can do, as a mid-to-small pharma company."

Name confusion. There is some concern on the panel on the name Tazoral and possible confusion with Tazorac. An Allergan official said the company has started new name testing and is willing to change the name, if necessary.

THE ADVISORY COMMITTEE'S DECISIONS

The FDA posed four key questions to the panel.

1. **Based on the clinical studies, is there adequate evidence for the effectiveness of Tazoral in moderate-to-severe plaque psoriasis? YES, unanimously.**
2. **Is there evidence of efficacy for very severe psoriasis? NO**
3. **Has the safety profile been adequately assessed, with respect to bone, triglycerides, teratogenicity, and long-term safety? NO**
4. **Do the benefits of Tazoral outweigh the risks for the proposed population with moderate-to-severe psoriasis? NO: Vote was 4 abstentions, 3 Yes, 9 No**

The panel clearly expressed the desire for Tazoral to be a part of the same risk management program as other marketed retinoids. An FDA official commented, "I think we've heard a fairly consistent message that you want a consistent program across the retinoids…and a high probability that this is an equivalent teratogen to other marketed products." Several panel members also wanted to see a concerted effort by Allergan to show it will discourage off-label use of Tazoral in acne. ♦