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"Tentative Approval": Understanding the FDA Ruling on Once-Nightly Sodium Oxybate

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Tentative Approval: Understanding the FDA Ruling on Once-Nightly Sodium Oxybate" is provided by Prova Education.

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Ms. Koblitz:
On July 18, 2022, once-nightly sodium oxybate for the treatment of narcolepsy received, quote, tentative approval from the FDA. Yet even though the FDA determined that the product meets the substantive requirements for approval, the company that developed it was not allowed to bring it to market. This delay was not the result of concerns with the product's manufacturing process, efficacy, or safety; these were not in dispute. FDA had determined that once-nightly sodium oxybate had demonstrated benefit in clinical trials based on its efficacy and safety in treating narcolepsy. No, this delay was based on a patent issue related to another manufacturer's risk evaluation and mitigation strategy, or REMS.

This is CME on ReachMD. I'm Sara Koblitz, attorney of Hyman, Phelps & McNamara. Before we get started, I should say that we have represented both of these entities, although our firm was not involved in this matter, and my comments today are based solely on publicly available information. With that out of the way, with me today to discuss this set of events is Dr. Michael Thorpy. Welcome.

Dr. Thorpy:
Good. Thank you, Sara.

Sara as a clinician, we're very familiar with the terms of a drug being either approved or not approved by the FDA. However, we're not that familiar with the term tentative approval. Can you explain a little bit about that?

Ms. Koblitz:
So tentative approval is a notification that a product is ready for approval for purposes of safety, efficacy, and quality, but that the product is not yet approvable for legal reasons. In other words, FDA will issue a tentative approval letter if a new drug application otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act. But there are patent or exclusivity issues that prevent FDA from doing so. Final approval will only be granted once any blocking patents or exclusivity have been extinguished or otherwise resolved.

Usually, we see tentative approval in the context of generic drugs. But it also arises in the context of a new drug approved in a hybrid application, called a 505(b)(2) new drug application, that builds off FDA's findings of safety and effectiveness for other drug products called the reference listed drug. This is because wherever there is reliance on a reference listed drug, patent and exclusivity protections govern approval, regardless of the safety and efficacy profile of the drug product.

Dr. Thorpy:
So we have absolutely no issue regarding the safety or the efficacy of once-nightly sodium oxybate. Sodium oxybate has been around a

long time; it's actually been available since about the year 2000. And so there's a lot of data with regards to the safety and efficacy of this product. And it's been used in a countless number of patients. This is not a generic or supplemental new drug application issue.

Ms. Koblitz:
Dr. Thorpy, can you give us some more details about the REST-ON trial?

Dr. Thorpy:
Sure. The REST-ON trial is a trial that was done with sodium oxybate. But it was done with a once-nightly formulation of sodium oxybate. Up until this time, the only form of sodium oxybate is a form that's given twice at night, once at the beginning of the night, and once in the middle of the night, 2.5 to 4 hours later. So this is a different formulation that allowed it to be given only once at the beginning of a night.

Now in the study, there were some 222 patients with narcolepsy. They were patients who had both cataplexy and didn't have cataplexy. So type 1 narcolepsy and type 2 narcolepsy patients. The majority were type 1 who had cataplexy. So we were able to look at that.

So in the study, there were 3 main endpoints to the study, one looking at excessive sleepiness. And this was measured by the Maintenance of Wakefulness Test, which is an objective test for sleepiness to see whether patients are more alert on the medication. And then there was also the Clinical Global Impression Scale of Change. And this is where the clinician rated whether the patient was improved if they were taking the medication. And thirdly, there is the cataplexy, the mean number of cataplectic episodes per week. Now the once-nightly formulation was compared with placebo, and it was a parallel design study so that both the placebo and the active drug were titrated up. So with regards to the main drug, the once-nightly formulation, it went from 4.5 g to 6 to 7.5 and then to 9 g. And then it was continued on at 9 g for a period of approximately 5 weeks after getting to that higher level.

Now the results of the study showed that there was a statistically significant improvement in alertness with the once-nightly medication compared with the placebo. And also the Clinical Global Impression Scale of Change was much more improved in the patients on the active medication. And the number of weekly cataplectic episodes were reduced. So these 3 endpoints were statistically significant.

In addition, there was the Epworth Sleepiness Scale. And this scale also showed additional improvement in the excessive daytime sleepiness.

Now the safety profile of the medication was much the same as we've known for oxybate in the past, so that some nausea headache anxiety were exhibited by some patients. But it was no more than what we see with regular sodium oxybate. So overall, this study showed that once-nightly sodium oxybate could be effective at treating excessive daytime sleepiness and cataplexy in patients with narcolepsy and that there was a good safety profile.

Ms. Koblitz:
So my understanding is that this product has a new formulation to meet the needs of patients that need a once-nightly dose rather than a twice-nightly dose of the product that's available on the market currently; is that correct?

Dr. Thorpy:
Yeah, that's right. So it gives a greater opportunity for patients who have narcolepsy.

So if once-nightly sodium oxybate's efficacy and the safety are not the issue, why was the product not approved for marketing? If you could break down the FDA process of approval for us, that would help us understand this process much better.

Ms. Koblitz:
So FDA approval hinges on the safety and efficacy of a proposed drug product. But for drugs that are generic versions or modified versions of previously approved moieties, like here with a once-nightly version rather than a twice-nightly version, patent and exclusivity issues can dictate timing. Here, the once-nightly version, Lumryz, is a modified version of Xyrem that's dosed twice. But because the application, quote, referenced Xyrem as the reference listed drug, the reference listed drug sponsor can litigate certain listed patents, which are patents that are listed in FDA as a resource called the Orange Book, prior to follow on product launch. And that's exactly what happened here.

The issue was a patent issue. As Jazz had listed a patent covering REMS in the Orange Book requiring Avadel to tell FDA whether the REMS would be infringed by the launch of the proposed drug product. FDA plays a ministerial role here and just takes at face value what the reference listed drug sponsor says the patent covers. Avadel, who sponsored Lumryz, made several legal arguments as to why the REMS patent should not have been listed and, therefore, not asserted pre-launch, but FDA would not address the issue. Ultimately, Jazz sued Avadel on the REMS patent, and Avadel countersued Jazz, arguing that the REMS patent should never have been listed in the first place.

On November 18, 2022, the US District Court ordered Jazz Pharmaceuticals' sodium oxybate REMS patent delisted from the Orange Book. Jazz has appealed and has been granted a stay until the appeal has been resolved. That means that if the REMS patent is delisted from the Orange Book, that it should not have been litigated before launch of the Avadel product. Jazz has appealed the decision that directs it to delist the patent and has been granted a stay until the appeal has been resolved. Because of that, we can't say that Avadel will be able to request that FDA convert its tentative approval to final approval until at least the new year when the litigation has subsided. But we're looking at probably a couple months into the new year given the briefing necessary for the Federal Circuit to decide. But at the latest, final approval will come at the expiration of the patent in question, which is June 2023.

Dr. Thorpy:
Well, we're all eager for this patent issue to be resolved so that this medication is available to us in June 2023.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Michael Thorpy, and here with me today is Sara Koblitz, attorney. We're just about to delve deeper into the tentative approval status of the pending treatment for narcolepsy.

Ms. Koblitz:
Dr. Thorpy, can you tell us about how these non-drug issues that are the basis of the delay in the FDA approval of once-nightly sodium oxybate are impacting clinical practice and patient care?

Dr. Thorpy:
Well, Sara, narcolepsy is a disorder that's a very difficult disorder to treat. Unfortunately, there is no cure for it so that patients have lifelong symptoms. And we are greatly concerned about being able to try to get the most effective treatment for our patients. We want to meet their needs in terms of improvement of their overall function, their cognitive function, and their psychosocial function. So we need to have medications that give us options for patients. And with once-nightly, it can make a big difference to patients because of the ease of their taking this medication so that this medication can really make a big difference to patients because they don't have to wake up in the middle of a night to take a second dose of a drug. So many of our patients have expressed to us already that they're eagerly looking forward to this medication, because it will be much easier for them. Some patients have great difficulty in waking in the middle of the night to take a second dose of oxybate. But with the once-nightly formulation, of course, it makes it very much easier for them.

So we're hopeful that this medication will become available to us as clinicians. It's going to give us a great treatment option for our patients. And we're going to find that patients will be more effectively treated if they're able to get this medication.

Ms. Koblitz:
So the issue behind the delay in the approval of the once-nightly sodium oxybate for narcolepsy was never about its safety and efficacy, as demonstrated from the data that Dr. Thorpy presented. It was a patent issue, which strikes us a little bit as it's part of the balance between incentivizing innovation and access to medicines, which puts FDA in a little bit of a sticky situation, where it has these drugs that are safe and effective and ready for approval, but given the need to protect innovation and incentivize innovation, FDA is stuck waiting on these products – the patent expiration and exclusivity expiration – to approve it. In other words, there's nothing about this tentative approval that suggests there's a problem with safety and efficacy.

Before we wrap up, what's your take-home message for our audience, Dr. Thorpy?

Dr. Thorpy:
Well, I think this whole process has been very disappointing for our patients because they've known that this medication has been available from the clinical research studies, and that it has the same, efficacy and safety as regular sodium oxybate, but they haven't been able to get access to it.

The availability of this once-nightly formulation of sodium oxybate is really going to make a big difference to patients. And patients have been eagerly waiting for this medication. And so soon, we should have it available to us. It's going to make life very much easier for our patients with narcolepsy, in that they don't have to wake up in the middle of the night to take a second dose. And we know that oxybate is a very effective drug for the treatment of narcolepsy.

We're really hopeful that in the middle of next year, in June, that this process will be over and that this drug will become available to our patients, because it really will make a big difference to the quality of their life if they're able to have access to this once-nightly formulation of sodium oxybate.

Ms. Koblitz:
The FDA approval process is just much more complicated than just the safety, efficacy, and quality of the product at issue. Unfortunately, there are significant legal issues involved which delay access to medicines for a lot of needy patients. But until those legal issues are resolved, particularly patent and exclusivity issues, FDA cannot approve a product. It's simply not in accordance with the

statute to do so.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Michael Thorpy, for joining me and sharing all of your valuable clinical insights. It was great speaking with you today.

Dr. Thorpy:
Thank you, Sara. I enjoyed it.

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