Hypoparathyroidism Association International Patient Conference

Takeda Q&A Session Summary

Bob Sanders, Hypoparathyroidism Association Board Chairman, welcomed all participants, thanked Takeda for attending and asked all to not record the session, as The Hypoparathyroidism Association would provide a summary.

Participants were introduced (bios are included as Appendix to these notes):

- Dr. Tom Koutsalis, VP and Head of US Medical at Takeda
- Cheryl Schawartz, Sr. VP and Head of US Hematology and Rare Disease
- Dr. Mannstadt, Chief of Endocrine Unit at Massachusetts General Hospital and Associate Professor in Medicine at Harvard Medical School

Danette Astolfi (Hypoarathryoidism Association Treasurer, pharmaceutical development professional and Natpara user) initiated the session with a commentary on the drug development process and how it applies to the recall of Natpara:

Natpara is a combination product, which means that there is both a drug and a device component. For a combination product, full development is done on the drug, on the device and on the combination of the 2 together. All these studies and their results are submitted to FDA in order to receive approval. When the product is approved, it is only approved according to *exactly* what was submitted (the manufacturing process and specifications, the dose, the label). So, while the rubber septum seems like a simple problem to fix, the Regulatory landscape requires that any changes be fully studied and characterized before FDA will consider approving them. Therefore, Takeda can't simply change out the septum or change the device. These may be potential solutions, but they will need to be done step-wise according to regulations and with agreement and oversight from FDA. Takeda is doing everything they can and are working closely with FDA to develop a mitigation plan and with the Hypoparathyroidism Association to understand the needs of the community at this time. Some questions that were submitted touched on this topic:

Q Why can't we use another device for Natpara (syringe, vial, other device)?

A That may be a solution long-term, but any change to the device or administration would need to be studied and approved before it could be marketed. Any solution that in any way requires a change to the Natpara product would require studies and approval. The type of studies needed depends on what the specific change is.

Q Why wasn't Natpara recalled in Europe?

A Every country has a different Regulatory authority. In US it is FDA and in Europe it is EMA. They evaluate drugs entirely independently. They can dialogue about a situation and work together, but they can also have differing opinions, leading to different outcomes in different regions.

Q Why can't we sign a waiver that we accept the risk of the particle?

A It is up to FDA to determine if the risk-benefit of a drug is appropriate for the market. As this is a new piece of information, the first step is for FDA to fully understand and characterize the risk. It's important to realize that FDA is not looking at this problem in isolation. They aren't looking at this as a rubber septum problem. They're looking at is as a rubber septum problem on a drug we know a lot about. We know this is a drug that has a black box warning, it has a REMS, it has

some other safety concerns and it isn't first line therapy. There's a lot to consider when evaluating if or how this rubber septum issue changes the overall risk profile of Natpara. As we move forward with the recall, if information changes that could change their opinion, but until there is any new information, FDA is looking at this in the context of what is already known about the drug, the device and the combination product.

It was noted that a recall decision does not reside with the manufacturing company, but with FDA. If something shows up in QC testing that is not exactly as defined in the application for approval, FDA needs to be notified and FDA will make a recommendation whether to recall. Although it is termed a voluntary recall, there is not an option to not recall a product if FDA recommends doing so, as FDA would take measures to remove the product from market anyway. FDA is also responsible for assigning a classification of a recalled product.

Q Why did FDA consider this a Class 1 recall?

A The concern is that if you are taking Natpara and your needle clogs due to an issue with the rubber septum, you would not receive your full dose and you could unexpectedly have a hypocalcemic event that could cause a life-threatening situation. FDA considers that it is safer for patients to have a *planned* transition off Natpara- under the guidance of a physician and with appropriate monitoring- and to go back to the medication they were taking before Natpara than to unexpectedly and unknowingly miss a dose of medication.

Q Have there been any issues seen caused by underdosing because of the rubber septum?

At this time, Tom introduced himself and thanked The Association for having Takeda come to the conference in order to answer some questions. He commented that Takeda's commitment to the hypopara community and to Natpara is the strongest commitment he can give to us. He has been with the product since the early days and understands the impact it has had in the community. Takeda has been devastated by this situation and is behind the community 100% and will continue to be there in the future. Tom explained that his very first patient in medical school was a patient with hypoparathyroidism who influenced his view of his career; that memory remains strong with him and drives his commitment to this community. While he cannot be in our shoes, he is with us and understands.

In terms of timelines, one of the things Takeda is trying to do is fix this issue in the long term; that is the priority. The quickest thing that can be done is to change the septum. Even that is a rigorous process; and it should be because it is important that this be done the right way. Takeda is working with FDA on a daily basis and there is a real partnership to resolve this as quickly as possible. In terms of the recall, the main point is that FDA has concerns for patient safety. The risk of patients are not receiving the dose of medication that they think they are getting is severe and this needs to be remedied before the drug can return for broad use. The particles were seen and flagged a few months ago during routine quality testing, which initiated the evaluation process. This evaluation and solution process is a team effort with Takeda and FDA with the goal of thoroughly resolving the issue. There was, of course, concern about critically ill patients who need a solution in the short-term. That is how the Special Use program came about. This was to develop the fastest solution possible while Takeda is still working on all parallel tracks to return Natpara to the market. Takeda was able to work with FDA to develop the single use option for these patients to avoid any life-threatening situations. One of the major challenges is that 1 month supply of

single use program is a year supply of product, so it does have to stay relatively limited to ensure there is a reliable supply for those patients who are incredibly ill.

Q Why don't you just offer single use to all of us? There are only 2700 patients in the US.

A Unfortunately, we just simply would not have enough product to offer it to everyone. The teams are working 24/7 to make this as fast as possible and it would not be enough to supply all patients with single use. We are processing as quickly as we can. If we could, that is exactly what we would do.

Q I am on the pump so I can draw out 3 days of medication at a time, but they won't let me do this. It is a waste of medicine that others could be using.

A The Special Use Program is very unique and is under very strict criteria; there is no flexibility whatsoever from a Regulatory point of view. It's something we cannot change. We understand that there is rationale in your case, but it's something we cannot do.

In response to this discussion, Dr. Mannstadt commented that, as a physician, he can prescribe an off-label medication or administration, but the manufacturing company cannot. There are different rules they need to follow, and they **cannot** give instructions for administration other than exactly what is approved. There are many, many drugs that are used off-label and the manufacturers cannot mention these uses at all.

FDA only approved Natpara to be used one way, so Takeda can't recommend it to be used any other way without going through the development process. Prior to the recall, a *doctor* could have prescribed it for a patient with an off-label mode of administration (like a pump), but Takeda cannot support this. However, now that we are in a Class 1 situation, the medication cannot be distributed at all, so physicians don't even have the option of prescribing it with an off-label administration. The Special Use Program only has 1 option for administration; there is no flexibility for off-label. The program mandates that only one dose can be used per vial and Takeda is obligated to retrieve the rest of the dose and document it. We don't want to put that program at risk by not following the rules in every case. We are having continual conversations with FDA about how this program may be able to change over time, but until we come to any other agreements, we are following the letter of the law.

Cheryl Schwartz introduced herself as the head of Takeda's US Hematology and Rare Disease business, which includes Natpara. Cheryl thanked the Hypoparathyroidism Association for having Takeda. We know that a lot of people have been reaching out to OnePath and we want you to know first and foremost that we are hearing your stories and take it to heart. We know how people are suffering due to this situation and I want you to know that it has a lot of impact on us all. We talk about it and think about it every day and it is very important to get this medication back. We know that some of you can't work and some are ending up in the hospital. So, first I just want to say is to reiterate our commitment as an organization to get this medicine back to all of you. I know there have been rumors and I want you to know it is top priority to this organization to get Natpara back to market as quickly as possible. That is my personal commitment and the senior leadership team all the way up through the whole organization. The other thing I wanted to say is that I can only imagine how frustrating it is to not have access to your medicine and not knowing when it will end. If I were you, I'm sure that the only thing I would want to know is when it is coming back. There's nothing

that Tom and I would love more than to be able to tell you a definitive timeline. Unfortunately, we do not have that because we are looking at a variety of different options in collaboration with FDA and evaluating a number of technical options. Our goal is to figure out the fastest path back. There might be an amazing way to get it back to patients, but may not be fast enough, so we need to do whatever we can short, mid and long term. I know it isn't a great answer for you, but I can tell you that as soon as we know, you will know. We have been working closely with The Association and they have been wonderful in terms of helping us communicate with the community and we really want to assure you that we will keep them, and you, abreast of any development. And that's why we are here today; we want to hear from you, be sure we are addressing any questions we can and share that we have teams working literally around the clock on this.

Q It sounds like there is going to be more clinical trials that will need to happen. Is that correct?

A Not necessarily. It depends on what the solution is going to be. If they were looking at a brand-new device, yes, there would be studies needed on that device. If they could switch out the septum, that would not necessarily need clinical studies. There are some simple changes that can be made to the device that do not require a full clinical study in patients.

Q How long would a clinical trial need to be if it's needed?

A It depends on exactly what is needed. If we're considering a new device, first the device needs to be developed, which isn't very fast. That needs to study the robustness of the device and ensure it is consistently and safely delivering the correct dose of the drug every time. Then there needs to be studies to ensure patients can use it without problem or risk. Finally, there could be clinical studies required to ensure it replicates the exact efficacy of the approved device. So, it is rather time consuming to start at the beginning, it would be years to develop a new device from scratch. That would be a long-term solution.

Q Do you have a device that you are using for another drug that you can switch?

A Devices are available, but it would still need to be fully studied and vetted. To move into an existing device can sometimes be more complicated than developing a new one because it may not deliver the exact volume of medication, causing a need for the drug to be reformulated at a different strength. These can be more longer-term solutions, but we are also considering shorter-term solutions like replacing the septum, which would be a much shorter development program. We are working on all of these at the same time.

Q Did you change the rubber lately or is it the same as the clinical trials?

A It is the same rubber that we used in the clinical trials.

Q So, has this been going on the whole time?

A We don't know. What we know is our quality checks are done regularly and we just found this very recently. Danette commented that unfortunately, it can happen that a new issue unexpectedly appears even in a product that has a long history. We see this in all products and, unfortunately, in pharmaceuticals as well.

Q What about using the new pen that is being introduced in Germany?

A There is no new pen being introduced in Germany.

Q From an advocacy standpoint, is there anything we can do that would likely affect the outcome of FDA or the process? Maybe through our legislators to apply pressure? Is it even wise?

A We can't advise you to act or not, but we can say that FDA is aware of the urgency of the situation. That is why they approved the Special Use program. It is an extremely unusual program and it's really a testament to the fact that they DO understand the impact to patients here. There

has not been a lack of responsiveness or dialogue with FDA. We are in regular discussions with them. What's happening now is that we are in problem solving mode. We are looking at the different options and trying to figure out the best options. There is a lot of back and forth in this dialogue because we have to evaluate options, provide data to FDA, they may ask questions and we go back and forth. FDA is very focused on this and it is a top priority for them as well. We haven't had a problem with that. The perception of the risk-benefit is becoming more and more clear as they are becoming aware of issues from their recall.

Q Is their awareness because of the advocacy that's been coming out of our group? I know there are individuals who are in regular contact with legislators and FDA. Would they be applying the same resources without this effort?

A I will say that from the beginning, FDA has been engaged and has devoted resources. They know the urgency. In all my career, I have never seen a Special Use Program. And the reason they did it is because they understand the uniqueness of the situation and the realize how critical this is. So, I think the partnership is there and they are responsive. And now it's a question of the back and forth and troubleshooting. But they are listening. They are aware of what is happening.

Q Can you even give us best case and worst case scenarios?

A I wish I could. Certainly, anything that involves running entire clinical trials and programs would take years. That may be a longer-term solution that we have in parallel, but that would not be the solution to get us to where we need to go in the short term. In parallel, smaller changes and adjustments, for instance, the septum, are on the table as possible options.

Q Can the Special Use Program stay in existence for that long?

A As long as we are able to keep it to relatively smaller numbers for the most critical patients so that our supply can keep up, it will continue.

Q Everyone will be critical by the time it is sorted out

A That's the concern, of course. And we certainly understand that pressure.

Q Since endocrinologists need to be certified to prescribe Natpara, why hasn't a protocol for withdrawal been established as part of that certification? Or a protocol for lab criteria to monitor patients appropriately?

A We have been working so hard with Regulators to get these first steps going that we haven't gotten there yet. I would put it as a bit of a lower priority and focus on getting Natpara back.

Q I think that question was about why protocols weren't developed before the drug went on the market?

A Danette commented that it was likely assumed that endocrinologists prescribing Natpara would understand hypoparathyroidism enough to be able to monitor and withdraw patients. The Hypoparathyroidism Association did have discussions with legislators that highlighted this concern and we recommended that, in future instances, recalls of drugs for rare diseases are done in conjunction with Key Opinion Leaders to ensure there are clear protocols in place and resources for patients who may need assistance.

Q When you solve the issue, how will the cost of the drug be impacts?

A For now, the Special Use Program will be free for all users. Once we get a regular supply back on the market, we don't anticipate any changes in terms of reimbursement structure. We have been having discussions with payers and Specialty Pharmas to keep them aware of what is happening. We don't expect any major changes.

Q Are you sending out supply that you have or are you continually making medication for this program?
A We are continually making it.
Q So, patients in the Special Use Program will continue to get medication; there is not a finite supply?
A Yes, that's what we are trying to do. The priority is to ensure all patients on the program will receive medication and that is why it is limited.
Q What are the criteria for patients being chosen for the Special Use Program?
A There is a committee of external and internal endocrinologists who assess each case as submitted by the HCPs; they go through the information provided to determine if the patient is in a life-threatening or critical stage or in a dire circumstance.
Q What is dire circumstance?
A It means life-threatening or critically ill.
Q About 2 years ago, I was asked to test a self-mixing device. Was that you? Is that device a possibility for a fix?
A There have been several devices along the way that are more user friendly, but the mechanism of the cartridge has not changed. You may have seen a prototype.
Q Does FDA require a device, or can you reclass it as a drug only.
A The issue there is the moment you change out of what was approved in clinical trials, you go back to square 1. The new administration would need to be approved. If you are considering removing the fixed dose syringe, it would open up a lot of questions about how the drug would be administered, what happens if a patient makes an error, etc, as the fixed dose pen ensure accurate and precise dosing. All of these questions would have to be fully addressed and timelines would be very extended in a situation like that.
Q Is Takeda doing anything to help patients during this time?
A We are evaluating that. If you have any concerns, reach out to your HCP, insurance or OnePath. For now, our main focus is getting the medicine back. But we are continuing to evaluate. That is another area that we will get back to you as we learn more.
Q It was published on the internet that Takeda was trying to sell this drug. Do you have the ability to do that during this recall process?
A There are no plans to do that. We are committed to this community, to this medicine and to getting the medicine back.

Someone commented about the communication of the recall. Some patients felt like they were the last to know about it. Bob commented that The Association decided to communicate the recall as soon as the press release was public because we wanted patients to find out as soon as possible. That meant that some patients found out from us instead of their doctor, but The Association felt that the information should be distributed quickly. Someone commented that some patients did not get letters for 1.5 weeks and didn't get a call from a case manager.

A We apologize that this happened. We attempted to communicate in every way possible. We don't have everyone's email or everyone's phone number, but we reached out in every way. It wasn't perfect and it doesn't excuse that you didn't hear about it in the best way. We will try to do better. Please let us know where we are not doing the best we can. We have representatives from OnePath here in the back. We are making every effort to make sure that, as information is

available, it is getting out. When the class 1 recall came out, it was an even more difficult situation because we were in the process of instituting the Special Use Program, so we needed to communicate first with the Special Use patients most immediately because we didn't want them getting confused and returning the products they just received. So, we had to have a specific cadence for that communication. It has been a challenge and we will strive to do better. Now that we are getting more into a process, we will have more time to think about how we are communicating, but because of the urgency of the situation, we wanted to make sure we were getting out information out in as many channels as quickly as possible so that patients could speak to their health care providers. That type of communication blast doesn't always come in a smooth process. You can reach out to your case managers and let them know if you have an email address or contact information where you would like to be contacted.

Q There have been reports and rumors that Takeda has spies in social media that is screen-shotting information. People are commenting on social media about an adverse event and they will get a communication from their case manager.

A There is no spy. We want to be aware of what is happening in the community. We do have people who are watching the public social media posts to make sure we are aware and are communicating appropriately about the ramifications of the recall. We look in all the public avenues. If you post something on the Hypopara Association Page or if you go to your local media, we are looking at that. We want to know the real-world response to this recall so that we can communicate that to FDA and explain to them the ramifications of what is happening. It helps them understand the urgency and it also allows us to appropriately find ways to help. And it gives us an opportunity to find ways to intervene to help patients in need. Bob commented that this is about collecting information to understand the situation and to help. Danette commented that it is also standard in pharma companies that all employees are obligated to report any adverse event they become aware of regarding a company product, even if they have no association with that product in their professional duties.

Q Wouldn't it make more sense to get information from the prescribing physicians instead of facebook?

A Many people don't report ALL AEs to their physicians, so the physicians are often not a complete source of information.

Q The absence of Natpara isn't giving adverse reactions, so many people may not consider them reportable to the physicians. Many people don't understand the nomenclature of adverse events, reporting requirements, etc. How is the risk of Natpara withdrawal being documented or analyzed and how should patients report this issue of discontinuation.

A Report any adverse events you are experiencing through OnePath and/or your HCPs. It's important for them to be reported so that they are documented and so FDA can see the impact. In this case, it is a bit unusual because the reaction is associated with not having the product, but having reports will help to qualify the impact of the recall. We do report all of this data that we capture to FDA. The information that patients give us is very helpful. If they don't know the impact, they will assume patients are being well-controlled on other medicines.

Q If we are having issues, is it better for us to come to you or have our physician come to you.

A You can report to your HCP and they can file a report.

Q Can we assume that our physician is reporting?

A In general, you can assume, but it doesn't hurt to ask. If you communicate any new symptoms with being off the medication, it will help FDA to assess the risk-benefit of the drug and the urgency of needing a solution available as soon as possible.
Q Have there been any adverse events from the rubber?
A We haven't seen any SAE related specifically to a blocked needle. We still need to do more analyses. But a patient might not even know if their needle was blocked or if they underdosed.
Q Do you know what other drugs use the same rubber septum in their delivery devices?
A We know that no other Takeda products use them, but we can't say where else the manufacturer uses them. The manufacturer will be notified of the issue and may need to evaluate any other products that could be similarly impacted.
Q Where is the cartridge made?
A It is made through a contract manufacturing organization, which is typical of most pharma products
Q Is this the same third party that it's always been? And the same process? Have there been any changes?
A No, any change to the manufacturing process would have needed to be approved in advance by FDA
Q What suddenly changed?
A We saw particles, which we had not seen before.
Q Has anyone seen these in use?
A It has been discussed that people have seen particles in their cartridges at home
Q Wouldn't using syringes prevent this issue?
A Again, an administration like this could potentially be suggested off-label by a physician when the medication is available again, but is not an approved administration and can't be used as a solution to the recall.
Q You were talking about long, short, mid-term. Could Natpara return to market with a short-term solution while you continue with the long-term solutions.
A Yes, if we could fix that septum and no particles appeared, it would change the risk benefit and then we could certainly work on any additional long-term solutions.