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Interview: Clinuvel, A Company That Does The Unusual

by Maureen Kenny

"There will be one price and no discounts, no backroom deals, no incentives off the record." In an interview with the *Pink Sheet*, Clinuvel UK's general manager Lachlan Hay talked about the company's unusual pricing policy for its equally unusual photoprotective therapy, *Scenesse* (afamelanotide), its frustrations at out-of-sync regulatory and market access systems, and how its plans for a US regulatory filing are going.

Clinuvel Pharmaceuticals Ltd. is a company that does the unusual.

Its novel systemic photoprotective product, *Scenesse* (afamelanotide), obtained EU approval at the end of 2014 under exceptional circumstances. There are no scientific instruments to quantify and measure the impact of the disease Scenesse treats – the rare genetic skin disorder erythropoietic protoporphyria (EPP) – or indeed the impact of the therapy itself. Scenesse was the first product where patients' views and experiences were formally integrated into the European Medicines Agency's decision-making process. Also unusually, Clinuvel has adopted a uniform global pricing policy for the product.

Last but not least, Clinuvel is a company that speaks its mind, most recently in regard to an important recent development that means Scenesse should be reimbursed across *Germany*, the largest European market for the product.

Clinuvel Chief Executive/Managing Director Philippe Wolgen has accused the German National Association of Statutory Health Insurance Funds (GKV-SV) of leaving "no stone unturned in its attempt to end the existence of Clinuvel." In the Australian company's *May newsletter*, Wolgen says insurers are "coordinating efforts internationally to cull health care costs, and will come up with any conceivable argument to lower prices of pharmaceuticals." The GKV-SV, he says, is "leading European insurers in curtailing the position of pharmaceutical companies."

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The *Pink Sheet* interviewed Lachlan Hay, Clinuvel UK's general manager and, like his boss, a straight talker. Among the topics covered were the company's pricing strategy, the broader importance of getting an agreement on coverage in Germany, its ongoing frustration with UK health technology assessment body NICE, the status of the product in the US, and the need for regulators, health technology assessors and payers to listen more to patients and physicians.

Shortly after our interview, at the company's UK offices in Leatherhead, just south of London, there was another positive development for Clinuvel. To determine whether the product should be made available under the National Health Service in England, *NICE* will assess Scenesse as a highly specialized technology. Clinuvel had been arguing for this approach for a long time, disagreeing with the NICE view that the product was eligible for review only under the mainstream single technology appraisal pathway.

Scenesse is available in Germany, Austria, the Netherlands, Italy and Switzerland. It will be some time before a NICE decision is made regarding England. In the meantime, Clinuvel is in market access talks with "a small number of Scandinavian countries", where, says Hay, "there is certainly demand for the product".

The following Q & A is an abridged and edited version of the interview.

Pricing

Clinuvel has said the annual cost of therapy with Scenesse ranges from €56,404 ($63,546) to €84,606 ($95,355) per EPP patient per annum.

Q **You've got a single, uniform European price and you won't budge on that. Is that correct?**

A It's not so much that we won't budge on price, we've set a very transparent price for all

Scenesse And EPP

Patients with erythropoietic protoporphyria, a rare genetic skin disorder, risk second-degree burns, swelling and burning if they are exposed to daylight. Clinuvel's Scenesse (afamelanotide) works by increasing the melanin content of the skin without having to expose it to the damaging effects of ultraviolet radiation. The benefits of treatment are a reduction in light sensitivity and a consequent – but limited, according to the European Medicines Agency – increase in the time patients can spend in daylight or sunlight. No other treatments are available for the condition. The product was approved in the EU under exceptional circumstances at the end of 2014.

Partly because of the difficulty of conducting clinical studies in patients who can see the results, ie pigmentation changes, and also because patients are understandably unwilling to expose themselves to sunlight-associated

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countries, treating all expert centres equitably. All of these [health technology assessment/pricing/reimbursement] agencies say to me, I want transparency, I want to know what everyone else is paying, and I said, OK that's the price and we can structure that way. We've said from day one... that there will be no arbitrage across countries.

It's bizarre to them. They've not seen this before. I think there's a certain element of disbelief. [They think:] "Okay, what you're saying publicly is this but really we think you're doing this."

There's an expectation that something is happening behind closed doors, confidentially between company and payer. We've said from the get go, there will be one price and no discounts, no backroom deals, no incentives off the record, it needs to be fair access and transparent and that's what we're living up to.

We didn't take the decision lightly but I think our genuine execution and straightness reflects how we've done things over an extended period of time.

pain as part of a clinical trial, Scenesse required a shift in how regulators reviewed the product, including greater consideration of patient testimony during the approval process.

The company hopes to market the product in the US but has yet to file for approval there.

Germany

Clinuvel announced in *April* that it had reached an agreement with the GKV-SV that should result in all state insurers (Krankenkassen) covering Scenesse.

Q **Germany will be your biggest market. This must be a major development for Clinuvel. Is that correct?**

A Absolutely. But also, Germany is a reference country [and] the GKV process is held up as being one of the higher-end processes. A lot of people will look to that and say,

this is a point of reference for us and if they've gone through that process and arrived at an agreement with GKV then I think that we can make that [work for us].
It's a twelve-month process basically. We went through the process [required under AMNOG, the German Pharmaceuticals Market Reorganisation Act]. There was a series of discussions, then that process went to arbitration and now we have the outcome.

It was a very transparent, structured process that they'd put in place. They said to us, this process will happen and this process will happen and this process will happen. It's very much stepped out, that doesn't exist here [in the UK].

Q **Why do you think that is?**

A To be fair, to have a very structured system like that and [put] really structured timelines in place is difficult. I mean these guys look at what, 50 or 60 drugs a year perhaps? New products. As part of that, they need to be able to plan their work but at the same time, national horizon scanning and these sorts of processes should be able to cut it down.

"It's bizarre to them. They've not seen this before. I think there's a certain element of disbelief." – Lachlan Hay, Clinuvel UK

Calculating the numbers affected

Q **Payers like certainty. In Germany, your largest market, you say between 500 and 1,090 adults could benefit from treatment with Scenesse. That's quite a wide range, isn't it?**

A There is always uncertainty when you're dealing with orphan indications and EPP is poorly understood still, even having worked with it for a decade. What we try and do is give the absolute worst-case scenario.

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When we started out working with orphan products, the payers weren't really sure what to do either. I think perhaps on several occasions they've been burnt by an orphan drug company, where [they were given an estimated number of patients] and then what they ended up paying for was triple [that].

When you are talking about medicines that have a high cost … you try to provide them with a realistic range. How do I come to a number of between 500 and 1,900 for Germany? I try and be as precise as I can. We give very clear estimates, so here in the UK we think there are 513 EPP patients who would be eligible for treatment.

What you try and do is take your known patient numbers, you take estimates from your treatment centers, you take estimates from your patient association, you take prevalence data and throughout all of that you come to a number and it's only fair to provide a range. Now the narrower the range, the better it is. For EPP this is an ultra-orphan disease, so we're not even talking tens of thousands of patients in most instances, we're only talking hundreds or thousands.

We speak to the physicians, the treating physicians and the academic physicians and say to them, what do you think of this number? What do you make of these prevalence numbers? Is the prevalence number for country x applicable to your country?

Again, that's something that you then have to convey back to authorities and sometimes they get it right and sometimes they get it wrong. Here in the UK, for example, I would argue that they got it wrong and we've had a bit of a back and forth with them on that but costing us and the patients 16 months of delay.

Asymmetry

Q **What's the basic problem regarding getting orphan drugs on to the market in Europe?**

A The mandate existing in Europe as a concept for approval of [orphan] products doesn't filter down… to a national level in terms of pricing.
At a national level… all of a sudden, from a pricing perspective, you go through

another review, a completely new review of your dossier despite the European [Medicines] Agency saying, well we see that there are no tools available, we accept that, we've spoken to patients. To have to go through this again, it's a frustration to put it mildly.

[I think the EMA is] trying to improve the tools that exist for the review of orphan products. Our case is certainly a good one from that regard ... it took them long enough, but for the first time they started talking to patients directly as part of the process. We said to the EMA for nine years, you need to speak to patients. We said it back in 2005 when we were building the program. It [only happened] in 2014 but we got there. (Also see " *INTERVIEW: Clinuvel's Philippe Wolgen on Scenesse and the patient factor* " - Scrip, 17 Feb, 2015.)

There's an asymmetry between a company and a regulatory authority in that we've done this for 12 years, we know our drug, we know our disease indication, we know the experts who will handle it and by and large, our scientific folks have become experts, respected experts, in this disease over one or two decades.

Now I walk into EMA and they're generalists. It may be that they've got a dermatologist or a gastroenterologist who sits on the board that's reviewing but the reality is they've never seen one of these patients before. Perhaps it's unfair to expect them to have that same level of knowledge but there needs to be an acknowledgement of that asymmetry of information. (Also see "*Diligence And Janitors Needed To Keep Europe Innovating, Says Orphan Approval Pioneer*" - Scrip, 22 Oct, 2015.)

There is a need to get [regulators more] invested in this. We have a clear responsibility and a clear drive to make this product – or whatever product it happens to be – available to a patient. I don't think there's the same level of drive from a regulatory perspective.

The UK And NICE

Q **What is the situation in the UK with regard to reimbursement and availability?**

A We are dealing with NICE at the moment. I find it very frustrating because [there is a gap between] what NICE say publicly and what happens privately. It hasn't been a transparent process. Mistakes have been made and apologies haven't been given. At the moment, I don't have a clear end date for a decision in England and that frustrates me but it frustrates patients even more.

We started speaking with NICE around the time the product was approved. We are still in that process so again, there's this delay. You have a product which is approved in 2014, you and I are having a conversation in the middle of 2017, the timeline that we received from NICE is that the product might not be available until 2019. All of a sudden, the social mandate that I get from the EMA for a 10-year exclusivity is cut down to five years. How am I supposed to react to that?

Again, it comes back to that level of expertise. I'm not saying that a pharmaceutical company should have carte blanche to do what it pleases. There needs to be a system that exists and is responsible and is transparent but I don't think we have that at the moment.

You can't expect them to be perfect but … if you say something publicly, you have to do it, that's my genuine view, and if that's not happening within any organization then there needs to be change.

Q **Are you confident you'll get Scenesse on to the market in the UK?**

A I am confident that the patients want it. I am fairly confident that if a regulatory authority or a payer takes on the same approach and tries to understand the disorder – and that's what we've seen [happening] over time – the product will be made available.

"It hasn't been a transparent process. Mistakes have been made

and apologies haven't been given."

Q **What advice can you give to other companies with ultra-orphan products?**

A Dealing with an unknown disease [is difficult]. Even if you are sitting across the table from a physician at a reimbursement authority, they have never seen a case of this before. You need to be very clear in terms of what your disease is and what your impact is but more to the point, I think you need to be very adamant, particularly in our case, about involving the patients as part of the discussion.
I can tell you about EPP, but why not speak to a doctor who has spent twenty or thirty years trying to manage this disorder [to find out] why it is that that particular physician wants a treatment, demands a treatment?

You need to bridge that asymmetry of knowledge somehow. [That may not be possible] in the space of two or three months ... but [you have to see whether you can] at least get them to see what you've seen over a decade and try and integrate that into part of the discussion. I still don't think NICE, for example, is capable of doing that.

Patient Registers

Clinuvel monitors the ongoing use of Scenesse in EPP patients under an indefinite post-marketing authorization program. This includes post-authorization safety study (PASS) protocols and a European EPP Disease Registry.

Q **How is the data collection progressing under the registry? What is your interaction with the EMA, two years after approval?**

A There's an ongoing dialogue with the EMA at appropriate points in time. The adherence to the post-authorization program from a patient and physician perspective has been good. I think that reflects the desire of the physicians and the patients to continue with the treatment when they understand that the ongoing

collection of data is to ensure the ongoing monitoring of the product and thus its maintenance on the market. There's greater compliance but there is a frustration expressed from time to time about the burden that's placed on physicians to try and capture data and the time they need to spend [during] each visit to do so while prescribing the drug under usual clinical conditions. This frustration and burden extends to the patient body at times too.

Q From your point of view, is that a good price to pay for getting the product on the market?

A When you do have an orphan product and you are going with a program which is restricted and perhaps, as in our instance, [there is] a complete lack of tools to measure the disease or a treatment for the disease, I think monitoring ongoing safety is a great value to everybody. From a commercial perspective, perhaps it's a barrier to entry for competition but more importantly, at this point in time, it's ensuring that our product is being used in the way that we want it to be used.

The US

Scenesse has orphan and fast-track status for the EPP indication in the US, where in July last year the Food and Drug Administration said it would allow Clinuvel to file a rolling New Drug Application for the product. (Also see "*PIPELINE WATCH: 13 Approvals, Two Filings And Two Launches*" - Scrip, 10 Jul, 2016.)

Q With regard to the rolling dossier, you've said in the past that you hoped to submit the first part in the first half of 2017.

A That's perhaps optimistic but ... we like to be aggressive in our targets. Certainly by the end of this year.

Correspondence with the FDA has been frequent during preparation of the rolling NDA filing. Again, it's a similar process. It took us 10 years to get the FDA to speak to patients. There's a learning experience that is happening on behalf of the authorities in the US and you can argue about whether it's happening fast enough but the same engagement by the regulator, a process that we went through in Europe, will have to happen in the States.

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Q **What is it that the FDA wants that the EMA didn't?**

A At the moment, the dossiers are different in terms of format, in terms of what they're looking for, the way that it's presented. You are dealing with different legislation but the pivotal trials that we're using are the same.

Q **What's the key difference then?**

A Let's be honest, the FDA wants to ensure that the FDA reviews drugs for Americans. So that's the process that they're going to go through and you have to adhere to that.

Q **Are you doing any additional trials in the States?**

A In Europe, the product is under a risk management plan and part of that is to collect ongoing safety and effectiveness data. The FDA has indicated an interest in that and would want to see some of that data. So, here in Europe we provided EMA with data from the Italian and Swiss programs that we had, so these were expanded access programs over extended periods of time and that certainly adds to the safety story and can add to the effectiveness story, depending on what's available. But I think the FDA would want to see data from the program here in Europe and in all likelihood, they'll want to replicate this work.

"Let's be honest, the FDA wants to ensure that the FDA reviews drugs for Americans."

Worth It?

Q **Has there been any point where you've thought it's not worth it?**

A Quite often when I speak to patients - and I do speak to a number of them - I will ask them, "Is this worth doing?" I challenge them, and it's unkind but you say to them,

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> "Should I be treating you?" I haven't had any of them say "no" yet. So, for me, that's a real validation of the worthwhileness of this program but one of the responses that I sometimes get back is, yes, it's absolutely worthwhile for us but even more so for the kids. We've been working on a pediatric formulation and we have a Pediatric Investigation Plan in place and we're following this to arrive at a pediatric dose. I don't, by any stretch, denigrate what's been achieved thus far, I think it's phenomenal, the folks who have worked to get this approved, but I'd like to think that we can treat children. I would like to think that we've got our first pediatric trials in two to three years.
>
> I think once you are able to treat all of those patients that you think you can help clinically, that's success.

From the editors of Scrip Regulatory Affairs.