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LETTER FROM LEADIANT BIOSCIENCES TO MINISTER BRUINS – 13 SEPTEMBER 2019

Minister voor Medische Zorg
Mr. Drs. B.J. Bruins
Directie GMT

Excellency,

Re: follow-up to our meeting on 5 September 2019

Leadiant would like to thank you again for our meeting on 5 September 2019. Further to our meeting, please find below our reaction to our conversation on how transparency and patient access to CDCA Leadiant as a reimbursed product can be improved.

Accessible innovative medicines at acceptable prices

Just like you, Leadiant believes that effective innovative medicines should be accessible to every patient in the Netherlands who needs them. We therefore find it encouraging that you invited us on 23 July 2019 for the follow-up meeting on 5 September 2019 to discuss the status and what steps would have to be taken as regards patient access to CDCA Leadiant via the basic package. We also understand that you have concerns about keeping the costs of medicines under control and we support your aim to arrive at a sustainable medicine supply.

As we explained during our first meeting on 1 October 2018, **Leadiant is sensitive to the issues surrounding healthcare costs sustainability** and is prepared to negotiate with the Ministry of Health as well as with Dutch insurers with the objective of finding mutually acceptable solutions to bridge the differences and to improve the current situation for patients with the serious degenerative disease Cerebrotendinous xanthomatosis (CTX). We have also done so in other countries. On that point, we informed you that we have recently concluded a **Commercial Agreement with the NHS England** for the routine commissioning of CDCA Leadiant (link).

During the meeting on 5 September 2019 we reiterated our **willingness to negotiate** price and reimbursement of our product CDCA Leadiant in the Netherlands, and we furthermore reiterated our **willingness to provide transparency as discussed**. We would like to use this opportunity to commit to this in writing and to provide some more context, also to address some recurrent misunderstandings that have been circulating about our company and our product.

Background

CTX is an extremely rare disorder. Recent estimates for the incidence of CTX range from about 1 in 135,000 to 1 in 460,000 in people of European family origin, and about 1 in 70,000 in people of Asian family origin. However, only around 300 people with CTX have been described worldwide. A bibliographic study of the epidemiology of rare diseases estimated that there are about 200 - 250 people in Europe with CTX. Prevalence is estimated at about 60 - 65 patients in the Netherlands.

The majority of the Dutch patients (around 45) are being treated by medical specialists in the **CWZ hospital in Nijmegen**. In 2018, CWZ was recognised by the Ministry of Health **as the national CTX expert centre** (link). By contrast, Amsterdam UMC is ultimately responsible for 2 patients (the main treatment relationship (*hoofdbehandelaarschap*) has not been transferred from CWZ to the Amsterdam UMC) (link). Due to the specific expertise of the specialists of the CWZ hospital of CTX and their active knowledge transfer about the disorder, there is a higher level of familiarity with the clinical features of the disease in the Netherlands, as a result of which the number of patients diagnosed with CTX in the Netherlands is probably higher than in other countries.

As a company we have committed to obtaining a marketing authorisation for a new medicinal product specifically indicated for the treatment of CTX, so that an authorised treatment becomes available for the 200 - 250 CTX patients in Europe. We **have succeeded in proving** to the European Medicines Agency (EMA) that our orphan drug is manufactured and tested with state-of-the-art methods. We have established, to EU standards, and for the first time, that CDCA is safe and effective for use in CTX (link). We have proven to the EMA's Committee for Orphan Medicinal Products that our product offers a significant benefit to CTX patients (link) despite the prior EU authorisation of another orphan drug for CTX (link). We are pleased that in November 2018 the Zorginstituut Nederland has confirmed the added therapeutic value (*therapeutische meerwaarde*) of our product (link), and has recommended that you (i.e. the Bureau Financiële Arrangementen) should negotiate with us (link).

The EMA approval process and the EU marketing authorisation also resulted, in this particular case, in the **investment in a tailor-made, dedicated European patient registry** which, if it can proceed as envisaged by the EMA, will significantly increase the understanding of this serious and neglected disease. We are very pleased that the Dutch CTX expert centre CWZ is one of the participating centres.

Leadiant is prepared to negotiate

We have been **waiting to negotiate** with the Ministry and with the Dutch insurance companies since June 2017, as is clear from the documents that have been published further to Wob-requests from third parties[1] (link) and analyses of the CDCA compounding case (link and link).

[1] It is important to note that Leadant has not filed any of the Wob-requests.

At the end of our first meeting on 1 October 2018 with you it was left somewhat open how to pursue negotiations and with whom (Ministry of Health or the insurers), since the Zorginstituut Nederland had not yet issued an advice further to our application concerning the reimbursement of CDCA Leadiant.

Furthermore, Leadiant has on different occasions reached out to the largest Dutch insurers to engage in negotiations. The only reason an *improvement* has not been determined yet, is that the insurers have been uninterested or unwilling to enter into any substantive negotiations. We still do not understand why **the insurers refuse to negotiate**. Insurers are currently paying the list price. Two years ago, we offered them a substantial, retroactive improvement in financial conditions. But it seems they would all rather pay more than talk to us. This is puzzling.

In April 2017 we submitted a "proefdossier" to the Zorginstituut Nederland for reimbursement of CDCA Leadiant as **hospital care (medical specialist care)**. However, during a meeting on 18 May 2017 the Zorginstituut suggested that we should consider submitting a **GVS application**. Because we were confident that CDCA Leadiant, as an orphan medicinal product that should be used under the supervision of a medical specialist, could qualify as hospital care, we pursued the route for reimbursement as medical specialist care, to be centralized via the CTX expert centre in Nijmegen. An **"add-on" application** was ready to file in September 2017. This avenue was blocked, however, on account of the fact that the insurers refused to co-sign with CWZ and submit the add-on request, and were of the opinion that we should sumit a GVS application (link).

As Leadiant was informed that the *ex gratia* reimbursement (*coulanceregeling*) would discontinue and a joint decentralized solution with the insurers did not appear to be feasible, Leadiant contacted every individual insurer on 22 December 2017 in order to find a constructive solution. In the messages to the insurers Leadiant committed to submit a GVS application (outpatient pharmaceutical care). However, further to the advice of the Zorginstituut Nederland of 22 November 2018, the insurers and the hospitals have asked you to reimburse CDCA Leadiant – as was also the case for the pharmacy compounded product – as medical specialist care (link) and to the best of our knowledge, our product is currently being reimbursed as medical specialist care.

Transparency

During our meeting on 5 September 2019 we discussed **transparency**. We are willing – as we have been before – to provide transparency as a starting point and as part of negotiations with the Bureau Financiële Arrangementen.

However, it is not yet clear to us what costs and investment data you are looking for. As you must know, allocating costs is not straightforward. It is also not yet clear what level of transparency and detail is requested, which method(s) and criteria will be used to assess the information, and when the dialogue as sought by you will be considered successful. During our meeting you admitted that you would not be able to tell us when enough would be enough.

In our experience a certain level of confidentiality is an important principle for arriving at a sustainable medicine supply. For example, if we are to negotiate with an insurer, we would have to discuss the number of patients insured with that insurer (children, adults); GDPR aspects of processing personal data of patients and their families (since this an ultra rare disease and information can quickly be relatable to individuals); hospital(s) where these patients are being treated; how the CTX patient registry will be dealt with; financial conditions; costs and pricing rationale; expected volumes; and any other information both parties may find relevant and necessary to reach a fair financial agreement.

That being said, we also understand that you would like to be assured in this situation that an agreement to be negotiated with Leadiant for the Netherlands is appropriate.

Our pricing is justified by our costs and investments. We have offered both to you and already to one insurance company, to give their **'clean team' experts insight** into our financials – as part of negotiations - so they can fully understand why it required many millions of euros to bring an orphan drug for such a rare disease to the market, and keep it on the market in compliance with all laws and regulations.

We have even **instructed a leading economist firm** to structure and categorise all the investments so that it becomes easier to understand why our pricing is not excessive or unfair at all. As we stated during our meeting on 5 September 2019 we are prepared to give the team of experts of the Bureau Financiële Arrangementen insight into their findings.

The insight we want to provide to the team of experts of the Bureau Financiële Arrangementen will surely **remove a lot of the misunderstandings** about our company and inaccurate suggestions that CDCA Leadiant is the same thing as a previously authorised product. Some of these misunderstandings we wish to already address in this letter.

Leadiant is a **research-based pharmaceutical company** that currently markets six products in Europe and/or the USA. Four of these are for the treatment of rare (orphan) diseases. Leadiant allocates approximately 20% of its revenue to the research and development of novel and effective therapies that address patient needs and improve quality of life. Currently the company is pursuing five projects for rare diseases from "pre-clinical" to "filed" stages. Some projects unfortunately failed recently, and some have succeeded. We obtained a marketing authorisation in the USA for the biological medicinal product Revcovi®, for the treatment of Adenosine Deaminase-Severe Combined Immunodeficiency (ADA-SCID) (link). We recently received a nomination for Revcovi as "Best Biotechnology Product" from the Prix Galien USA 2019 (link).

A pharmaceutical company that seeks a marketing authorisation for a disease with an estimated affected population in Europe of around 200 – 250 patients (as is the case with CTX) will have to make similar costs as a pharmaceutical company that seeks a marketing authorisation for a product that is used by 300,000 patients.

CDCA Leadiant has been developed and brought to market at substantial cost.

Our **investments were not meaningfully reduced simply because of the existence of old products** such as the *molecule* CDCA which was authorised decades ago, by another company, for another therapeutic indication (treatment of gallstones), in another country. **CDCA Leadiant is not a "copy" of an old product**.

CDCA Leadiant meets the strict designation criteria for orphan medicines, which follow from the European legislation. In the opinion of the EMA and the European Commission, Leadiant has demonstrated sufficiently that patients who suffer from CTX will derive a "significant benefit" from its medicine. Based on a comparison with existing authorised medicines and methods, Leadiant has shown that there is no satisfactory method for the treatment of CTX. The designation and marketing authorisation as an orphan medicinal product therefore already shows that CDCA is not a "copy" of another product. The Xenbilox dossier, therefore, has not been "copied" either. There was very little from the old "dossier" that could be re-used. We basically had to **start building the dossier for the EMA from scratch** (and by the way, any pharmaceutical company could have done what we did).

Furthermore, it is important to note that the **current standards and requirements** that are imposed upon pharmaceutical companies for example manufacturing, marketing authorisation, marketing and pharmacovigilance of (orphan) medicinal products, **are more extensive and significantly more strict** than the requirements that applied in, for example, 1999.

As part of authorising CDCA Leadiant, there was a need to bring manufacture and testing of the medicinal product and particularly the **Active Substance Master File (ASMF)** for the active pharmaceutical ingredient (API) up to modern practices suitable for the current requirements of the regulatory authorities. New analytical technologies and modifications are continually being developed providing greater assurance of quality. The manufacturing process and testing of both the drug substance (the API[2] CDCA) and drug product (CDCA Leadiant) have been revised, after a thorough assessment of the process performance under relevant manufacturing variables. The specifications for both the drug substance and drug product have been overhauled to be compliant with the state of the art technology, and multiple new test methods considered more accurate for release have been developed and validated. In particular the method for testing impurities has been updated from a qualitative to a quantitative test and all actual and potential impurities were investigated for risk to patients.

> To illustrate that this type of investment is common, we would like to refer to a recent presentation by ACE Pharmaceuticals concerning the drug rediscovery of Broxil® (pheneticillin K) and of 6-Thioguanine, during the 7th annual ZonMw Conference "Goed Gebruik Geneesmiddelen" on 4 April 2019 (link). In the case of Broxil the need to bring manufacture and testing of the API up to modern practices suitable for the requirements of the regulatory authorities caused a 50-fold price increase for the API.

[2] API: active pharmaceutical ingredient.

Furthermore, Leadiant created a new and comprehensive body of evidence of the safety and efficacy of CDCA for CTX. In designing our clinical study programme (described in detail in the EMA's EPAR at pages 17-39 - link), Leadiant had to take into account that with this disease it is unethical to apply the standard clinical research method of *prospective*, placebo-controlled studies (by which one "arm" of the study gets the product under review, and another "control arm" receives placebo). Given this impossibility, we conducted *retrospective* studies, which methodologically are no less thorough than prospective studies. These clinical studies were **entirely new studies, creating new data sets.** Taking into account that the new clinical studies were retrospective, the evidence of safety and efficacy were obviously established using actual patient records, i.e. records of patients having been administered (since its authorisation) CDCA products. The retrospective studies were not a matter of simply using existing, available data. As such, raw data was discoverable, but that raw data was not readily available. Obtaining the data required cooperation of treating physicians and patients, and the data had, moreover, not been assessed within the rigid framework of a clinical study. The existing data could therefore not be readily used for marketing authorisation application.

The body of evidence gathered by Leadiant – including the two new retrospective studies regarding the treatment of CTX – constitutes the **largest ever collection of clinical data for CTX**. It took Leadiant almost two years to collect all the data. The process included the necessary steps in a GCP (Good Clinical Practice) compliant clinical study, including the set-up of protocols, necessary administrative and committee approvals, data collection, statistical analysis, reporting, etc. The process was outsourced by us to a Clinical Research Organization (CRO) with all the capabilities necessary for the task. The protocols had to be submitted to the relevant approval committees and the CRO had to go through all the data, including patient files. As with prospective clinical trials, the data had to undergo statistical treatment and analysis. In this respect, the main difference with a prospective clinical trial is that the data is collected in a different way.

Another complicating factor was the "comparator". In order to obtain a marketing authorisation, the applicant must compare the clinical data with other data. In the case of CTX, the (only) comparator is the natural history of the disease, for which **a model had to be built**. The problem here was that there was very little information available about the disease, since prevalence is estimated at about 200 - 250 patients in Europe. Consequently, the marketing authorisation dossier needed to be built up from scratch to prove efficacy to the EMA.

Our efforts were therefore new, and CDCA Leadiant must be recognised as a new medicinal product. Assertions that CDCA Leadiant is an "old" product authorised on the basis of "old" tests must be rejected in the strongest terms, as well as any assertions that the API can be considered "the same" as the finished medicinal product.

The marketing authorisation not only ensured careful EMA consideration of all the evidence developed on quality, manufacturing controls, efficacy and safety for CTX patients. It also resulted, in this particular case, in the **investment in a tailor-made, dedicated European patient registry** which, if it can proceed as envisaged by the EMA, will significantly increase the understanding of this serious and neglected disease (the registry was put into effect last

week). Additionally, the company committed to **developing a paediatric formulation** of CDCA Leadiant (destined to 30-60 patients in the EU and currently ongoing).

With regard to pricing, we would furthermore like to note that while the list price of CDCA Leadiant in the Netherlands appears high for an individual patient, the list price **is already the lowest in the EU**. Also, our orphan drug is similarly priced to 12 comparable orphan drugs.

In addition, we note that the Zorginstituut Nederland has been in possession of the **pharmaco-economic data** on CDCA Leadiant since March 2018, but unfortunately refused to review these data.

Furthermore, we have **submitted hundreds of documents** to the Authority for Consumers & Markets (ACM), which is conducting a very thorough and detailed investigation of the financial justification of our pricing (link). The ACM is specifically tasked with competition oversight and the enforcement of consumer protection laws. The ACM therefore also represents the interests of the public. Although we understand that there is public interest in these investigations, there should also be a certain level of trust in how independent authorities such as the ACM operate.

In the meantime, as you will understand, we want to negotiate in confidence, to protect the orderly proceedings before the ACM, and to make sure that we do not inappropriately disclose confidential information to our customers and competitors in the Netherlands (the collective insurers together with their foundation Pharmagister and a hospital pharmacy) who have put a replacement product on the market and are apparently preparing to do so again.

A comparison between an authorised product and a pharmacy preparation is not fair

During our meeting you referred to the **alleged price differential** between our product (approved by the EMA) and the cost of an ingredient used by the pharmacy in Amsterdam that has made their own "compounded" version of our product, charging EUR 25,000 per year. You mentioned that the public would like to be able to **compare price and quality**.

Based on media coverage since April 2018, the documents that were published by the Dutch Health and Youth Care Inspectorate in November 2018 (link) and the documents that the Ministry of Health has released further to Wob-requests from third parties (link), it is hard to avoid the impression that CDCA Leadiant was the case that **the Dutch "bereidingslobby"** (link) of the insurers, Pharmagister/CbusineZ and policymakers had been waiting for some time, and that CDCA Leadiant is only used to set an example.

Shortly after obtaining the European marketing authorisation for CDCA Leadiant in April 2017 and our meeting with the Zorginstituut Nederland in May 2017 to discuss our "proefdossier" for reimbursement of CDCA Leadiant as **medical specialist care**, we were informed in June 2017 that at least one insurer planned to try and manufacture its own CDCA product regardless of any offer by Leadiant. In fact, this insurer informed us that he had sourced the raw material so that a pharmacy could start compounding capsules.

Of course, when you are an insurer working together with a Dutch pharmacy, you can make CDCA capsules more cheaply when you do not need to invest in a marketing authorisation dossier for the entire EU and in manufacturing factories approved by the EMA. Through the documents that were released by the IGJ (link) and the Ministry of Health (link), the public can read that the insurers/Pharmagister decided to purchase an active ingredient that is tested under a Chinese pharmacopoeia from 1995 ("CP95 standard"), even when the report of a meeting between the IGJ and the hospital suggests that they had the choice to buy an active ingredient with a higher quality. They also decided to use an importer that did not comply with Good Distribution Practices and has no storage facilities (link) and is still not included on the list of trustworthy API suppliers of the KNMP and the NVZA (link). Furthermore, they must have known that certain undesired substances were used in the production, such as barium chloride, since the Certificate of Analysis refers to this substance (link). They must have realized that the testing methods from the Chinese Pharmacopoeia from 1995 are out-of-date. The IGJ has found that the unknown impurities exceed the legal limits for unknown impurities (0.25%) by no less than a factor 8 to 10 (link). It also seems that there were serious concerns about the stability of the active ingredient, but the hospital still wanted to continue using the same ingredient, perhaps pressured by the insurers. It appears that the insurers – via Pharmagister – were the architects of the plan and they still seem to finance and support this project, including more than € 1 million from Menzis in 2018 (link, p. 61). The insurers have also organised a collective boycott of their competitor (link), to make our authorised product unavailable to give a pharmacy a reason to compound it (link). We were somewhat surprised that this information – which has been readily available in the public domain – did not receive any attention in Dutch media and in the Parliament. It has furthermore been largely ignored that the insurers and the pharmacy are not only a customer of Leadiant, but also its competitor. This means that when the insurers ask for cost information from Leadiant, they can do that to know how much they will charge themselves. Also, the hospital can decide, as a healthcare provider, whether to prescribe its own product or its competitor's product.

It has been ignored in the public debate about pharmacy compounding as well that pharmacies do not need to have their manufacturing processes checked by EMA or the IGJ. There is no product control by any independent regulatory authority before or after compounding. Furthermore, a pharmacy will have no obligation to supply the market under Dutch[3] or European[4] law, and is not subject to any of the 28 obligations imposed on marketing authorisation holders (link), each subject to substantial fines. Such a pharmacy will not have to (as we do) establish a tailor-made European patient registry to collect a further 5 years of clinical data. And the pharmacy will not need to ask EMA every year to have its marketing authorisation renewed.

As long as the stakeholders **refuse to talk to us**, none of these aspects can be discussed, and no understanding can be created. We believe we should talk, and negotiate, as we expected the Dutch stakeholders to do earlier.

[3] Article 49 of the Dutch Medicines Act.
[4] Article 81 of Directive 2001/83/EC.

But what surprised us most, perhaps, is how the **public health element** of replacement compounding has been dealt with. The Dutch government supports the marketing authorisation process as such, but has not yet articulated a view on the value intrinsic in obtaining EMA approval for the entire EU and corresponding compliance with quality and safety standards and regulations, including the EU rules regarding the manufacturing, pharmacovigilance and the Falsified Medicines Directive. There have been many dozens of press articles as well as your recent letter of 8 April 2019 about pharmacy compounding to the Parliament (link). None of them explains the reasons why the marketing authorisation system was created after the thalidomide disaster in the 1950s, and regulators across the EU decided that untested medicines should never be put on the market again (link). None of the articles mention that the Netherlands was instrumental in creating the international Resolution stating that pharmacy compounding should be a *complement* to the marketing authorisation system, not a *replacement* for authorised products (link). None of them discuss the consequences of setting aside the marketing authorisation system and the Orphan Medicinal Products Regulation. It should not be about small or large scale, but about **safe** scale. The press did not report on the documents that were disclosed by your Ministry further to the Wob-request of a third party.

Conclusion

These matters are worthy of discussion. Our conclusion, therefore, is that **we should talk**. We hope that this letter can pave the way to a negotiated solution acceptable to all the parties. We trust that we can engage in a good discussion to achieve a constructive end result by mutual agreement.

Yours sincerely,