COUPRY

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DELIVER

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Date:	7 September 2018	Ons kenmerk:	14354
Subject:	Enforcement request Competition Law	Uw kenmerk:	

Dear mr Broers,

1.1 The Pharmaceutical Accountability Foundation (hereafter: **the foundation; [**official Dutch name: Stichting Farma ter Verantwoording]), who contacted me and dr. R. Meijer (attorney in Amsterdam) to represent her interests, hereby requests the [Dutch] Authority for Consumers & Markets (hereafter: **the ACM)** to impose Leadiant Biosciences Ltd. (hereinafter: **Leadiant**) a fine pursuant to Article 56 of the Dutch Competition Act, or to take enforcement action against Leadiant in another manner.

1.2 To summarise, according to the foundation, Leadiant is abusing its dominant [market] position by asking for an excessive price for the drug CDCA-Leadiant, which it markets as an orphan drug on the Dutch market against the disease Cerebrotendinous Xanthomatosis (hereinafter: **CTX**). Due to her behaviour, recipients of the medicine are being exploited and / or the Dutch health care system is disadvantaged. This behaviour can only be stopped by an intervention of the ACM.

1.3 The foundation turns to the ACM, because it has concrete indications that the abuse takes place and has taken place on the Dutch market.

1.4 Below we explain the above.

2. Facts

2.1 Leadiant Biosciences Ltd, based in the United Kingdom (London), is the European subsidiary of Leadiant Biosciences S.p.A, a holding company based in Italy (Rome), which also has a subsidiary in the United States (Leadiant Biosciences, Inc.).

2.2 Leadiant only brings two products to the market in Europe, namely:

- CDCA-Leadiant (brand name and in full: Chenodeoxycholic acid Leadiant) / chenodeoxycholic acid (active substance), and
- Natulan (brand name) / procarbazine (active ingredient), this is a medicine against a form of Hodgkin disease.

2.3 CDCA-Leadiant is a drug that helps against the rare metabolic disease CTX (a so-called orphan disease). On the basis of epidemiological estimates, the disease CTX may affect 1 in 50,000 people in the Netherlands – approximately 340 people. Currently only 52 people in the Netherlands are diagnosed. It is expected that the number of people diagnosed will increase by at least three per year when heel prick screening is extended with CTX. Proposals for this are already pending.[1]

2.4 CDCA-Leadiant contains the active substance chenodeoxycholic acid (chenodeoxycholic acid or chenodiol, hereinafter referred to as: **CDCA**). This substance is the only known effective drug for CTX. It does not heal but inhibits the progression of the condition.

2.5 CDCA is a bile acid that is extracted from the bile of oxen, sheep or chickens. Treatment of CTX with CDCA has been known since 1975 and described in at least 70 scientific publications (mainly case studies and in any case no major clinical trials, **Appendix 1**).[2] The standard dose for adults is 250mg 3 times a day.

2.6 However, CDCA was initially registered and marketed for another indication as a medicine. On September 22, 1976, CDCA received the approval for the indication 'dissolving cholesterol gallstones' (**Appendix 2**) and was marketed under the Chenofalk brand on the Dutch market.[3] Since around 1990, CDCA no longer meets the

[1] Gezondheidsraad, advies *Neonatale screening: nieuwe aanbevelingen*, 8 april 2015, p. 48 (https://bit.ly/EdFn35).

[2] Appendix 1: EMA (https://bit.ly/2MUj4Ry).

[3] Appendix 2: S.W. Schalm en G.P. van Berge Henegouwen, Behandeling van galsteendragers met chenodeoxycholzuur, NTVG 1978, 122, nr. 8, p. 266.

international state of science and practice to treat this indication; the crushing of gallstones then becomes the standard (**Appendix 3**).[4]

2.7 It is certain that Chenofalk has in any case been prescribed off-label to CTX patients in the Netherlands since 1991. This in response to a scientific article in the Dutch Journal of Medicine (**Appendix 4**).[5]

2.8 In 2008 and 2009, Sigma-Tau Pharmaceuticals (hereinafter**: Sigma-Tau**), which later renamed itself Leadiant,[6] acquired the rights (and marketing authorization) of Chenofalk in the Netherlands and Chenix in Belgium, respectively. Sigma-Tau already held the rights (and marketing authorization) of the CDCA drug Xenbilox on the German market. The related acquisitions in 2008 and 2009 by Sigma-Tau were aiming to use the registration dossiers of the CDCA medicines for the registration of CDCA for CTX.[7, 8] Another intention is not plausible. After all, why would Leadiant invest in the take-over of a medicine for an indication that since 1990 no longer met the international state of science and practice and with which therefore no money could be made anymore for this indication?

2.9 In November 2015, the Dutch registration for the affordable Chenofalk was cancelled at the request of Sigma-Tau. It is unknown whether Sigma-Tau at that time informed the Medicines Evaluation Board (MEB) that approximately 52 patients were being prescribed Chenofalk *off-label* for CTX. However, the MEB cannot prohibit a cancellation proposed by the owner.

2.10 On 16 December 2014, the European Commission gave Chenodeoxycholic acid Sigma-Tau an orphan 'designation',[9] after which the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the CTX indication for CDCA on 15 September 2016,[10] and the European Medicines Agency (hereafter: EMA) registered CDCA Leadiant as an orphan drug on 10 April 2017.[11]

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[4] Appendix 3: K.J.van Erpecum et. al., Schokgolflithotripsie van galstenen, NTVG 1990, 134, nr. 3, pp 112-115.
[5] Appendix 4: G.P. van Berge Henegouwen en K.J. van Erpecum. Galsteentherapie; nieuwe hoop voor patiënten met chronische leverziekten. NTVG 1991, 135, nr. 16, p. 696.
[6] It was not a company takeover, see website Leadiant (https://bit.ly/2PD3x5E), Business Wire (https://bit.ly/2MSbuHg) and EMA (https://bit.ly/2NMUJtk).
[7] See website Pharmaceutical business review (https://bit.ly/2MQ24ff).
[8] See website Biocentury (https://bit.ly/2M4PoMI).
[9] EU/3/14/1406 (https://bit.ly/2wOmxGr).
[10] EMA/CHMP/542534/2016, Summary of opinion (https://bit.ly/2CqACA0).
[11] EMA, EPAR Product Info CDCA Leadiant, Registration number EU/1/16/1110/001.

2.11 By obtaining European orphan status, Leadiant is allowed to market the medicine CDCA exclusively on the market for the CTX indication in the European Union for ten years, and thus also in the Netherlands. Leadiant did this in July 2017; it then put the medicine (CDCA-Leadiant) on the Dutch market.

2.12 With the acquisition of orphan status, Leadiant has exorbitantly increased the price of the medicine compared with ten years ago by a factor of 500:

- In 2008, the capsule price of Chenofalk was (rounded) EUR 0.28 or EUR 306.60 per patient per year (based on 3 capsules per day).
- In 2017, the capsule price of CDCA-Leadiant is EUR 140 or EUR 153,300 per patient per year (based on 3 capsules per day).

2.13 For a more detailed description of the facts and context of Leadiant conduct that led to this enforcement request, see **Appendix 5** (publication NRC of 25 August 2018).

3. Abuse of Economic Dominance

"Take medicines for rare diseases. It can make sense to give companies an exclusive right to sell such what is known as "orphan drugs" if that's the only way to make a treatment available to patients. But there's no need to give that protection if pharmacies already have effective alternatives that are in line with general practice, well-known and safe.
That's why the Commission has made it clear that in the future, companies won't necessarily get exclusive rights to sell their product in that case. And like that, pharmacies and other suppliers can compete with their own treatments for rare diseases."

Margrethe Vestager
Copenhagen, 20 August 2018[12]

[12] EU Commissioner for Competition; speech 20 August 2018 during the NorWHO conference in Copenhagen (https://bit.ly/2Q7VyP5).

3.1 Economic Dominance

3.1 First and foremost, Leadiant has a dominant position on the relevant product market. The relevant product market in this issue concerns 'treatments against the CTX disease'.

3.2 As said, CTX is an orphan disease and Leadiant has the exclusive right to market CDCA-Leadiant for the CTX indication in the Netherlands for a period of ten years (2017-2027). Because no alternative medicines for CTX are available on the Dutch market, Leadiant is monopolist for the duration of the orphan registration and therefore has a dominant position as referred to in Article 24 of the [Dutch] Competition Act for that period.

3.2 Excessive Pricing

3.3 Leadiant requests EUR 140 per capsule for a medicine that cost no more than EUR 0.28 per capsule ten years earlier. Raw material prices have risen in recent years, especially for the pharma-grade CDCA that complies with the European Pharmacopoeia, but it is not plausible that through this the price of CDCA has increased five hundredfold. The foundation regards this as an indication of an excessive price.

3.4 In April 2018 the costs of pharmaceutical compounding of CDCA in the AMC / UMC were approximately EUR 25,000 per patient per year.[13] When this is compared with the price that Leadiant asks for their medicine, the difference remains big. The costs of treatment of a patient per year with CDCA-Leadiant is approximately EUR 130,000 higher than the costs of a pharmacy compounded product. The foundation also regards this as an indication of an excessive price, even if the above-mentioned pharmacy compounded price would be the cost price.

3.5 CDCA-Leadiant is not a new medicine: exactly the same substance was already registered since 1976 and it was already known that it helped against the CTX disease. There is no innovation by Leadiant of CDCA-Leadiant as a basis for the indication CTX, except two limited clinical studies with existing patients in the Netherlands and Italy,

[13] These costs consisted of EUR 24,000, - costs of raw materials and tests, and EUR 1,000, - for magistral preparation. Because Leadiant's sales market is much larger than the number of patients supplied by the AMC / UMC, the raw material for Leadiant is considerably cheaper.

with which Leadiant obtained the orphan registration from the EMA.[14] It is salient that the Dutch study was done with the now no longer available Xenbilox, and the Italian study with a locally pharmacy-compounded product. Leadiant did not perform the studies with its 'CDCA-Leadiant' product. In short, related to the studies Leadiant has not incurred costs that could explain an increase in the price.[15] Leadiant simply asks a price for CDCA-Leadiant, which, without any justification or objective substantiation, is disproportionate to the effort made to produce the medicine.

3.6 The Foundation realizes that the medicine is produced for a limited patient population. However, production costs are not so high that the drug cannot be produced economically at a significantly lower price than Leadiant currently requires. Production has been taking place since 1976; the required knowledge and production methods are available and the research costs do not have to be written off anymore. The considerably lower costs of pharmaceutical compounding also confirm that the drug can be economically viable for a small patient population at a much lower price.

3.7 In view of the above, the following conclusion is realistic:

(i) the price of CDCA Leadiant cannot be explained on the basis of the production costs of the medicine,[16]

(ii) in comparison with earlier available versions of CDCA, the price of CDCA Leadiant, also measured according to objective criteria, is inexplicably high.[17]

3.3 Abusive behaviour

3.8 Leadiant was only able to implement the exorbitant price increase of CDCA-Leadiant by conduct that qualifies as abuse under the competition law. In summary, the foundation bases this statement on the fact Leadiant first ensured that it was the only

[14] As an aside, there is no patent on the medicine, which, moreover, does not affect the exclusive market right for the indication CTX, based on the orphan drugs regulations.

[15] This view of the foundation is also confirmed in the (draft) report of the National Health Care Institute (ZiN) about the possible inclusion of CDCA-Leadiant in the medicines reimbursement system (GVS). In it ZiN states that the own product Chenodeoxycholic acid Leadiant was not studied in the study submitted by Leadiant, see ZiN, GVS report chenodeoxycholic acid (Chenodeoxycholic acid Leadiant®), August 2018 (draft), p. 11.

[16] Production costs include, in particular, the costs of raw materials, costs of chemical or biotechnology for production, costs for quality controls, research and development costs, packaging costs and a reasonable profit margin. See also A.M. Hill et. al., the Essential Medicines List, BMJ Global Health 2018, 3 (https://bit.ly/2wOfxcv).

[17] In this context, the foundation also feels supported by the opinion of the Minister of Health, Welfare and Sport (answering parliamentary questions about stopping preparation CDCA by Amsterdam UMC, answer questions 8 and 9 (https://bit.ly/2PKBamb).

one with a marketing authorization for CDCA in the Netherlands. Subsequently, they removed the registration with the indication 'dissolving cholesterol gallstones' from this medicine. At the same time they applied for the orphan registration for CTX, which they obtained without much effort with regard to research and with which they became the sole provider of CDCA. Subsequently, they misused that position as a monopolist by charging exorbitant prices.

3.9 As explained above, CDCA was only registered for the indication 'dissolving cholesterol gallstones'. It is certain that Leadiant acquired the rights and marketing authorization from Chenofalk with the primary purpose to obtain the orphan registration of CTX for CDCA. It is also certain that Leadiant removed the registration of Chenofalk for the indication 'dissolving cholesterol gallstones'. And the foundation considers it plausible that Leadiant knew that in the European Union at that moment, or within the foreseeable future, no more CDCA was traded for the indication 'dissolving cholesterol gallstones', so that any parallel imports of off-label products would no longer be possible.

3.10 Leadiant has therefore speculated – according to the foundation all facts indicate that this was a deliberate strategy – that it would not only obtain the orphan registration for CTX with CDCA but also that it would be the only producer of CDCA on the market. It is certain that the acquisition of the orphan registration was not surrounded by major uncertainties and business risks, as the effect of CDCA against CTX disease has been known for years and described in detail in the scientific literature. Leadiant must have known what it would get, namely the exclusive right to an orphan drug in the knowledge that previously existing alternative medicines would no longer be available due to its own actions. Under these circumstances and in that knowledge, Leadiant has been able to raise the price for CDCA Leadiant exorbitantly, and the actual behaviour qualifies as abuse of its dominant position.

3.11 In this context, it is also relevant that CDCA cannot be re-marketed by a pharmaceutical manufacturer for the indication 'dissolving cholesterol gallstones', because this method of treatment has no longer met the international state of science and practice since around 1990. That treatment method can therefore no longer be obtained from market registration, unless supported by evidence from new clinical trials. Given the alternative and already effective treatment methods, it is unlikely that new clinical trials will be carried out on this small market for dissolving gallstones with CDCA.

3.4 Abuse in the sense of exploitation of customers

3.12 CDCA-Leadiant is now the only effective medicine for the treatment of CTX. Patients need CDCA for life. Customers of CDCA Leadiant are hospitals that purchase the medicine for patients.

3.13 CDCA Leadiant is not included in the [Dutch] basic healthcare package; it is therefore not a reimbursable medicine under the [Dutch] Healthcare Insurance Act. This means that patients with only a basic healthcare package insurance have to carry the costs themselves (together with the other hospital costs).[18] The foundation considers that the price of EUR 153,000 per year for a lifelong treatment cannot be carried by an individual patient. Judged according to reasonable norms, the individual patient is being exploited.

3.14 In July 2017, the 52 CTX patients were confronted with the exorbitant price increase. Where they previously paid EUR 308 per treatment per year in 2008, EUR 153,300 will have to be paid since July 2017. Patients had to find an urgent solution to the exorbitant price increase of the drug. The fact that these patients have found a 'solution' with a lenient insurer or in the pharmacy compounded CDCA in AMC doesn't make the actions of Leadiant less wrongful. These patients, as well as the patients who were diagnosed since, are living in constant uncertainty as to whether they will be able to continue to use the medication; paying out of pocket is not an option.

3.15 Charging the above mentioned high price for CDCA-Leadiant qualifies under competition law as exploitation of customers. This statement is based on the following fact that:

(i) the patient is fully dependent on the medicine,
(ii) in ten years the price of the drug has risen by a factor of 500, without the production costs having risen (significantly), and
(iii) it is unlikely that the exorbitant price is objectively justified.

3.16 Even if it would show that insurers, possibly together with the involved hospitals treating CTX patients, would reimburse the costs of CDCA-Leadiant for these patients, there will still be exploitation of users for the above-mentioned three reasons.

[18] An additional health insurance policy will probably not fully cover these costs.

3.17 The fact that the costs per treatment are paid out of the insurance premiums does not change such a judgment.[19] This would most likely lead to an increase in insurance premium for the insured which is undesirable in the efforts to keep health care accessible at an affordable price. The same applies when the costs are (partially) covered from the hospital budget. In fact, this would lead to 'cannibalizing' of other care in the hospital in question, which is obviously undesirable in the context of keeping health care available and accessible. In both cases, Leadiant is negatively affecting the Dutch healthcare system with her actions.

3.18 However the case is looked at, Leadiant receives a price for its medication, which, without any justification or objective substantiation, is disproportionate to the effort made to produce the medicine, regardless of whether the price is individual or (to some extent) is collectively raised. Because of its course of action (§ 3.3) and exorbitant asking price, buyers of the medicine are exploited and / or the Dutch health care system is disadvantaged.

4. Priority

4.1 The ACM gives priority to supervision on the healthcare market. The mitigation of the price of expensive medicines is high on the (national) political agenda. The costs of expensive, effective medicines put pressure on the proper functioning of the health care system. This applies even more to medicines whose prices are inexplicably high and have been set in violation of competition law.

4.2 The ACM states among other things about its priorities with regard to the prices of medicines:

"The ACM ensures that manufacturers of medicines adhere to the rules for competition. We tackle cartels, abuse of market power or strategies aimed at excluding competition or impeding entry. This type of behaviour is disadvantageous for the consumer."[20]

[19] As an aside, this dilution takes place exclusively within the insurer, because these costs are not settled ex post.
[20] See website ACM (https://bit.ly/2NQBPlf).

4.3 At the beginning of this year, the chairman of the ACM wrote with good reason that competition law also applies to medicines under patent.[21] Despite the exclusive right and use of patents, abuse of the applicable competition provisions is still prohibited. This argumentation also applies to medicines with an orphan registration.

4.4 The Leadiant case presented is typical of the abuse of a dominant position. The foundation does not exclude the possibility that other similar cases occur in the Netherlands. The ACM must therefore, in light of its authority to act in this case, send a clear signal to the market that this behaviour, with which customers and the Dutch health care system are disadvantaged, cannot be accepted.

5. Admissibility

5.1 In accordance with its statutory objective – for which the foundation makes concrete and actual efforts – the Foundation strives for the benefit of the general interest: "that medicines and other medical technologies are available on the market in a sustainable and socially acceptable manner, in which context the foundation attaches value to fair pricing and distribution that is in line with written and unwritten national, European and international legal norms." (**Appendix 6**)[22]

5.2 The importance that Leadiant refrains from abuse of a dominant position and the importance that the CDCA-Leadiant medicine becomes available in a fair and accessible manner is therefore a direct interest of the foundation on the basis of the aforementioned specific statutory objective.

5.3 The foregoing is that the foundation is an interested party within the meaning of Article 1:2 paragraph 3 Awb [General Administrative Law Act] and that the foundation is therefore admissible in this request for enforcement.

[21] See website ACM (https://bit.ly/2Cot0Oo).

[22] Appendix 6: See website Pharmaceutical Accountability Foundation (https://bit.ly/2Cngtef).

6. Conclusion

6.1 Leadiant has consciously and strategically worked towards a situation in which they became the sole seller of CDCA: the only effective medicine against CTX. In this process it has acted step by step, ensuring that the previously available alternative medicines have disappeared from the market and that the prices per capsule have subsequently been increased by a factor of 500 to EUR 140. Leadiant has not offered any objective justification for this exorbitant price increase, and this justification does not exist according to the foundation.

6.2 The facts put forward by the foundation make it clear that Leadiant, with their abusive behaviour, acted purely for their own gain, while the patients had no choice; they are completely dependent on the medicine of this manufacturer. Leadiant has by its conduct excluded previously available options from the market, and has, with an exorbitant asking price for the only remaining medicine, seriously exploited customers of the medicine, and that exploitation still continues. In addition, Leadiant has disadvantaged the Dutch health care system with their actions and continues to disadvantage the health care system.

6.3 In view of this, the foundation requests the ACM to establish that Leadiant is acting in violation of Article 24 of the [Dutch] Competition Act and to impose a fine on Leadiant pursuant to Article 56 of the [Dutch] Competition Act or to take action against Leadiant in a different manner.

6.4 The foundation is available to give a further explanation of the above request.

Sincerely,
also on behalf of Rogier Meijer

Jan-Koen Sluijs