ALLEN & OVERY

Excessive pricing and orphan drugs: Leadiant sanctioned by the Italian Antitrust Authority

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In a long-awaited decision published on 31 May 2021, the IAA found that Leadiant infringed Article 102 TFEU through a multifaceted strategy that led to it obtaining an excessive price for its CDCA Leadiant® medicine. A number of lessons can be learnt from this case.

Key takeaways

- Several EU national antitrust authorities may investigate potential excessive pricing of the same drug.
- Agreeing prices with national medicines agencies does not provide a safe harbour from antitrust enforcement.
- Pharma companies should base prices on their own relevant costs and not rely on benchmarks.
- Antitrust authorities will scrutinise increases in prices of orphan medicines.

Setting the scene: finding the cure for rare diseases

Before the EU Orphan Regulation was introduced in 2000, there were only 15 medicinal products with a European marketing authorisation (MA) intended for rare diseases. This poor record was generally explained by the

imbalance between the risk and reward for pharmaceutical companies in developing treatments for rare diseases: small consumer markets for these treatments were considered insufficient to recover product development costs.

The EU Orphan Regulation provides various incentives to develop medicines, both pre- and post-marketing, with the granting of so-called 'orphan market exclusivity' as the key incentive. This incentive grants developers of designated orphan medicines exclusive marketing rights throughout the EU single market for a 10-year period after receiving the MA.

The new European regulatory environment, together with similar global developments, have substantially contributed to filling the gap between the needs of patients with rare diseases and the needs of pharmaceutical companies to achieve market-driven commercial innovation. In the period 2000-2021, 2,552 orphan designations were issued by the **European Commission**. Despite this progress, there are still **significant unmet medical needs**, as over 90% of the known rare diseases have no approved treatment options available.

Recognising that there is still a lot that needs to be done in the fight against rare diseases, the current debate concerns the price of orphan drugs. It has been **recently stated** that "as a matter of fact, the diseases, not the drugs, are the orphans because all drugs are very expensive". This issue is indeed very delicate: striking the right balance between rewarding the pharmaceutical companies for the costs incurred and the risks taken in developing orphan drugs and the payment of fair prices by the national healthcare systems to the pharmaceutical companies is key to ensuring that proper incentives are available for curing rare diseases. Unsurprisingly, Leadiant has already announced that it will appeal the IAA decision (the Decision) as it "raises several questions" and risks "undermining proper initiatives for bringing and maintaining in the market newly authorised medical products for rare diseases".

While there is an ongoing debate over whether there is a need to improve the current regulatory framework, there is a broad consensus that, when necessary, the antitrust authorities have a role to play in protecting patients. Such *ex post* intervention in a process that is supervised by national competent authorities responsible for human medicines (National Medicines Agencies) can result in uncertainty. However, the Decision provides a number of helpful indications to the industry.

The Leadiant case: the build up to the IAA's probe

The Italian Leadiant case – and similar cases in Spain, the Netherlands and Belgium - concerns the treatment of cerebrotendinous xanthomatosis (CTX), a rare metabolic disorder. The facts leading up to the IAA's enforcement, as alleged by the IAA and relevant for the Italian investigation, are as follows.

In 2008, Leadiant purchased a drug based on chenodeoxycholic acid (CDCA) to treat gallstones, which is also prescribed off-label to treat serious diseases such as CTX, with the brand name Chenofalk®. A few months later, Leadiant entered into an exclusive supply agreement with the only credible supplier of CDCA in Europe – the Italian chemical company PCA – enabling Leadiant to obtain exclusive control of the medicine's active ingredient.

Once it had obtained a leading position on the EU national markets for marketing Chenofalk®, Leadiant changed the name to Xenbilox® and, in mid-2014, increased the price from EUR660 to EUR2,900 per pack.

In December 2014, Leadiant obtained the preliminary "orphan" designation for Xenbilox® and, therefore, started to benefit from a 10-year orphan market exclusivity period.

In January 2016, Leadiant started marketing Xenbilox® in Italy. Until then, the Azienda Ospedaliera Universitaria Senese (AOUS) had been carrying out the pharmaceutical preparation of the medicine in its laboratory (galenic compounding). By exploiting its exclusive CDCA supply contract with PCA, Leadiant prevented Italian hospitals from continuing to be able to source the active ingredient and prepare the medicine. This forced hospitals to import Xenbilox®, the only CDCA-based medicinal product available, at the aforementioned significantly increased price.

In November 2016, Leadiant also strengthened its position by entering into a new agreement with PCA. This granted it increased exclusivity and, therefore, hindered the production of galenic compounds based on CDCA both in Italy and in the rest of Europe.

Between the end of 2016 and the beginning of 2017, Leadiant implemented a strategy to artificially differentiate the medicine. It withdrew Xenbilox® from the German market and established a German company (Leadiant GmbH) to acquire the MA for the identical orphan drug CDCA Leadiant®. The aim of this strategy was to ensure that the owner of the orphan medicine CDCA Leadiant® was formally distinct from the owner of Xenbilox® so that the competent authorities would not associate the two medicines when determining their reimbursement price.

In June 2017, upon the introduction of CDCA Leadiant® on the Italian domestic market, Leadiant started negotiations with the Italian Medicines Agency (AIFA) to set the price for CDCA Leadiant® and to add it to the list of medicines reimbursed by the Italian National Health Service (INHS). The initial price submitted by Leadiant was EUR15,506.97 per pack. AIFA deemed this cost unjustified, and responded that an adequate price should not exceed that of Xenbilox® by more than 10% (the maximum value attributable to the benefit associated with the registration of the orphan therapeutic indication).

After a long negotiation that, according to the IAA, was "prolonged by an intentional delaying and obstructive behaviour by Leadiant", the parties agreed on an ex-factory price for CDCA Leadiant® of between EUR5,000 and EUR7,000 per pack. This price was agreed after the IAA opened its abuse of dominance investigation on 8 October 2019.

The Decision: a narrow market definition

In the Decision, the IAA first assessed whether Leadiant should be considered dominant. Adopting a well-established approach in pharmaceutical cases, the IAA focussed on the actual therapeutic interchangeability (ie which molecules are regarded by the attending physicians as reasonably close substitutes for treating a medical condition). In its assessment, the IAA considered CTX as an ultra-rare disease and, therefore, identified the relevant market as relating to the production and sale of medicines for the treatment of CTX.

CTX has been mainly treated with CDCA, with very limited and now obsolete alternative therapeutic options based on cholic acid, ursodeoxycholic acid and statins. However, these alternatives were not considered to be as effective as CDCA in treating CTX. The lack of therapeutic alternatives to CDCA for the treatment of CTX led the IAA to define the relevant market at the level of the single active ingredient (ATC5), consistent with the IAA case law in the *Aspen* case.

The Decision: dominance linked to orphan designation

In this market, Leadiant was found to be dominant. Since 2016, CDCA Leadiant® has been the only CTX drug authorised in Italy, and the orphan designation granted it a statutory 10-year market exclusivity period over any similarly effective treatment for CTX until 2027. Furthermore, the applicable regulation prevents pharmacists from creating a galenic compound with the same active ingredient, the same dosage, and the same overall composition if, in the national market, there is an industrial product that is authorised for a specific therapeutic indication. This hinders the possibility of creating a CDCA-based galenic compound as a viable alternative to CDCA Leadiant® and, in the IAA's opinion, this will remain the case until the expiry of Leadiant's patent in 2027.

The Decision: complex exclusionary strategy

The IAA concluded that Leadiant had abused its dominant position as a result of a complex exclusionary strategy, which culminated in obtaining an excessive price from AIFA.

In particular, the IAA contested the multifaceted "preparatory" strategy of Leadiant who:

- Increased the price for Xenbilox® (the off-label drug) in order to prepare the market to pay a premium price for the future on-label drug.
- Artificially differentiated the orphan drug from Xenbilox® by withdrawing it from the market and obtaining an MA for CDCA Leadiant® through a different company to avoid justifying the price increase from a mere repurposing (new therapeutic indication already treated with an old off-label drug).
- Unduly prolonged negotiations with AIFA, including by delaying the provision of data on costs.

The IAA then applied the *United Brands* test to determine whether the price obtained for CDCA Leadiant® was excessive. This is a two-fold test: the first part calls for a cost-price analysis, followed by a determination of whether the difference is excessive; the second part requires determining whether a price is either excessive in itself or by comparison to competitors' products.

The cost-price analysis was carried out by the IAA, who applied two distinct methodologies. First, the IAA assessed the internal rate of return of the CDCA project (financial methodology). It then ran a cost-plus analysis (accounting methodology).

The internal documents found during dawn raids played a decisive role in the outcome of the cost-price analysis. First, the IAA noted that all the pricing hypotheses made by Leadiant were based on the maximum price that the customer was willing to pay for the drug irrespective of the actual costs of the CDCA project. Second, the IAA used the same cost of capital relating to the CDCA project (WACC) as Leadiant had in its internal documentation. Third, the IAA rejected the possibility that Leadiant could lose its exclusivity before the end of the 10-year period – which would have decreased the price granted by AIFA – noting that, in its internal documentation, Leadiant had stated that "the agreement reached with AIFA will be maintained for the entire period with a 100% probability".

Interestingly, in assessing the cost of capital, the IAA noted that the price increase of Xenibilox® - which was part of the abusive strategy and aimed at financing the CDCA project – substantially decreased the risk borne by Leadiant in its efforts to obtain orphan designation. Moreover, the legal costs for defending Leadiant against several antitrust complaints could not be taken into account, being the consequence of the very same infringement contested by Article 102 TFEU.

As to the second part of the *United Brands* test, namely whether the price was either excessive in itself or by comparison to other benchmarks, the IAA stated that – contrary to the conclusions reached by Advocate General Wahl in the *AKKA/LAA* case – it is sufficient to demonstrate that the price is excessive in itself. In order to substantiate this conclusion, the IAA stated that the benchmark of 75 orphan drugs marketed in Italy proposed by Leadiant was not significant, as these medicines had different therapeutic indications and, therefore, could not be compared with CDCA Leadiant®. Moreover, the IAA rejected the comparisons with the prices obtained for CDCA Leadiant® in other EU Member States, as these prices could be affected by the same abusive strategy. In addition, it noted that each Member State has its own different pricing and reimbursement system.

The IAA then assessed whether the price was excessive in itself. In conducting this evaluation, the IAA considered the Leadiant case to be an example of "repositioning", as described in the **Study to support the evaluation of the EU Orphan Regulation** (July 2019). In essence, "repositioning" covers all those cases in which existing treatments are "reinvented" as orphan medicines. The rationale behind incentivising the registration of these products as orphan medicines is that this enables regulators to better monitor the products' effectiveness, quality and safety. However, as had occurred with CDCA Leadiant®, obtaining an MA as an orphan medicine often involves substantial increases in the price of the medicine. The modest level of the R&D investments by Leadiant in relation to a medicine that was already available to patients was decisive in the IAA finding that CDCA Leadiant®'s prices satisfied the second prong of the *United Brands* test.

The IAA concluded that, since June 2017, Leadiant had charged unjustifiably excessive prices for its own CDCA-containing orphan drug. Interestingly, in setting the amount of the fine at EUR3.7 million, the IAA took into account that parallel investigations into the same product have been initiated by other national antitrust authorities.

Takeaways for avoiding future antitrust enforcement

There are several lessons to be learnt from this case for pharma companies operating in the EU:

- Excessive pricing cases are likely to be investigated by several antitrust authorities within the EU, despite involving the same product. This trend, which is particularly burdensome for the company under investigation, will probably continue given the differences in healthcare systems and the fact that prices are set at the national level.
- Agreeing prices with National Medicines Agencies does not prevent the relevant antitrust authorities from applying Article 102 TFEU. This should not come as a surprise. There are several previous examples, for instance in the telecom sector, where the pricing approved by the sector regulator did not shield the dominant company from the enforcement of antitrust rules.
- Pharmaceutical companies should base their pricing analysis on their own relevant costs rather than on customers' willingness to pay, as their internal documentation may very well end up in the hands of the antitrust authorities, whose investigative powers have been sharpened by the recent implementation of the ECN+ Directive.
- In the absence of a solid *ex ante* analysis based on internal costs and projections, it is unlikely that benchmarks (ie prices charged for other medicines and/or in other geographic markets for the same medicine) would be considered sufficient to show the fairness of the price.
- Increasing the price of a newly authorised orphan medicine that was already available to patients at a far lower price (repositioning) will most likely continue to be subject to significant scrutiny; in such cases, modest R&D investments may make it difficult to justify significant price increases.

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