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The same, but better – Shire v European Medicines Agency (T 80/16)

The General Court approves of innovator's improved follow-on orphan drug with same active as its earlier product

Summary

In its judgment of 22nd March 2018 (T-80/16), the General Court held that the European Medicines Agency (EMA) was wrong to refuse validation of Shire's application for orphan designation for its intrathecally administered formulation of the active ingredient idursulfase (Idursulfase-IT) on the basis that the issuance of a marketing authorisation for Elaprase®, which contained the same active, precluded it from doing so. In the court's view, the EMA misapplied the procedure for orphan designation. According to the court's decision, the existence of an earlier authorisation for an orphan product does not preclude issuance of a new orphan designation for a follow-on orphan product having the same active as long as it meets the designation requirements. In line with this conclusion, the court annulled the EMA's refusal decision.

The decision is good news both for patients suffering from rare diseases and innovator companies that would like to improve on existing orphan products.

The EMA's refusal decision

The EMA had argued that Shire's application for orphan designation for Idursulfase-IT had not been timely filed because Shire had already obtained, in 2001, an orphan designation for the active ingredient idursulfase for the treatment of Hunter Syndrome and was granted a marketing authorisation in 2007 for the orphan medicinal product Elaprase® containing idursulfase. In its opinion, Elaprase® and Idursulfase-IT were the same medicinal product and fell under the same orphan designation. Therefore it took the view that, since an application for orphan designation had to be made before the application for marketing authorisation, Shire's 2015 application for orphan designation of Idursulfase-IT was too late. According to the EMA, Shire should have applied to vary its existing orphan designation for Elaprase®. However, this would have meant that Idursulfase-IT could not have benefited from a new 10-year period of orphan market exclusivity. Shire disagreed with the EMA's assessment of the facts and applied for annulment of the refusal decision.

Not the same medicinal product

The court found that the EMA had not followed the correct procedure when it conducted its validation procedure for Shire's application for orphan designation. It took the view that despite the facts that Idursulfase-IT and Elaprase® contained the same active substance and were both for Hunter Syndrome and that the application for Idursulfase-IT was submitted by the same sponsor as Elaprase®, this did not necessarily mean that both medicines were the same. A more detailed assessment was necessary. Elaprase® was administered intravenously, rather than intrathecally, in a formulation that was different from the one used for Idursulfase-IT. In addition, Idursulfase-IT targeted a specific subpopulation of patients with Hunter syndrome. According to Shire's application, Idursulfase-IT would not replace Elaprase®, but would constitute a supplementary treatment for patients suffering from a particular severe form of Hunter Syndrome that caused cognitive impairment and a reduced life expectancy. Therefore it was "apparent from the file before the Court" that Elaprase® differed from Idursulfase-IT in its composition, method of administration and therapeutic effects.

In the court's view, the EMA should have proceeded to validate the application for orphan designation because the validation stage was purely administrative in nature. It was only at the second stage of the procedure that the Committee on Orphan Medicinal Product (COMP) was to adopt an opinion as to whether the application met the criteria for orphan designation set out in Article 3(1) of Regulation (EC) No 141/2000 (the Orphan Regulation) namely:

"3(1) A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

- (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and

- (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that **the medicinal product will be of significant benefit** to those affected by that condition." (our emphasis added)

Limited scope of original orphan designation

The EMA had further argued that the designation decision of 2001 related in general to the active substance idursulfase for the treatment of Hunter syndrome, without further specifics, as a result of which that decision also covered Idursulfase-IT which was the subject of the 2015 application. It found support for this view in the 2003 orphan communication which states that if the same sponsor applies for a marketing authorisation for a second subset of a designated orphan condition for which it obtained marketing approval for a first subset already, the second authorised indication will be covered by the marketing exclusivity granted on the initial authorisation.

The court noted that it was quite normal that, where an application for orphan designation had been submitted at the development stage of a medicinal product, it was described in respect of its active substance. It was only at a later stage of its development that the medicinal product became tangible for the purposes of its future marketing. The 2001 orphan designation led to the development of the medicinal product Elaprase®. According to the court, accepting that the original broadly formulated designation could prevent any subsequent request for the designation of a new medicinal product containing the same active substance would run counter to Article 3(1)(b) and the objective and general scheme of the Orphan Regulation.

> "... it was in the interest of patients ... to have access to a similar medicinal product that gave them a significant benefit compared to a previously authorised orphan product, even if the later product contained the same active substance."

Any "significant benefit" counts

In the court's view, it was apparent from the second alternative of Article 3(1)(b) of the Orphan Regulation that a medicinal product may be designated as an orphan product even if a treatment exists for the condition in question, provided that it represents a "significant benefit" to those affected by the condition. It highlighted that the "clinically relevant advantage" and the "major contribution to patient care", which enable the potential orphan medicinal product to be described as being of significant benefit, could be established only by comparison with treatments that had already been authorised. In particular, the court pointed out that the 2003 orphan communication expressly states that particular benefits for a sub-sample of the population can provide a significant benefit and that "where there are serious and documented difficulties with the formulation or route of administration of an authorised medicinal product, a more convenient formulation or route may be considered as a significant benefit".

Accordingly, the court concluded that the justification for orphan designation could be based on the assumption of a more efficient formulation and means of administration than an authorised medicinal product with the same active substance which was intended to treat the same condition. Shire's application stated that Idursulfase-IT would provide a significant benefit to persons suffering from Hunter Syndrome, compared to Elaprase®, on account of its therapeutic effects as well as its composition and means of administration.

Accordingly, the court held that it was the COMP's responsibility at the second stage of the procedure to assess whether the characteristics of Idursulfase-IT would likely be of significant benefit to patients with Hunter Syndrome, taking into account the relevant scientific evidence.

"Global marketing authorisation" concept is irrelevant in the context of the Orphan Regulation

The court also noted that the concept of "global marketing authorisation" of Directive 2001/83/EC (the Medicinal Products Directive) and the consequent curtailing of the regulatory data protection period for variation applications of an approved medicinal product was not applicable in the context of an application for orphan designation. The Orphan Regulation provided for separate and distinct procedures concerning orphan designation and the application for marketing authorisation, as highlighted e.g. by criteria such as "significant benefit" as a prerequisite for orphan designation.

No duplication of exclusivity

The court also did not share the EMA's view that a possible "duplication" of orphan market exclusivity "would lead to a misuse of the provisions of [the Orphan Regulation] and would be contrary to its purpose". The court held that it was in the interest of patients suffering from a rare disease to have access to a similar medicinal product that gave them a significant benefit compared to a previously authorised orphan product, even if the later product contained the same active substance. According to the court, the argument advanced by the EMA and the Commission would lead to a sponsor such as the applicant being deprived of any opportunity to demonstrate scientifically that its product entails significant benefit to patients suffering from the condition at issue within the meaning of the second alternative of Article 3(1)(b) of Orphan Regulation.

In this context, the court made reference to the recent Court of Justice decision in Teva v EMA (C-138/15 P) which confirmed that the 10-year period of market exclusivity of an approved orphan product does not preclude a second, similar product, which has been authorised by way of derogation under Article 8(3) of the Orphan Regulation, to benefit from a new 10-year period of orphan market exclusivity, as long as it also fulfils the designation requirements set out in Article 3(1) of the Orphan Regulation. This decision had been taken notwithstanding the fact that the sponsor for both products was the same.

Conclusion

The General Court's decision is part of a series of recent decisions, in which the EU courts have affirmed that the Orphan Regulation should be interpreted so as to achieve its aim of incentivising research into rare diseases.

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