Testimony Before the Food and Drug Administration's Cellular, Tissue, and Gene Therapies Advisory Committee Regarding Andexanet (Andexxa)

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November 21, 2024

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Public Citizen strongly opposes the supplemental application to convert the accelerated approval of andexanet to full approval.[1]

Based on our assessment of the presented evidence, the postmarketing trial (ANNEXA-I) failed to verify a potential net benefit for andexanet in acute intracerebral hemorrhage subjects who were treated with apixaban or rivaroxaban.

The trial showed a 12% difference in favor of andexanet over usual care on a short-term primary efficacy endpoint. Measured 12 hours after randomization, this endpoint was a composite of three components, including hematoma expansion.[2] Although this 12% difference was statistically significant, its clinical usefulness is questionable for several reasons. First, hematoma expansion was the primary driver for the positive difference, given that the results for the two other components of the primary endpoint differed only slightly between the two groups.[3] Second, hematoma expansion 12 hours after randomization is an earlier time than guidelines recommend. Because no imaging data were collected beyond 12 hours, delayed hematoma expansion is unknown.[4] Third, because hematoma expansion was measured as a dichotomized response, it does not fully capture the treatment effect on this outcome. The FDA had relayed some of these issues to the drugmaker who appears to have dismissed them.[5]

[1] AstraZeneca. Label: andexanet alpha (Andexxa). 2024. https://www.fda.gov/media/113279/download?attachment. Accessed November 20, 2024.
[2] Food and Drug Administration. FDA briefing document, supplemental application sBLA# 125586/546 for Andexxa (coagulation factor Xa [recombinant], inactivated-zhzo), Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. November 21, 2024. https://www.fda.gov/media/183674/download. Accessed November 20, 2024. PDF p. 7, 26.
[3] *Ibid*. PDF p. 8.
[4] *Ibid*. PDF p. 26.
[5] *Ibid*. PDF p. 10.

In terms of risks, 35 (15%) of the andexanet-treated subjects suffered thrombotic events, compared with 16 (7%) of those who received usual care.[6] This twofold increase was statistically significant. It also was clinically important because it was largely driven by brain thrombosis in the andexanet-treated subjects (n = 21, 9%) than in the usual-care group (n = 4, 2%).[7]

Although death rates were comparable between the two groups (28% for andexanet and 26% for usual care), the rate of death attributable to thrombotic events was more than twice as high in the andexanet-treated group.[8]

Other important methodological issues not discussed in the FDA briefing document may suggest that certain aspects of ANNEXA-I may have tipped the scales in favor of andexanet. For example, whereas both the safety analysis and sensitivity analyses for efficacy included 474 subjects, the primary efficacy analysis excluded 70 of these subjects.[9] It is not clear whether this exclusion favored andexanet. Additionally, given that 162 (79%) of andexanet-treated subjects received a low dose of the drug,[10] the findings may not be generalizable to those receiving a high dose. Moreover, the fact that 11% of the usual-care subjects received "no treatment" also may have disadvantaged this group.

In 2018, the clinical reviewers of the accelerated approval application for andexanet concluded that the uncertainty regarding the clinical benefit of the drug, in combination with concerns about its safety, results in an unfavorable overall benefit-risk profile.[11] However, the FDA director responsible for reviewing the drug application downplayed this concern, arguing that risks are "mitigated" by drug-label warnings.

Six years later, there is still no acceptable evidence to support the benefit of this expensive drug (priced in 2020 at $27,500 for a low dose in adults).[12] We urge the FDA not to grant andexanet full approval. Instead, the agency should require a new optimally designed trial powered to assess all key clinical outcomes.

[6] *Ibid*. PDF p. 23-24.
[7] *Ibid*. PDF p. 24.
[8] *Ibid*. PDF p. 26.
[9] *Ibid*. PDF p. 16.
[10] *Ibid*. PDF p. 17.
[11] Food and Drug Administration. Summary basis for regulatory action for ANDEXXA/coagulation factor Xa (recombinant), inactivated-zhzo. May 3, 2018. https://www.fda.gov/media/113954/download. Accessed November 20, 2024.
[12] Mahan CE. Reply to "key points to consider when evaluating Andexxa for formulary addition." *Neurocrit Care*. 2020;33(1):323-326.