Citizen's Petition to the FDA,
2.12.2020
Clark Anderson

The following document, dated 2/2/2020, is a ***Citizen Petition*** to the U.S. FDA: https://www.fda.gov/regulatory-information/dockets-management/comment-proposed-regulations-and-submit-petitions

A. Action Requested:

In this petition I implore the FDA to revoke approval of the drug tolvaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD). FDA approval of tolvaptan was described in a 13-page letter dated April 23, 2018, signed by Norman L. Stockbridge of the CDER, FDA. The letter, identified as NDA Approval 20441, states in part: "We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text." The approval letter can be obtained in full at url: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/204441Orig1s000Approv.pdf.

NB: I perceive that certain FDA staff will be unable to evaluate fairly my petition because of inherent conflicts of interest. Those engaged in the approval of tolvaptan (especially, Drs. Stockbridge and Thompson) should therefore be excluded from the review of my petition.

B. Statement of Grounds:

Tolvaptan was approved by the FDA in April, 2018, for the treatment of ADPKD following the publication of several papers describing lengthy clinical trials. Enthusiastic about a new drug for PKD, I studied these papers with assiduous care. My analysis concluded that the results were seriously flawed and that the drug's efficacy was so doubtful that it could not be considered therapeutic. Further, the statistics were faulty, which would negate any claim to statistical significance of a perceived benefit; and an obvious alternative hypothesis that would render the result a side effect of the drug was not considered.

In judging tolvaptan useless, I must account for its acclaim by distinguished medical journals such as the New England Journal of Medicine and for its approval by the FDA and the EMA, as these institutions enjoy wide reputations as trusted judges of quality science. The explanation for the acclaim, I surmise, is that the reviewers were misled by the adroit obfuscation of the published results; drug efficacy was exaggerated and the primary data were obscured. The reviewers were likely deceived; they apparently failed to scrutinize the basic data! I can find no evidence in the tolvaptan review at the FDA website that the reviewers actually plumbed the investigators' data; they appeared to take the authors' conclusions of efficacy at face value.

Calling attention to further shortcomings of the FDA review, I point out that the last sentence of the Summary Review dated April 23, 2018, reads, "Ultimately it will be for patients to decide if tolvaptan is the drug for them." This statement I interpret as a blatant abdication of FDA responsibility. It reflects, I sense, an underlying faint-hearted attitude of the review group. For an FDA official to defer drug approval to patients is anathema to the basic FDA duty. Patient preferences are easily manipulated by advertising and the placebo effect; patients are unable to make these decisions. Rather, licensing authority rests with the FDA. (The quotation cited is the final sentence of a Benefit-Risk Assessment on page 4 of an 18-page document identified at the FDA website as Summary Review 204441Orig1s000.)

Further, the life-threatening side effects of the drug were sufficiently alarming that the licensing agencies, both the FDA and the EMA, affixed limitations on the use of the drug, limitations that were so restrictive as to suggest *de facto* disapproval. Note well that these limitations resulted from judgements about side effects alone, not from lack of efficacy.

Thus, I conclude not only that the studies of tolvaptan indicate it to be of negligible efficacy, but the supporting studies themselves are severely flawed. Further, the presentation of the clinical studies was deceptive, misleading the reviewers into overlooking the basic shortcomings of the drug. The reviews were likely superficial, accepting the sponsors' word for efficacy and failing to look searchingly at the data. And, the drug is dangerous.

These grounds underlying my petition I have described in detail in a recently published manuscript in the journal Clinical Nephrology, entitled *Doubts about the Efficacy of Tolvaptan for Polycystic Kidney Disease*. The paper is attached and is available on-line at: DOI 10.5414/CN109927Letter. e-pub: January 30, 2020.

C. Environment impact:

We claim categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter."

D. Economic Impact:

The economic impact information will be submitted upon request of the commissioner.

E. Certification:

I, the undersigned, certify, that, to the best of my knowledge and belief, this petition includes not only all information and views on which the petition relies but all known data and information unfavorable to the petition.

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End of: Citizen Petition 12.5.2019