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October 28, 2002

VIA TELEFACSIMILE
Confidential Communication/ Privileged Legal Opinion

Drs. G.W.F. van der Kloet-Dorleijn
EP&C
P.O. Box 3241
2280 GE Rijswijk
The Netherlands

Re: U.S. Patent No. 4,711,880
CRYSTALINE DISODIUM 3-AMINO-1-HYDROXYPROPANE-1,...
Your Reference: 992066/TK/AGR
Our Reference: STAHL=2

Dear Drs. van der Kloet-Dorleijn:

Per your request for us to provide a short opinion on the validity of the claims of the above-identified Stahl patent 4,711,880, hereinafter sometimes the '880 patent, owned by Novartis, particularly in view of the translation of the Argentine patent publication 218,558, as well as other evidence you have provided to us, but without our having studied the prosecution history of the application which matured into Stahl '880, we advise as follows:

Summary Opinion[1]

Based on our initial study and present understanding, all the claims of Stahl '880 are invalid, in our opinion.

[1] Please be advised that our opinion is not a guarantee. The patent law in the U.S.A. is complex and is not consistently applied by patent examiners or the courts, or even by patent attorneys. Moreover, our analysis is hampered by not having reviewed the prosecution history of the application which matured into USP '880, and therefore out analysis is incomplete. Consequently, there is no certainty, if suit were to be filed, that the Court or Jury would agree with our opinion.

The '880 Patent

The Stahl USP '880, patented in 1987 and based on an application filed in 1986, in turn a division of an application filed July 29, 1985, is directed to the disodium salt of the now well-known bisphosphonate commonly called "pamidronate", said to be in a novel crystal modification containing water of crystallization.

Column 1 of the patent acknowledges that the disodium salt was previously known and mentioned for oral administration, from DE 2,553,963 (this document is identified by a different number at column 1, line 44 as DE 2,443,963).

Thus, from the specification (description) itself of the Stahl USP '880, the only feature which appears to be alleged as being novel is the hydrated form of the disodium salt. Such description alleges that the hydrated crystalline form is surprisingly stable (see especially column 2, lines 35-44, and lines 59 *et seq)*.

The Claims

Claim 1 appears to be clearly anticipated by the Argentine patent publication 218,558[2]. Example 2 of the Argentine patent publication '558 indicates that the disodium salt "could be purified by crystallization from water or aqueous ethanol". Dr. de Gelder reproduced Example 2 of AR '558; at page 4, part 5 of his report, he shows the production of the crystalline product from aqueous ethanol as stated in Example 2 of the Argentine patent publication. On page 7, part 5, Dr. de Gelder concludes that such material is pure pentahydrate.

Moreover, even without the recrystallization, the process of Example 2 of the Argentine patent publication (part 3 at the bottom of page 3 of Dr. de Gelder's report) turns out to a mixture of hydrated forms, namely dihydrate, tetrahydrate and possibly some pentahydrate (part 3 at page 6 of Dr. de Gelder's report).

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[2] While I do not see any date of publication, I am assuming consistent with the information provided to me that the Argentine patent publication was published more than one year prior to the filing date of the Stahl parent application 759,985 of July 29, 1985, i.e. the Argentine patent publication was published prior to July 29, 1984, and is thus prior art under 35 USC 102(b).

As claim 1 only requires the dissodium salt to contain water of crystallization, claim 1 is clearly anticipated by the Argentine patent publication.

Claims 2 and 3 more specifically recite the pentahydrate form and are either anticipated or made obvious by the Argentine patent publication.

Claims 4-7 are essentially product-by-process claims, or hybrid product-by-process claims, and fall in the same category as claim 1 because, for purposes of patentability or validity under U.S. law, the process language does not affect the claims unless the process results in a change in the product itself. According to our present understanding, the product is the same in all cases in claims 1 and 4-7, and such product corresponds to what is recited in claim 1, and therefore these claims are invalid for the same reasons as claim 1.

According to the information you have provided, claim 8 is merely another way to recite the crystalline pentahydrate form of claim 3. Consequently, our opinion concerning claim 8 is the same as indicated above with respect to claim 3.

Claim 9 merely calls for a pharmaceutical composition including the hydrated compound of claim 1. As such hydrate form of the compound was previously known from the Argentine patent publication, and as pharmaceutical use of the disodium salt *per se* was known from DE 2,553,963, it would have been obvious to use the compound of claim 1, known from the Argentine patent publication, in the very same pharmaceutical composition. Therefore, it is also our opinion that claim 9 is invalid.

Conclusion

As stated above, our opinions given above have been made without analysis of the prosecution history of the application which matured to Stahl '880. If my subsequent study of this prosecution history turns up additional information that might affect the basis of our opinions above, then our opinions may change.

Moreover, if any factual statements made above are incorrect, or you are aware of any additional information that might affect the basis of our opinions above, that information should be brought to our attention.

Lastly, to protect the privileged nature of this and my earlier communications on this subject, the distribution of the present letter and my earlier communications should be limited only to those employees or officers of the client company who need to see it, and they should be cautioned to treat such communications as privileged and confidential.

You have asked me to procure a copy of the prosecution history of the '880 patent, and we will do so. We will then give you our further opinion after our further review.

Sincerely,

Sheridan Neimark

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