FEIBA

MEDICAL ASSESSMENT

1. The Company have submitted two documents as written representations to the Medicines Commission. Document one identifies the points at issue under Section 21(3) of the Medicines Act 1968 and incorporates enclosures A to I. Document two refers to data on heat treatment of the product.

2.1 "The Committee considered that inadequate evidence of efficacy had been provided for haemophilia A patients with Factor VIII inhibitors and agreed that point 2 of the Section 21(1) letter had not been answered".

2.2 As further evidence of efficacy, the Company have enclosed anecdotal reports, an open uncontrolled study, a paper exposing the clinical problem demonstrating the need for different therapeutic approaches in haemophilia A, and a series of references to support possible mechanisms of action of the product.

2.3 Previous evidence submitted by the Company to support the efficacy of the product includes a study by Hilgartner et al in which 165 bleeding episodes in 46 Factor VIII inhibitor patients and 3 Factor IX inhibitor patients were treated and the effect was similar to treatment by Factor VIII concentrate in haemophiliacs without inhibitor. However, in this study only 20% of patients had a significant rise in inhibitor titre.

Another previously submitted study was a double-blind randomised clinical trial by Sjamsoedin et al, where single administrations of Feiba were significantly more effective than the non-activated Factor IX controlled preparations. Also in the appeal submission to CSM the Company submitted an editorial from The New England Journal of Medicine by Roberts, who stresses the need to use a product such as Feiba only in major bleeds in haemophiliacs with inhibitor titres above 10-20 Bethsda units.

3. New Evidence

3.1 The Company have submitted a retrospective study comparing the use of Factor VIII and Feiba in the treatment of haemophilia A patients with an inhibitor Factor VIII. This study amounted to a questionnaire sent to consultants in haemophilia centres who have used the product on a named patient basis.

Eight consultants had apparently used Feiba on 33 patients and case reports on 27 were enclosed. It is very difficult to assess such semi-quantitative data as it is not always clear what was the magnitude of the inhibitor titre before treatment.

However there does seem to be a general professional confidence in the product, although it is quite clear that different consultants have different criteria for its use. It is also noted that this enclosure excludes a significant number of consultants working in the field of haemophilia and thus should not be taken as a "poll" of haemophilia treatment in this country.

3.2 A paper is presented: "The evaluation of the clinical efficacy of Feiba in minor bleeding episodes" by Bossner and Jourdan. This records 33 bleeding episodes in 9 patients, in which there was reasonable response to the medicament. Six of these were considered to have high-inhibitor titres.

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In the absence of more definitive raw data there is no reason to think that the preparation was not effective in the patients studied.

3.3 A series of cases are reported by Dr Michael Diaz, who reports on surgical operations performed under Feiba cover. Again, this report is semi-quantitative but there is strong indication that the preparation was effective in patients who had moderate to high inhibitor titres.

4. The management of haemophilia

4.1 Enclosure D. is a paper by Kesteven et al, published in Thromb.Haemostas. 1984. The thrust of this paper is that patients with mild haemophilia having low inhibitor titres are at risk of dramatically increasing the inhibitor titre if bleeding episodes are treated with Factor VIII concentrates; the author reflects that when this happens patients need to be treated with Feiba or another product Autoplex.

5. Mechanism of action

5.1 Despite intensive effort on the part of the Company and other investigators it is still not clear the precise chemical nature of Feiba, nor its exact mechanism of action. A number of possible alternatives are proposed but none of these advance the argument in relation to efficacy, which can only be seen in the clinical situation ultimately. However, none of these papers discredit the possibility that Feiba does have activity and that it is effective in the treatment of haemophilia A, although the route or routes of action has yet to be determined.

5.2 The only possible concern is whether an unidentified chemical entity may have adverse effects which would reduce the value of the efficacy of the product. This question has not been addressed in detail by the Company but except for the possibility that Feiba may induce an anamnestic response no definitive adverse event has emerged as being related to the product.

6. Other enclosures

6.1 The enclosures F. to I. relate to pharmaceutical issues only.

7. Heat-treated Feiba

7.1 The secondary document draws to the Commission's attention that heat treatment has been added to the manufacturing process of Feiba to decrease the risk of transmitting viral diseases. A report by Dr Anderle of Immuno certifies that the heat treatment method has no adverse impact on the efficacy and safety of the preparartion. He quotes 8 patients and notes large variations in the in vitro efficacy parameters, such as the activated partial thrombo-plastin time. However, he does identify in these patients no sign which could be indicative of a thrombogenic effect and no rise in inhibitor titre after treatment.

The electrophoretic strip indicates that there is no formation of neoproteins but it appears that after reconstitution of the bulk powder, the concentration of Feiba needs to be adjusted so that the potency is retained as advertised.

The efficacy of the the heat treatment is only demonstrated in relation to the virus ATCC VR-68 at $60^{\circ}C/10$ hrs. It would be normal practice to demonstrate the heat treatment method effective against a wider range of viruses and it is noted in the revised data sheet that the Company does not claim total viral sterility but says "despite the measures taken to reduce the risk, the transmission of viral hepatitis or other viral infections cannot be ruled out."

Despite this caution, it is currently thought that if the method of heat treatment is performed as stated in this document there is little risk of the AIDS implicated virus being transmitted through administration of the product.

8. Summary

8.1 The data for the efficacy of the product has not been presented in the carefully controlled manner which would normally be expected for a new chemical entity. However, the condition being treated is not amenable to control experiments and under no circumstances may placebo be used. There is a reasonable assumption that the product is efficacious in stemming bleeding in patients with haemophilia A who have moderate to high titres of inhibitor against Factor VIII. It is less certain whether the product is equally effective in those patients with low inhibitor titres. However, it would appear that such a product as Feiba is the only practical solution for treating a haemophilia A patient who has very high levels of inhibitor. It is understood that currently (1984) over one million units/year of Feiba have been used in the UK by consultant haemolologists obtaining the drug on a named patient basis. There is also another unlicenced product similarly being used on a named patient basis.

It would thus appear that although there is no generally agreed definition of the chemical entity involved in Feiba, there is evidence of efficacy - albeit in varying degrees - and the only evidence of harm has been in the earlier studies where patients have contracted hepatitis.

8.2 The present suggestion of heat treating the product may further diminish the risk of hepatitis and would seem with our current knowledge to be a reasonable measure against the introduction of AIDS.

8.3 However there is presently no substantive evidence of Feiba being used on a long-term basis, or being used by patients who may keep the product at home for self-injection and there is no statistical quantification of the risks associated with an induced anamnestic response.

8.4 The Commissioners may consider that despite lack of classical efficacy data, the risk benefit ratio is favourable and that the contemporary demand for the product is an indicator of professional confidence and indicates the need for the product to be regulatorily controlled. The Commissioners will however also note that the circumstances of the efficacy data may not currently provide adequate confidence for the use of this product outside of expert haemophiliac centres, nor for the use of the product in those patients who do not exhibit inhibitor titres. It is estimated that currently only 10% of patients suffering from haemophilia A in the United Kingdom exhibit inhibitor titres against Factor VIII concentrate. Thus the Commissioners may wish to consider that if they were to recommend the grant of a licence then:-

(a) the indications might, at this stage, be limited to use in patients exhibiting Factor VIII inhibitor titres and;

(b) the sale or supply be limited to recognised haemophilia centres.

DR P N ADAMS

10 June 1985

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