RESTRICTED

Mr Davey PS/MS(H)

From: Mr Wilson MCA
Date: 15 December 1989

cc: Dr Metters DCMO
Dr K Jones MCA
Dr H Pickles ISD
Dr Rotblat MB3A
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copy to Dr Regma

FACTOR VIII - PROFILATE

1. MS(H) has indicated, via your minute of 6 December, that she would prefer 'regulatory action' to be taken against the Factor VIII product PROFILATE. This was in response to my submission dated 24 November. She asked for a note on the consequence of such action. Advice to that end is set out in the Annex.

2. Briefly, regulatory action could involve

   a. immediate suspension of the product licensing for which we have to be satisfied that this is necessary in the interests of safety;

or b. a proposal to suspend, giving the company appeal rights provided they gave notice within 28 days. Any suspension would not then take effect until the appeal rights had been exhausted which could take several months.

The Annex refers to the consequences of taking either course, for the company, for patients and for the Licensing Authority.

IMMEDIATE SUSPENSION

3. Professional advice is that, on balance, we do not have sufficient evidence to support immediate suspension. This position was reached taking into account the theoretical risk posed by the deficiencies noted by the inspectors, the lack of problems in the batch release of

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the product from NIBSC and the fact that there is no clinical evidence about the use of the product which gives rise to concern. On the basis of that advice, immediate suspension would cause unwarranted concern to the many patients who are or have used PROFILATE. Such action has to be seen also in the context that (having studied the company's dossier) we now think it most likely that the Licensing Authority will be able to agree their application for a variation to their existing licence before the end of January) (The Committee on Safety of Medicines will consider it on 25 January). Once that variation is agreed it will no longer be possible for the company to market further supplies of the heptane treatment PROFILATE in the UK. The company has. we understand, ample stocks of the new (solvent detergent treated) PROFILATE and will wish to supply it to the UK market without delay.

4. So immediate suspension is now likely only to cut short cessation of supply of the product by a matter of a few weeks. With that in mind and given the lack of clinical evidence of any abnormal safety hazard, the concern immediate suspension would cause to haemophiliacs and the serious public questions to which it would give rise, our advice to Minister must remain strongly against such action. It is true that we cannot say that there is not a potentially greater risk of infection from Profilate because of manufacturing deficiencies. But that risk has to be assessed as very remote given the usage of Profilate in recent years.

PROPOSAL TO SUSPEND

5. As an alternative, we could however inform the company that we propose to suspend the licence (but not with immediate effect) unless they are willing voluntarily to cease to market the heptane treatment product. A proposal to suspend would leave the company in no doubt that we were dissatisfied both with their lack of progress in putting right the deficiencies and with the present situation regarding the production process. It would seem fully warrantable. Such action by the Licensing Authority would not be made public. The company could then choose to exercise its 'appeal' rights but we think this is unlikely. The company must indicate whether or not it wishes to do so within 28 days. Any such action would in practice be likely to be overtaken by the grant of the variation before end January and the company will no doubt take that into account in deciding how to respond.

6. We should seek in discussion with the company to press them to exchange existing heptane treatment PROFILATE held by health authorities in the UK for the new product. We believe that the company may be receptive to this approach and will be anxious to co-operate.

CONCLUSION

7. If the Minister wishes regulatory action to be taken we would accordingly advise that this should not be with immediate effect.

8. Is the Minister content? If so we will proceed urgently with action as at 5 and 6 above. We would be happy to discuss if she wishes.

GRO-C

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Enclosure

ANNEX

FACTOR VIII - PROFILATE

1. Regulatory action in this case could take two forms, both exercising powers available to the Licensing Authority under S.28 of the Medicines Act 1968. This empowers the Licensing Authority to suspend or revoke a product licence. Where it appears to the Licensing Authority that, in the interests of safety, it is necessary to do so, a licence can be suspended with immediate effect. Professional advice, as reflected in the submission of 24 November, is that there is insufficient evidence to warrant this action. But if the licence were immediately suspended the main consequences would be as below.

For the company

2. a. it would no longer be able to market the product in the UK for a maximum of 3 months initially;

b. in order to secure that the suspension could last for longer than 3 months other regulatory action would be taken which would give the company a right to make representations against, in effect, continued suspension BEYOND 3 months. These representations would be heard by a body independent of the Licensing Authority but the final decision to continue the suspension would be for the Licensing Authority (subject only to review in the Courts eg judicial review);

c. we would also invite the company to withdraw stocks from the UK market (to leave the product on the market would not be consistent with immediate suspension). [If they did not co-operate (and we cannot require them to do so) then DH Procurement Directorate would put out a Hazard Alert to hospitals to take stocks out of use. Individual patients would be invited to return to hospital any stocks they had at home.];

d. we would also inform other regulatory authorities eg in the EEC and also WHO of the action taken which could well have consequences for the company in any other markets where they sell heptane treatment Factor VIII.

For haemophiliacs

3. a. those currently using PROFILATE would need to be switched to another Factor VIII product (unless they were willing to continue with PROFILATE and their physician wished to prescribe it and could obtain supplies). The Blood Products Laboratory would be able to supply the bulk of PROFILATE users for some months at least but some may be supplied (because of consultant preferences) with other products. There is at present only one other relevant licensed Factor VIII product available - Koate HT from Bayer - though a licence for a new monoclate product from Armour should be granted very shortly. Other unlicensed products might be used more extensively than at present. We

cannot say that patients switching from PROFILATE to other commercial products would necessarily be transferring to a potentially less risky product. Indeed we suspect that in some cases the reverse might be the case;

b. there may be in the order of 2,000 patients currently using PROFILATE.

c. a much higher number will have used PROFILATE at some stage in recent years;

d. patients who are or have used PROFILATE may need counselling from their doctors to reduce, as far as possible, any unnecessary alarm and concern. Stress would need to be laid on the purely precautionary nature of the action being taken and the lack of any firm evidence that PROFILATE had caused either higher Hepatitis infection or any HIV infection.

For the Department and Licensing Authority

4. a. Any announcement of immediate suspension would give rise to public/Parliamentary questions about the basis for the action proposed which could receive considerable media attention;

b. It would not be easy to explain why action was being taken now when it could not be shown that the problem was a new one. Attention might rapidly switch to that issue with accusations of negligence by the Licensing Authority. It would be possible partially to answer this by reference to the fact that when our Inspectors first identified the deficiencies (February 1988) the BPL could not have made up the then considerable bigger share of the UK market held by PROFILATE and that we could not be confident that more acceptable products would have been available. Clinicians could have chosen, on a named patient basis, to prescribe products without a UK licence, with a possibly greater risk than PROFILATE. But that response would in turn raise concerns about other products and would be an admission that we had regarded the product as potentially unsafe for nearly 2 years.

5. If the decision were that the licence should be suspended but without immediate effect the consequences would be:

For the company

a. the company would be informed that the Licensing Authority proposed this action. They would have 28 days in which to decide whether or not to make representations against that proposal;

b. if they did not take up that option the product licence would be suspended after 28 days unless the company voluntarily ceased to market the product in which case the formal regulatory action could (but need not) be dropped;

c. if the company decided to make representations these would be either orally or in writing (or both) to a 'Person Appointed' by the Licensing Authority who would subsequently make a report of his findings (but without a recommendation) to the Licensing Authority. The final decision would then rest with the Licensing Authority. There is no statutory time limit by which such decisions have to be reached.

d. Once a proposal to suspend a licence was implemented the company can no longer market the product in the UK. If suspension had followed the process at 5 above an invitation to the company to withdraw stocks or a Hazard Alert to health authorities would not seem appropriate.

For haemophiliacs

6. a. if the company, facing suspension, decided to cease supply, then some would need to switch to other products when existing stocks available to them were used up. By then it could well be the case that the 'new' PROFILATE (not the heptane treatment product) would be available. If the company ceased to supply the heptane treatment product ahead of the availability of the new product they would be likely to indicate that this was for commercial reasons;

b. the prospects of causing serious concerns amongst haemophiliacs and hospital specialists would be much reduced as compared with immediate suspension and there would be less likelihood of patients being switched to other commercial products which might not be any safer (see 3a above).

For the Licensing Authority

7. a. the Licensing Authority would not be obliged to publicise either the proposal to suspend or any final suspension. But we should need to tell the EC Committee on Proprietary Medicinal Products of the suspension (Community obligation).

b. we would not be obliged to tell directors of haemophiliac reference centres but once the suspension had been given effect we would wish to do so on the expectation that they would not then seek to publicise the matter.

c. if the company, facing possible suspension, ceased to supply the product, there would be no action required of the Licensing Authority.

MCA December 1989