1. Dr K Jones MCA/Ch E

2. Lord Hunt PS(L)

From: Dr I Hudson MCA/L

Date: 29 March 2001

Copy: See copy list attached

Sourcing of Plasma Derived Medicinal Products

Purpose

1. Further to MCA's earlier submission of 15th November, and Andy McKeon's note of 13th February, this is to inform you of the advice given by the Committee on Safety of Medicines (CSM) at their meeting on 22nd March

Recommendation

i. Accept the CSM's advice to keep Pulmocis on the market.

ii. You should instruct MCA to seek the companies agreement voluntarily to remove Vasculocis and Betafact/Novofact from the UK market.

iii. In the event that the above recommendation is unsuccessful, non-emergency procedures to obtain withdrawal of the products should be initiated through:

(a) in the case of Betafact/Novofact: referral to CPMP

(b) in the case of Vasculocis: non-emergency action under Schedule 2 of 1994 Medicines Regulations should be initiated.

Timing

3. Immediate: You will want to make a decision promptly on the CSM's advice.

Background

4. · CSM met on 8th November 2000 and recommended that the precautionary measures currently in place for UK sourced plasma should be extended to include medicinal products with source plasma derived from countries with

one or more confirmed case of vCJD. That is to say, effectively, products containing plasma-derived constituents that are sourced from France should be removed from the UK market .

- You decided that, before considering what action to take, the supply position should be investigated by MPI Division and advice from CPMP should be awaited, given that they were considering this issue.

- You asked CSM re-review this issue based on the outcome of the above.

- There are three products affected by the CSM advice, all sourced from French plasma. These are Pulmocis, Vasculocis, Novofact (previously known as Betafact).

Supply situation

5. You were informed by Andy McKeon on 13th February that the supply situation was as follows:

"*Pulmocis. A diagnostic agent in lung perfusion imaging, particularly in detection of pulmonary embolisms which is a life threatening condition. It is used on a daily basis in almost every nuclear medicines department. There is currently no alternative licensed source and discussions with Schering (the licence holders) and CIS (the manufacturers) have revealed that as they supply to a number of countries they are not prepared to switch to a non-French plasma solely for the UK. We can seek alternative American sources but these would need to be licensed and is a long term option.*

Vasculocis. A diagnostic agent in blood pool imaging and heart studies. It is not widely used and there are alternatives for most of its uses but withdrawal would result in short term impact in patients. Some plasma volume studies might be impossible but I understand the clinical impact is unlikely to be significant.

Betafact/Novofact. A Factor IX product. It has only been used at St. Thomas' about a year ago. It is not currently used by them. The manufacturers confirm that no other UK centre is sourced by them. It is also not on the Oxford Haemophilia Centre's database of products used in the treatment of haemophiliacs in the UK, nor is it in the guidelines on therapeutics products to treat haemophilia. The Haemophilia Society may be concerned that Ministers have not implemented the CSM's advice and suspended or revoked the licence even though the product is not used in Britain. Alternatives are available."

Usage of Vasculocis and Betafact/Novafact:

MPI has looked further at the usage of Vasculocis. Its usage is small and is concentrated mainly in a few centres. There are alternatives. However immediate suspension would not allow those centres that do use the product time to introduce alternatives, and therefore a delay of 3 months would be prudent on these grounds. Betafact/Novafact is not currently used in the UK.

French Expert Group and CPMP position

6. A detailed evaluation was carried out by the French Agency for the safety of health products. This concluded that it was still acceptable to use French plasma for the manufacture of plasma-derived medicinal products.

7. The CPMP TSE expert group on human TSE's and medicines derived from human blood and plasma considered this issue on 1st December, and recommended that a detailed evaluation should be undertaken in any country where cases of vCJD are found. Furthermore, the Expert Group recognised that any precautionary measure based on population exclusion can be expected to have a large impact on the overall supply of plasma-derived medicinal products and that such measures could become progressively impracticable should the epidemiology of vCJD change. The Expert Group's report made reference to the latest recommendations from France on the analysis of risk of transmission of vCJD by blood and its derivatives. The French Advisory Committee recommended that "*fractionated products manufactured from plasma undergo a number of steps during fractionation which increases their safety level and that the risk presented by any individual product was not sufficient to propose that it should be prohibited.*" The CPMP Expert Group report has been adopted by the CPMP.

Position of CSM in the knowledge of supply issue and CPMP position

8. The Biologicals Sub Committee of the CSM met on 12th March and the CSM met on 22nd March to review the previous conclusions of the CSM, in light of the above. The Main Committee noted the conclusions of the Sub Committee on Biologicals, the French Government's Expert Group report and the position of the CPMP. It was considered that the advice given by the CSM and its Expert Group on BSE in November 2000 should not be changed. Based on precautionary principles, plasma sourced from countries with one or more confirmed cases of vCJD should not be used in the manufacture of medicinal products. The CSM also noted the supply issue based on the information provided by MPI, DH for Pulmocis, Vasculocis and Betafact (FIX) subsequent to the CSM's meeting in November 2000 and that that the precautionary measures were based on the understanding that this would not create a supply problem. MPI considered that the clinical impact of the removal of Vasculocis and Betafact from the market was unlikely to be significant. However, there is a supply problem for Pulmocis, which is used in pulmonary embolism diagnosis. In view of this, there was a scientifically justifiable case to allow Pulmocis on the UK market. In reaching this recommendation, the Committee considered the following:

- There is a clinical need for Pulmocis and no alternative immediately available should this be withdrawn; and it will take a considerable period of time to find an alternative source plasma.
- The volume used, including the quantity of human albumin administered, is small and this product is usually for single use.

- On balance, there is a real clinical risk if this product is withdrawn as compared with a presently perceived risk of transmitting of vCJD through the use of French source plasma for the preparation of the albumin carrier.

9. The Committee endorsed the recommendation that the Department of Health should keep the issue of source plasma under constant review and for Pulmocis, DH should encourage the manufacturer to change the plasma source.

Options for Ministers for removal of Vasculocis and Betafact/Novofact from the UK market

10. The options are:

(a) Voluntary action by the MA holders. This will be explored with the companies concerned.
(b) Urgent Suspension of the MA
(c) Non urgent procedure under the regulations. Lawyers will advise whether suspension, revocation or variation is the appropriate action.

11. The situation for the Vasculocis and Betafact/Novofact are different because Vasculocis is a national license and Betafact/Novofact were licensed via the European mutual recognition procedure, with France as the Reference Member State. The procedure for suspension or variation of Betafact/Novofact requires that it is referred to the CPMP for consideration. The final opinion is sent to the European Commission, and the Commission's decision is binding on all the Member States. The regulations do permit urgent action by individual Member States in exceptional cases ". Where urgent action is essential to protect public health, until a definitive decision is adopted the Member State may suspend …." Whilst the review by the CPMP may be a slow process, Member States may take action during this time should the risks change.

12. For Vasculocis the normal procedure for suspension would be that consultation with the CSM is required before a MA can be suspended on grounds of safety. The MAH may make representation to the CSM before a full decision is made. This decision is subject to an appeal procedure. However there is provision for suspension to have an immediate effect " where it appears to the licensing authority that, in the interests of safety, it is necessary to suspend the authorisation with immediate effect, for a period not exceeding three months…. " This period of suspension can be extended.

13. For both Vasculocis and Betafact/Novofact, careful consideration needs to be given on whether immediate suspension is justified in the circumstances, as the action is precautionary. This would be HSD's preferred option, as it would be consistent with the approach taken on products make from UK plasma. However, it could be seen as difficult to justify at this point and may be vulnerable on legal challenge. It should also be recognised that if immediate suspension is not used at this stage, it will not be an available option later unless there is a change of circumstances.

Other considerations

14. There may be considerable outcry from Europe if such action was taken, but that is a secondary point behind consideration of risk/benefits for patients. It should also be recognised that the Commission's opinion, following CPMP review, in the case Betafact/Novofact may be that it is acceptable to keep this product on the market. This opinion would be binding on the UK. Any decision by the Commission on Betafact/Novofact may have an impact on the action which can be taken with respect to Vasculocis.

15. This submission has been prepared and agreed with MPI and SOL. The views of HSD have been sought and included.

Dr. Ian Hudson
Director, Licensing Division
Room 11-216 Ext GRO C
Market Towers

COPY RECIPIENTS

Ms E De Zoete PS/PS(L)
Ms Sammy Sinclair PS/SoS
Mr P MacNaught PS/PS(PH)
Mr I Dodge PS/MS(H)
Ms H Kelman APS/MS(H)
Mr J Adedeji PS/MS(C)
Mr K Holton PS/PS(H)
Mr D Murphy Sp Adv
Mr S Stevens SP Adv
Ms R Wetterstad PS/P/S-CE
R Dickson PS/CMO
Dr P Troop DCMO
Dr K Jones MCA/ChE
Dr M O'Mahony PH6
Dr M McGovern HSD2
Dr A Wight PH6
Mr C Lister PH6.2
A Harvey PH6
Mr R Alder MCA/ES
Dr G Munro MCA/I&E
Dr J Raine MCA/PL
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Dr Lam MCA/L
Mr GRO-A
Ms GRO-A
Dr N Morrow NIO
Ms S Tallentire NIO
Ms M Murray COMMS
Mr R Beasley COMMS
Miss E Hands COMMS
Mr A McKeon MPI
Dr K Ridge MPI
Mrs I Izzard MPI
Mr M Brownlee MPI
Ms. J Draper SOLC5