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For the attention of Dr. J. Purves,
Superintendent Pharmaceutical Officer

Your ref

Our ref CDS/ER/177

Date 13 November 1989

Dear Dr. Purves,

PRODUCT LICENCE APPLICATION 0010/0163 : KOATE HS
ADVERSE EVENTS REPORTED IN CONNECTION WITH KOATE HS

Please find attached summaries of a cluster of adverse events, namely seven cases of hepatitis, which were reported from Japan where Koate HS is a marketed product. The delay in reporting these events is due to subsequent investigations aimed at ascertaining the source of infection.

As a result of these adverse events, Cutter Biological voluntarily recalled five batches, namely lot numbers (i) 60F009, (ii) 60F036, (iii) 60F038, (iv) 60F006, (v) 60F034. As noted in the attached conclusion, it has not proven possible to implicate any one product or any one lot as the source of infection.

The occurence of these events resulted in an FDA inspection of Cutter's Berkeley manufacturing site. A summary of the inspector's observations together with Cutter Biological's responses are also attached for your information.

Yours faithfully,

GRO-C

Craig D. Simpson
SENIOR REGISTRATION OFFICER

cc: Dr. R. Wheywell
Dr. G. Macdonald

PRODUCT LICENCE APPLICATION 0010/0163 : KOATE HS

SAFETY UPDATE : ADVERSE EVENTS IN JAPAN

SUMMARY

Thus far in 1989, seven subjects with haemophilia A who had been receiving Koate HS developed hepatitis B.

6/7 subjects received Koate HS lot 60F036
5/7 subjects received Koate HS lot 60F038
4/7 subjects received Koate HS lot 60F009
1/7 subjects received Koate HS lot 60F006
5/7 subjects received Conco-eight HT (Green Cross)
1/7 subjects received Koate HT

The lot numbers for Conco-eight were not recorded except on one occasion. Thus, a cluster evaluation was not possible. The immune status of the subjects is not available.

On the evidence available, it is not possible in any case to implicate any one product or any one lot. Neither is it possible to determine whether these are new infections, re-infections, or reactivations.

Lot 60F024 shared a partial pool with lot 60F036 and was also voluntarily withdrawn. There have not, however, been any problems reported with lot 60F034.

| Case Number/Details | Center | Product Used | Type of Heating | Dose Given Units | Date Given | Lot Number | Laboratory Tests | Date of Sample MM/DD/YY | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 1<br>Severe hemophilia A<br>13 years | ? | Conco-eight (Green Cross Alpha) | Dry | 600 | 11-24-88 | ? | Negative | 2-1-89 | |
| | | Koate-HS (Cutter) | Wet | 500<br>14,250<br>1,000<br>1,000<br>10,000 | 12-19-88 )<br>12-23 to 29/88)<br>1-10-89 )<br>1-18-89 )<br>1-23 to 30/89) | 60F036 and 60F038 | Raised enzymes<br>Positive HBsAg<br>HBeAg<br>HBeAb<br>HBcAb (IgM)<br>HBcAb | 3-13-89<br>3-20-89 | HBsAg and HBsAb negative by 4-10-89 |

Comment:
Hepatitis B exposure probably during November or December 1988. No family history or other route of exposure elicited. Thus both Conco-eight or Koate-HS suspect. Exposed to two lots of Koate-HS and only one lot of Conco-eight. However dry heating is less effective than pasteurization. No details of treatment prior to November could be obtained and no information on the lot number of Conco-eight used. Therefore evidence inconclusive.

| Case Number/Details | Center | Product Used | Type of Heating | Dose Given Units | Date Given | Lot Number | Laboratory Tests | Date of Sample MM/DD/YY | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 2<br>Severe hemophilia A<br>1 year old | ? | Conco-eight<br><br>Green Cross (Alpha) | Dry | 250 U<br><br>Twice per week | 12-87 to<br><br>12-88 | L 135<br>L 138<br>L 140 | Negative HBsAg<br>Borderline HBsAb<br>Elevated enzymes | 11-26-88 | |
| | | Cutter Koate-HS | Wet | 250 U Twice per week | Started 12-24-88 | 60F009<br>60F036<br>60F038 | Positive HBsAg | 4-8-89 | Positive serology including HBcAb 4/12/89 |

Comment
Patient probably exposed to hepatitis about October/November 1988 (prior to first usage of Koate-HS). Thus based upon laboratory data Conco-eight is the more probable source of infection, but this cannot be confirmed absolutely.

| Case Number/Details | Center | Product Used | Type of Heating | Dose Given Units | Date Given | Lot Number | Laboratory Tests | Date of Sample MM/DD/YY | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 3<br>Severe hemophilia A<br>4 year old | ? | Conco-eight (Green Cross) | Dry | 250 U twice per week | 9-87 to 6-4-88 | ? | NANB hepatitis | 5-24-88 | |
| | | Koate-HT | Dry | 250 U twice per week | 6-4-88 to 9-27-88 | | | | March 1989 Hepatitis vaccine commenced |
| | | Koate-HS | Wet | 250 U twice per week | 9-27-88 | 60F009<br>60F036 | Improved NANB<br>Positive HBsAg<br>Positive HBcAb (IgM) | 2-21-89 | |

Comment

Exposure to hepatitis B probably February/March 1989 although earlier exposure is possible with an attenuated virus transmitted by one of the dry heat treated preparations. The influence of the hepatitis B vaccine is difficult to assess. Has the possibility of transmission by the vaccine been eliminated (not as far as we can ascertain)?

| Case Number/Details | Center | Product Used | Type of Heating | Dose Given Units | Date Given | Lot Number | Laboratory Tests | Date of Sample MM/DD/YY | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 4 | Sendai | ? | ? | ? | ? | ? | NANB | 1983 | No details |
| | | Koate-HS Cutter | Wet | 5,000 U | 11-14 to 11-16-88 | ? | Negative | 8-1-88 | |
| | | | | 3,000 U | 3-20 to 3-26-89 | | Negative enzymes | 11-11-83 | |
| | | | | | | | Positive HBsAg Elevated enzymes | 3-20-89 | |

Comment

The evidence suggests exposure at latest about December 1988 or January 1989. This subject is a severe hemophilic who must have previously received blood products or even blood, but no record is available. He had NANB hepatitis in 1983. The lot number of Koate-HS supplied by BYL on questioning is 60F006. Other possible routes of exposure could not be excluded by patient's physician. The possibility of a prolonged incubation period by an attentuated virus cannot be eliminated. No conclusion can be drawn.

| Case Number/Details | Center | Product Used | Type of Heating | Dose Given Units | Date Given | Lot Number | Laboratory Tests | Date of Sample MM/DD/YY | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 5<br>Severe hemophilia<br>3 years old | Yamaguchi | Conco-eight (Green Cross) | Dry | 375 U/day | 12-17-88 | ? | Negative | 1-6-88 | |
| | | Koate-HS (Cutter) | | 250 U/day | 12-18-88 to 3-26-89 | 60F036<br>60F038 | Positive HBsAg with elevated enzymes<br>Also HBcAb positive<br>HBsAb negative | 3/7/89 | |
| | | Packed RBC | | 1 unit | 12-17-88 | | | | |

Comment

Exposure probably early 1989/late 1988, but of course could have been as early as August 1988. Has remained HBsAg negative. Any of the infusions (blood or either Factor VIII concentrate) could have transmitted Hepatitis B. Information on Conco-eight not available.

| Case Number/Details | Center | Product Used | Type of Heating | Dose Given Units | Date Given | Lot Number | Laboratory Tests | Date of Sample MM/DD/YY | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 6 | Hyogo | Conco-eight-HT (Green Cross) | Dry | 298 vials | 12-15-87 to 12-17-88 | ? | | | |
| 5 years old | | Koate-HS | Wet | 750 U/day | 12-27-88 to) 6-23-89 ) | 60F009 60F036 60F038 | Negative | 12-28-87 | Never any clinical symptoms |
| | | | | | | | HBsAb positive HBcAb positive | 6-5-89 | |

Comment

Seroconversion appears to be complete by June 1989. The liver enzymes are normal. Hepatitis testing only performed previously in December 1987. Thus infection probably occurred between December 1987 and early 1989. No definite relationship to the coagulation factors can be confirmed.

| Case Number/Details | Center | Product Used | Type of Heating | Dose Given | Date Given | Lot Number | Laboratory Tests | Date of Sample MM/DD/YY | Comments |
|---|---|---|---|---|---|---|---|---|---|
| 7<br>5 years old | Okinawa | Koate-HT | Dry | 23 vials | 1-5-88 to<br>8-1-88 | ? | Negative | 7-1-88 | |
| | | Koate-HS | Wet | 38 vials | 8-15-88 to)<br>5-31-89 ) | 60F009<br>60F036<br>60F038 | Positive<br>HBsAg<br>Enzymes<br>normal | 6-10-89 | |
| | | | | | | | Positive<br>HBsAg<br>HBeAg<br>HBeAb<br>HBcAb<br>Enzymes<br>raised | 7-4-89 | |

Comment

No positive HBsAb recorded. The possibility exists that this subject was exposed to hepatitis B through Koate-HT, although the incubation period is rather lengthy. It is unfortunate that no laboratory testing was carried out between July 1988 and June 1989.