The European Agency for the Evaluation of Medicinal Products
Post-authorisation evaluation of medicines for human use

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EMEA PUBLIC STATEMENT

EMEA update on hexavalent vaccines: Hexavac and Infanrix Hexa[1]

Since the EMEA Public Statement on 28 April 2003, the EMEA's Scientific Committee (Committee for Proprietary Medicinal Products, CPMP) has continued to monitor all data submitted and has reviewed the conclusions taken by a number of specialised Expert Groups and Working Parties with regard to Hexavac and Infanrix Hexa. Based on this review, the CPMP concluded in its November 2003 meeting that there was no change in the benefit/risk profile of these products and therefore recommended no changes to the present conditions of use.

The CPMP has continuously monitored all suspected adverse drug reactions reported for the hexavalent vaccines as part of routine pharmacovigilance. Since the products were authorised (in 2000), over a period of 3 years, 4 sudden unexpected deaths (SUD) in close temporal association with hexavalent vaccination have been reported in children during the second year of life (3 in Germany, 1 in Austria).

A statistical analysis based on an epidemiological approach to this problem was performed on data from Germany. This retrospective analysis has shown that the observed number of cases of SUD in the second year of life within 48 hours of Hexavac administration exceeded the expected number of cases[2]. This finding was based on 3 cases amongst more than 700,000 children being given a booster[3] in the period analysed (November 2000 - 30 June 2003).
The CPMP experts considered that this temporal relationship raises a possible signal for Hexavac vaccination and SUD, but they acknowledged some inevitable limitations of the data sources and methods used to calculate the expected numbers. In any case a signal only raises a suspicion, and does not prove a cause and effect relationship. Further studies are needed to establish whether or not there is a risk.
The CPMP has also conducted further reviews on quality and additional safety aspects of the hexavalent vaccines and has consulted widely with its experts and Working Parties. In so doing it finds no evidence for a link between quality or safety aspects of these vaccines and SUD.

Based on a thorough review of all available data, the CPMP therefore reaffirms its position that there is no plausible biological cause for an association between hexavalent vaccines and SUD in the second year of life. The Committee agrees that a possible signal has been generated, but that this does not currently constitute a risk to public health.

It is known that a very small number of children die in their early years due to a number of causes, some of which are unknown. The fact that a child dies shortly after being vaccinated may lead to the reporting of this event to the responsible Health Authority as temporally associated to vaccination.
Being aware of this possibility, and taking into account the findings for Hexavac suggested by the statistical analysis, the following actions are being undertaken to find out whether the signal is confirmed or not.
Prospective and retrospective studies to investigate SUD will be conducted by independent institutions and will be assessed by Regulatory Authorities. These active surveillance programs, starting from early 2004, should facilitate the collection of further data and monitoring of vaccines by the

[1] This is an updated Public Statement that should be read in conjunction with the statement previously published in April 2003 (http://www.emea.eu.int/pdfs/human/press/pus/851903en.pdf).
[2] The expected number of cases is derived from national statistics in Germany.
[3] Additional injection given in the second year of life to stimulate the immune memory.

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Authorities and the Marketing Authorisation Holders. The results will be followed closely so that timely regulatory action can be taken, if necessary.

On the basis of the current information, the CPMP:

- Reaffirms its position, based on a thorough review of all the data, and finds no plausible biological cause for an association between the hexavalent vaccines and SUD in the second year of life.

- Recommends that no regulatory action against the vaccine should be taken based on this unconfirmed signal.

- Recommends no changes to the present conditions of use for hexavalent vaccines and asks health care professionals to closely follow the product information of Hexavac and Infanrix Hexa[4].

- Reminds health care professionals that, as with all medicines, they should report suspected serious adverse reactions occurring in association with vaccines to the responsible Health Authority.

- Concludes that vaccination offers benefits to the individual child and to the general population that far outweigh possible risks of existing vaccines, including hexavalent vaccines; vaccination should continue according to national vaccination schedules.

The CPMP will continue to monitor these two hexavalent vaccines in the light of any new information.

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[4] For further information on both vaccines, please refer to the European Public Assessment Reports, which are available on the EMEA website at (http://www.emea.eu.int/htms/human/epar/g-lepar.htm).