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26/5/12

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Department of Health
OFFICE OF THE SECRETARY
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28 March 2006

MEMORANDUM CIRCULAR
No. 2006 - 0020

TO : **CLUSTER HEADS, BUREAU/SERVICE DIRECTORS, CHD DIRECTORS, CHIEFS OF MEDICAL CENTERS & HOSPITALS AND OTHER CONCERNED OFFICES**

SUBJECT: **Withdrawal of Morupar, Morubel and Morbilvax Vaccines produced by Chiron Vaccines, Italy**

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Attached for information and appropriate action, is a self-explanatory letter from the World Health Organization (WHO) Country Representative concerning the also attached letter from the Director of Immunization, Vaccines and Biologicals, WHO Headquarters, Geneva on the information that as a precautionary measure, on 16 March 2006, WHO has withdrawn MMR vaccine (Morupar) produced by Chiron Vaccines, Italy from the list of qualified medicines (see also attached rapid alert document from the Italian Regulatory Authority). As stated, the Department of Immunization, Vaccines and Biologicals of the WHO is advising the withdrawal with immediate effect and until further notice, of measles and measles-rubella vaccines (Morubel and Morbilvax) also produced by Chiron Vaccines Italy considering that these products contain similar concentrations of dextran.

Consequently, WHO advises UN agencies to put on hold in countries any remaining stocks of the above-mentioned products. Further, these precautionary measures have been communicated to the UN procuring agencies.

In this regard, you are hereby advised to disseminate this information to all concerned Offices for necessary actions and report any adverse events in relation to the use of these vaccines accordingly.

For compliance.

By the authority of the Secretary of Health:

MARIO C. VILLAVERDE, MD, MPH, MPM, CESO III
Assistant Secretary

WHO - 671 URGENT

WORLD HEALTH ORGANIZATION
WESTERN PACIFIC REGION

ORGANISATION MONDIALE DE LA SANTE
REGION DU PACIFIQUE OCCIDENTAL

OFFICE OF THE WHO REPRESENTATIVE IN THE PHILIPPINES
Department of Health, San Lazaro Compound, Sta. Cruz, Manila, Philippines
P.O. Box 2932, 1000 Manila, Philippines

In reply please refer to: WP/2006/0629/jb (EPI)
Prière de rappeler la référence:

Dr Ma. Virginia G. Ala
Officer-in-Charge
Bureau of International Health Cooperation
Department of Health
San Lazaro Compound
Sta. Cruz, Manila
Philippines

24 March 2006

Dear Dr Ala,

Subject: **Withdrawal of Morupar Vaccine by Chiron Vaccines, Italy**

Please refer to the attached self-explanatory letter from the Headquarters. As a precautionary measure, on 16 March 2006, WHO has withdrawn MMR vaccine (Morupar) produced by Chiron Vaccines, Italy from the list of prequalified vaccines (see attached rapid alert document sent by the Italian Regulatory Authority). In addition, the Department of Immunization, Vaccines, and Biologicals of the WHO is advising the withdrawal with immediate effect and until further notice, of measles and measles-rubella vaccines (Morubel and Morbilvax) produced by Chiron Vaccines, Italy in view of the fact that these products contain similar concentrations of dextran.

WHO also advises UN agencies to put on hold in countries any remaining stocks of the above-mentioned products. These precautionary measures have been communicated to the UN procuring agencies.

We have received notice that the Philippines has purchased 20,000 doses of Morupar 10vials x 1DS GB/E PAHO with expiry date of 31 October 2006 invoiced on 13 September 2006 through Market Link. Kindly share the above information with the relevant unit/s of the Department for necessary actions. Let us know if there are reported adverse events in relation to the use of these vaccines and the potential implications of this withdrawal in the country.

Thank you and we hope to hear from you soon.

Yours sincerely,

Dr Jean-Marc Olivé
WHO Representative

Encls.: As stated.
cc: EPI/WPRO

World Health Organization

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In reply please refer to: QSS/ND/cc (2006-090)
I8-370-43 EURO

Your reference:

Dr Baoping Yang
Regional Adviser, EPI
World Health Organization
Regional Office for the Western Pacific
P.O. Box 2932
United Nations Avenue
Ermita
Manila
1000

22 MAR 2006

Dear Dr Yang,

This is to inform you that as a precautionary measure, on 16 March 2006, WHO has withdrawn MMR vaccine (Morupar) produced by Chiron Vaccines, Italy from the list of prequalified vaccines (see attached rapid alert document sent by the Italian Regulatory Authority). In addition, the Department of Immunization, Vaccines and Biologicals of the WHO is advising the withdrawal with immediate effect and until further notice, of measles and measles-rubella vaccines (Morubel and Morbilvax) produced by Chiron Vaccines, Italy in view of the fact that these products contain similar concentrations of dextran.

WHO also advises UN agencies to put on hold in countries any remaining stocks of the above-mentioned products. These precautionary measures have been communicated to the UN procuring agencies.

WHO will follow up with Regional Offices to obtain information regarding potential implications of withdrawal of these measles-containing vaccines in the countries of the regions supplied with the Chiron vaccines and to obtain data on reported adverse events in relation to the use of these vaccines. The technical focal points, should you have any queries, are Dr Nora Dellepiane and Dr Adwoa Bentsi-Enchill (Quality, Safety and Standards team).

Yours sincerely,

Dr Jean-Marie Okwo-Bele
Director
Immunization, Vaccines and Biologicals

cc: Dr J. Andrus, AMRO/PAHO
Dr D. Nshimirimana, AFRO
Dr N. Emiroglu, EURO
Dr S. Youssouf, EMRO
Dr A. Thapa, SEARO
Dr D. Wood, WHO/HQ
Dr N. Dellepiane, WHO/HQ
Dr A. Bentsi-Enchill, WHO/HQ

DEPART... 7-27

ENCLS.: Rapid alert
Briefing notes (20 March 2006)

Agenzia Italiana del Farmaco

AIFA

RAPID ALERT

15 MARCH 2006

FROM: Italy Agenzia Italiana del Farmaco (AIFA) Pharmacovigilance Unit
via della Sierra Nevada 60 00144 Roma

TO: Dr. Nora Dellepiane Immunization, Vaccines and Biologicals/FCH WHO
Dr. Adwoa Bentsi-Enchill, MB ChB, MSc Immunization, Vaccines and Biologicals/FCH WHO

SUBJECT: Suspension and recall of Morupar Vaccine MMR by MAH Chiron
Embargo until 3 pm (UK time) of 16 March 2006

REASONS FOR *ALERT*:

In the first months of 2006, five cases of serious adverse allergic reactions were reported with vaccine Morupar, so having regard the evidence of risk and the availability of safer alternatives than Morupar, the National Committee has decided the suspension of sale and the recall of vaccine.

Morupar is a lyophilised vaccine containing the live, attenuated viruses of measles, mumps and rubella, nationally authorized and MAH is Chiron Srl. This vaccine is licensed in Italy ((only UE Member State) since 1990 and it is registered in other 23 extra UE countries
Morupar is indicated for active combined immunization against measles, mumps and rubella and it is one of the three MMR vaccines available in Italy. The other two MMR vaccines are MMRII (Aventis Pasteur) and Priorix (GSK).The monitoring ADRs has shown a greater number of allergic reaction with Morupar than with other vaccines MMR. In 2005 all reports submitted in the years 2001 to 2004, and attributed to MMR vaccines, were reviewed with more detailed analysis, included the reporting rate by region, the distribution of ADR by SOC and a description of ADRs with suspected allergic manifestations. The following conclusions were drawn:

- in the years 2001-2004 suspected allergic reactions were reported approximately 5 times more frequently following administration of Morupar than after administraton of other MMR products; this is true for both serious ADRs and non serious ADRs.

- in 2004, geographical differences in reporting rates are not evident, and the

frequency of serious allergic reactions was 6 -12 times higher for Morupar than for the other MMR products. Anyway the frequency of these reactions for Morupar was in the range expected for MMR vaccine according literature

An inspection of the production site has not highlighted critical aspects of the vaccine production process.

No conclusive evidence regarding the possible causes of suspected allergic reactions seen after administration of Morupar was therefore available. However the product contains dextran which has been reported in the literature as a possible cause of allergic reactions and which is not present in the other MMR products.

After this analysis, AIFA informed healthcare professionals by a Dear Doctor Letter and request Chiron:

- to update SPC
- investigate the possible mechanisms by which allergic reactions arise following Morupar administration and in particular to study the possible role of dextran in the pathogenesis of allergic reactions
- provide an update on the project regarding the elimination of dextran from Morupar

The situation was closed monitored without particularly serious adverse reaction in 2005. In the first months of 2006 cases of serious adverse allergic reactions were reported, so having regard the evidence of risk and the availability of safer alternatives than Morupar, the National Committee has decided the suspension and the recall of vaccine.
A public announcement will be released tomorrow at 3pm (UK time , 16 italian time)

Name of person responsible for sending message:
Dr. Mauro Venegoni

BRIEFING NOTE

Issue: **Suspension and recall of Morupar® MMR vaccine (produced by Chiron)**
Date: **20 March 2006**
Originator: **Department of Immunization and Biologicals, (WHO/FCH)**

Issue:

On 15 March, the Italian vaccine regulatory authority (Agenzia Italiana del Farmaco (AIFA)) provided to WHO a rapid alert (anticipated to be released on 16 March) announcing the suspension and recall of Morupar® MMR Vaccine, produced in Italy by Chiron. The action taken by AIFA does not include the suspension of the marketing authorization for Morupar® but only the suspension of the commercialisation and the recall of the vaccine.

Morupar® is a freeze-dried vaccine containing live attenuated viruses of measles (Schwarz), mumps (Urabe AM-9) and rubella (RA 27/3). The vaccine has been licensed in Italy since 1990 and has been on the WHO list of pre-qualified vaccines since 2002. Information from the manufacturer indicates that it is registered in 23 other countries.

Current pharmacovigilance data from Italy indicate **risk estimates of 12.4 per 100,000 doses for all allergic reactions** for January 2005 - February 2006 (13.9 per 100,000 doses in 2004). Based on six **"potentially vaccine-associated cases of anaphylaxis", a risk estimate of 1.2 cases per 100,000 doses[1] is** reported.

In view of the expected announcement, WHO issued a message to UNICEF and PAHO indicating, as a precautionary measure, the withdrawal of the MMR vaccine from Chiron from the WHO list of pre-qualified vaccines as of 16 March 2006, and to put any remaining vaccine in countries on quarantine until further notice.

Background:

An increased risk of allergic reactions following Morupar® was brought to WHO's attention in 2005 following an initial signal in the context of a mass immunization campaign in Brazil, which then led to a more in-depth review of Italian pharmacovigilance data. The Global Advisory Committee on Vaccine Safety (GACVS) was briefed on the observed increase at its June 2005 and Dec 2005 meetings, specifically with a presentation on comparative analysis of Italian safety data for Morupar® and two other MMR products used in Italy. Those data showed an approximate two-fold increase in allergic reactions reported following Morupar® versus the other two products. An increase in overall adverse event reports in Italy was partly explained by a new pharmacovigilance system put in place since 2004.

To date, no conclusive evidence is available of the cause or mechanism of the increased allergic reactions. However, a strong hypothesis raised in the GACVS discussions (and other reviews) is a potential association between dextran (used as a stabilizer in Morupar® and not present in the other MMR vaccines in Italy) and the increased allergic reactions. It was further hypothesized that this may be mediated through an impact on the complement activation system.

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[1] This risk is based on 5 cases of potential anaphylaxis reported in 2006 and 1 case prior to 2006; further information is pending to confirm the diagnosis of anaphylaxis. The generally accepted risk of anaphylaxis for measles-containing vaccines in the literature is 1 case per million doses while that for severe hypersensitivity reactions (or anaphylactic reactions) is approximately 1 per 100,000 doses .

Prior regulatory actions in Italy (and reported to WHO as at Dec 2005) included:

- Revision of the summary product characteristics (SPC) in Italy.
- Production of a "Dear Doctor Letter" highlighting the reported increased risk, however reminding health professionals that the risk-benefit profile of the vaccine remained favourable.
- A process put in place for development of a dextran-free vaccine by Chiron and reactogenicity studies planned (comparing risk of allergic reaction between dextran-containing and the dextran-free product).
- Plans to test complement activation in vitro.

An update on the topic has been scheduled (prior to recent developments) for the June 2006 GACVS meeting.

The recent Italian regulatory decision was taken in the context of (i) the availability of safer alternative MMR products, (ii) a need to ensure safety and continuation of the measles elimination campaign, and (iii) delayed timelines being followed by the manufacturer to progress with the production and evaluation of a dextran-free vaccine and proposed in vitro studies. The following additional factors were reportedly taken into account by Italian authorities:

1. No new risk data emerged in 2005 while awaiting the production and evaluation of the dextran-free vaccine. However, since the beginning of 2006, 5 serious allergic reactions were reported in Italy.
2. Risk-benefit analysis in Italy was based on a comparative analysis of the three MMR products available/used in the current measles elimination campaign.
3. The measles vaccination campaign in Italy is NOT affected by this decision and is ongoing.

WHO recommendations and actions:

1. As a precautionary measure, WHO is withdrawing with immediate effect from the WHO list of pre-qualified vaccines, in addition to the MMR vaccine, the measles-rubella (MR) and monovalent measles (M) vaccine products from Chiron, both of which contain dextran. UN supply agencies and countries are advised to put any remaining vaccine in the countries on quarantine, until further notice. (Note: The decision by the Italian regulatory authority does not extend to the MR and M products which are not used in Italy and for which no safety data have been made available).

2. A complete risk-benefit analysis with respect to the use of MMR, MR and M vaccines from Chiron, including a review of programmatic implications, is ongoing. This will take into account the following, when complete information is available:
   (i) Supply of the Chiron MMR, MR and M vaccines by UNICEF and PAHO and in-stock availability (per country).
   (ii) Availability of replacement stocks of measles-containing vaccines for supply by UNICEF and PAHO.
   (iii) Further epidemiological analysis of available adverse event data as well as efforts to obtain data from countries using these vaccine products to better quantify the risk of allergic reactions.