March 24, 2006

Notification

PFSB/SD Notification No. 0324001

To: Commissioner of Prefectural Health Department (Bureau)

Director of Safety Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Implementation Methods, etc. of Early Post-marketing Phase Vigilance for Prescription Drugs

Implementation method of the early post-marketing phase vigilance (hereinafter referred to as "EPPV") for prescription drugs has been provided in the Notification No. 166 by the Director of Safety Division, Pharmaceuticals and Food Safety Bureau and Notification No. 1810 by Director of Evaluation and Licensing Division, Pharmaceuticals and Food Safety Bureau, Ministry of Health and Welfare, dated December 27, 2000, "Guideline on Implementation Method of Early Post-marketing Phase Vigilance for Prescription Drugs" (hereinafter referred to as "Joint Notification").

The "Ministerial Ordinance on Good Vigilance Practice for Drugs, Quasi-drugs, Cosmetics, and Medical Devices" (Ordinance of the Ministry of Health, Labour and Welfare No. 135 of 2004; hereinafter referred to as "GVP Ordinance") came into effect on April 1, 2005. Basically, the implementation methods of EPPV should be considered in relation to respective drug. The standard method shall be shown as follows. This notification asks for your understanding and cooperation in making these methods widely known to affiliated vendors.

The Joint Notification shall be abolished.

1. The marketing authorization holders (hereinafter referred to as "MAHs") shall prepare an EPPV plan based on the provision of Article 10, Paragraph 1 of the GVP Ordinance. A sample form is shown in Appendix 1.

2. The MAHs shall have medical representatives (hereinafter referred to as "MRs") provide the following explanation and make the following request for cooperation to medical institutions using the drugs which MAHs have marketed, in principle, prior to their actual supply.

If MRs cannot provide the explanation or make the request for cooperation before supply, the content of the explanation and request for cooperation shall be provided to medical institutions in writing before supply, followed by the MRs' explanation and request for cooperation within approximately 2 weeks after the start of supply.

- The drug is subject to EPPV, and the drug is under the EPPV period.
- The medical institutions are required to make efforts to use the drug properly and to immediately report to the MAHs in the event serious adverse drug reaction and infection occur for which a relationship with the drug is suspected.

3. The MAHs shall make the request for cooperation, etc. to the medical institutions which use the drug, in principle, approximately once every 2 weeks or more frequently for 2 months after the start of supply and with appropriate frequency thereafter (approximately once per month or more frequently).

4. The MAHs shall prepare the EPPV report after the end of the EPPV period. A sample form is shown in Appendix 2[1].

5. The MAHs are to submit the EPPV report with EPPV plan to the Drug Safety Division, Office of Safety[2], Pharmaceuticals and Medical Devices Agency within 2 months after the end of the EPPV period.

[1] The forms in Appendix 1 and 2 are for reference and the form shall be submitted in the original form in Japanese.
[2] An EPPV report shall be submitted to the Office of Safety 2 due to organizational restructuring after the issue of this notice.

Appendix 1

Early Post-marketing Phase Vigilance (EPPV) Plan

<table>
<tr><td rowspan="4">Drug subject to EPPV</td><td>Brand name</td><td colspan="2"></td></tr>
<tr><td>Generic name</td><td colspan="2"></td></tr>
<tr><td>Approval (license) number
Date of approval (license)</td><td colspan="2"></td></tr>
<tr><td>Therapeutic category</td><td colspan="2"></td></tr>
<tr><td colspan="2">Purpose of EPPV</td><td colspan="2"></td></tr>
<tr><td colspan="2" rowspan="3">Number of medical institutions for which EPPV is to be conducted (by type)</td><td>Type</td><td>Number of medical institutions</td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
<tr><td colspan="2">Method of EPPV
(provision of information on proper use to medical institutions, method of request for cooperation and warning, and their implementation frequency)</td><td colspan="2"></td></tr>
<tr><td colspan="2">Period of EPPV</td><td colspan="2">From MM DD, YYYY to MM DD, YYYY</td></tr>
<tr><td colspan="2">When EPPV service is partially outsourced, the outsourcee’s name and address and the scope of the outsourced service</td><td colspan="2"></td></tr>
<tr><td colspan="2">Other necessary matters</td><td colspan="2"></td></tr>
<tr><td colspan="2">Remarks</td><td colspan="2"></td></tr>
</table>

Date of preparation: MM DD, YYYY

(Date of revision in case of revision)

Marketing Supervisor-General or Safety Management Supervisor

Note: In the line of the number of medical institutions for which EPPV is to be conducted (by type), provide this information separately for “hospitals” and “clinics” as defined in Article 1-5 of the Medical Care Act (Act No. 205 of 1948).

Appendix 2

Early Post-marketing Phase Vigilance (EPPV) Report

<table>
<tr><td rowspan="4">Drug subject to EPPV</td><td>Brand name</td><td colspan="2"></td></tr>
<tr><td>Generic name</td><td colspan="2"></td></tr>
<tr><td>Approval (license) number
Date of approval (license)</td><td colspan="2"></td></tr>
<tr><td>Therapeutic category</td><td colspan="2"></td></tr>
<tr><td colspan="2">Date of launch</td><td colspan="2">MM DD, YYYY</td></tr>
<tr><td colspan="2">EPPV period</td><td colspan="2">From MM DD, YYYY to MM DD, YYYY</td></tr>
<tr><td colspan="2" rowspan="3">Number of medical institutions for which EPPV is to be conducted (by type)</td><td>Type</td><td>Number of medical institutions</td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
<tr><td colspan="2">Estimated number of patients</td><td colspan="2">(Describe the method used to calculate the estimated number of patients.)</td></tr>
<tr><td colspan="2" rowspan="2">Occurrence of serious adverse drug reaction, etc.</td><td>Type of adverse drug reaction, etc.</td><td>Number of cases</td></tr>
<tr><td>(Classify by Preferred Term [PT] of each System Organ Class based on the Medical Dictionary for Regulatory Activities/J [MedDRA/J].)</td><td></td></tr>
<tr><td colspan="2">Safety measures taken during the EPPV period</td><td colspan="2">(Describe in detail in the attached paper.)</td></tr>
<tr><td colspan="2">Remarks</td><td colspan="2">(Provide the name and contact phone number of the person in charge of this report.)</td></tr>
</table>

I hereby submit the early post-marketing phase vigilance report.

MM DD, YYYY

Address (location of principal office for corporations)

Name (representative's name for corporations)

To: Director of Office of Safety, Pharmaceuticals and Medical Devices Agency

Note: In the line for the number of medical institutions for which EPPV is to be conducted (by type), provide this information separately for "hospitals" and "clinics" as defined in Article 1-5 of the Medical Care Act (Act No. 205 of 1948).