THE MINISTRY OF HEALTH

ORDER

on approval of The Guideline on clinical safety data management/the Periodic Safety Update Reports for marketed medicinal products

Taking into account:

– provisions of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved with changes and completions through Law no. 594/2002, with further changes and completions through Law No. 594/2002, with further changes and completions;

– provisions of Government Ordinance No. 152/1999 on medicinal products for human use, approved with changes and completions through Law No. 336/2002, with further changes and completions,

on seeing The Approval Report of the General Pharmaceutical and Medical Devices Directorate No. MC 4.659 of 12 April 2005,

based on Government Decision No. 168/2005 on organisation and functioning of the Ministry of Health,

the minister of health hereby issues the following order:

Article 1. – Approval of the Guideline on Clinical Safety Data Management/the Periodic Safety Update Reports for marketed medicinal products, provided in Annex*) which is an integral part of the order.

Article 2**.** – The present order is to be published in the Official Gazette of Romania, Part I.

Minister of Health,
Mircea Cinteză

Bucharest, 19 April 2005.
No. 410.

*ANNEX**

GUIDELINE
on clinical safety data management/the Periodic Safety Update Reports for marketed medicinal products

CHAPTER I
Introduction

Article 1. – The present Guideline is a transposition of the CPMP/ICH/4679/02 guidance providing practical recommendations for the preparation of Periodic Safety Update Reports (PSUR) for marketed medicinal products.

Article 2. – (1) The PSUR is a practical and achievable mechanism for summarizing interval safety data, especially covering short periods (e.g., 6 months or 1 year), and for conducting an overall safety evaluation of medicinal products

(2) It is a tool for marketing authorisation holders (MAHs) to conduct systematic analyses of safety data on a regular basis.

(3) in addition to covering ongoing safety issues, the PSUR should also include updates on emerging and/or urgent safety issues, and major signal detection and evaluation that are addressed in other documents.

Article 3. – (1) PSURs are of value and importance to all parties in protecting the public health.

(2) has been designed for the purpose of harmonising PSURs submitted to competent authorities from the perspective of both content and format as well as introduction of the concept of international birth date (IBD)

Article 4. – This guideline addresses only provisions of Chapter VIII Periodic Safety Update Reports of the Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities considered to need further clarification.

Article 5. – This addendum addresses the following concepts not previously addressed by Chapter VIII Periodic Safety Update Reports of The Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities:

a) Summary bridging report;
b) Addendum report;
c) Proprietary information;
d) Executive summary;
e) Risk management program;
f) Benefit-risk analysis.

CHAPTER II
General principles

II.1 One report on one active substance

Article 6. – For preparation of a report on an active substance, provisions of section VIII.2.1, One report for products containing one active substance authorised to one marketing authorisation

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* Published in the Official Gazette of Romania, Part I, No. 461 bis, 31 May 2005

holder, are to be taken into account, as stated in the Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities.

Article 7. – (1). It is recommended that information on all indications, pharmaceutical forms and dosage for the active substance be included in a single PSUR, with a single data lock point common for all aspects of product use.

(2) There is a great advantage to having a consistent, broad-based examination of the safety information for the active substance(s) in a single document.

(3) When relevant, data relating to a particular indication, dosage form, or dosing regimen should be presented in a separate section within the body of the PSUR and any safety issues addressed accordingly without preparing a separate PSUR.

Article 8. – (1) There are instances when separate PSURs might be considered appropriate.

(2) The regulatory authorities should be notified and their agreement obtained at the time of authorisation

(3) Examples include:

a) Fixed combinations – Options include either a separate PSUR for the combination with cross-reference to the single active substance(s) PSUR(s) or inclusion of the fixed combination data within one of the single active substance PSURs.

b) When an active substance is used in two or more different pharmaceutical forms (e.g., systemic preparations versus topical administration), two or more PSURs, with the same or different IBDs, can be useful.

II.2 International Birth Date and Frequency of Reporting

Article 9. – Provisions of section VIII.2.5.3, Preparation of PSURs according to the International Birth Date as included in the Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities shall be taken into account with reference to International Birth Date and Frequency of Reporting.

Article 10. – (1) Whenever possible, PSURs should be based on the IBD..

(2) If, in the transition period to a harmonized birth date for that product, the use of a local approval date is appropriate, the MAH can submit its already prepared IBD-based PSUR plus:

a) line-listings and/or summary tabulations covering the additional period (when the additional period is less than 3 months for a 6-month or annual PSUR, or 6 months for a longer duration PSUR) with comment on whether the data reveal a new and important risk; or

b) an addendum report when the additional period is greater than 3 months for a 6-month or annual PSUR, or 6 months for a longer duration PSUR (see section II.5 Addendum Report).

II.3 Synchronization of national birth dates with the IBD

Article 11. – For Synchronization of national birth dates with the IBD, see section VIII.2.5.3 Preparation of PSURs according to the International Birth Date of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities.

Article 12. – For drugs that are on the market in many countries, the MAH can synchronize local or national birth dates with the IBD.

Article 13. – (1) For a drug where the IBD is not known, the MAH can designate an IBD to allow synchronization of reports to all regulatory authorities.

(2) Once an IBD is designated, the MAH should notify the regulatory authorities, and the IBD should be adhered to thereafter.

Article 14. – (1) It is recognized that long intervals between approvals could put the drug in a 5-year cycle in one region and a 6-month cycle in another region.

(2) For practical purposes, if a single date (month, day, and year) for the IBD is not attainable, the MAH can contact the regulatory authorities to negotiate a mutually acceptable birth month and day.

(3) For example, where there are different approval dates, it can be useful for reports to be submitted on the same month and day (e.g., every January 18 and July 18), whether every 6 months, annually, or every 5th year.

II.4 Summary bridging reports

Article 15. – (1) A summary bridging report (SBR) is a concise document integrating the information presented in two or more PSURs to cover a specified period over which a single report is requested or required by regulatory authority.

(2) The report should not contain any new data but should provide a brief summary bridging two or more PSURs (e.g., 2 consecutive 6-month reports for an annual report or 10 consecutive 6-month reports to make a 5-year report).

(3) The summary bridging report is intended to assist regulatory authorities with a helpful overview of the appended PSURs.

(4) The PSUR data should not be repeated but should be cross-referenced to individual PSURs.

(5) The format of the summary bridging report should be identical to that of the usual PSUR, but the content should consist of summary highlights and an overview of data from the attached PSURs.

(6) Upon request from the regulatory authority, a summary tabulation of serious, unlisted reactions should be included in the summary bridging report.

Article 16. – (1) Summary bridging reports can be used in situations where the MAH prepares short duration reports (e.g., 6-month or annual reports) indefinitely, especially if new indications or formulations are likely to be introduced over time.

(2) For reports considered out of date relative to a particular regulatory authority's requirement, an Addendum Report could also be submitted

(3) For a PSUR that spans longer time intervals (e.g., 5 years), an addendum report would only be considered appropriate if the time since preparation of the 5-year PSUR and the locally-required report is greater than 6 months.

Article 17. – (1) The ordinary SBR should not include line listings

(2). If summary tables covering the period of the appended PSURs are considered appropriate, there should be a clear agreement/accord that the tables will be generated from live databases, which change over time as cases are updated.

(3) These tables will then reflect the most up-to-date data available at the time they are generated.

(4) It is recognized that the case counts in these summary tables can differ somewhat from the contents of the individual tables in the appended PSURs.

(5) A general overview describing the differences should be provided

II.5 Addendum Report

Article 18. – (1) MAHs should set IBDs for all their products and can synchronize their local renewals

(2) However, when a requested or required report covers data that fall outside the defined period, use of an addendum report is recommended.

Article 19. – (1) An addendum report is an update to the most recently completed PSUR when a regulatory authority requests or requires a safety update outside the usual IBD reporting cycle.

(2) An addendum report should be used when more than 3 months for a 6-month or an annual report, and more than 6 months for a longer-interval report, have elapsed since the data lock point of the most recent PSUR.

(3) It might also be appropriate to provide an addendum to the summary bridging report.

Article 20. – (1) The addendum report should summarize the safety data received between the data lock point of the most recent PSUR and the regulatory authority's requested cut-off date.

(2) It is not intended that the addendum report provide an in-depth analysis of the additional cases, as these can be included in the next regularly scheduled PSUR.

(3) Depending on circumstances and the volume of additional data since the last scheduled report, an addendum report can follow the format provided in Chapter VIII Periodic Safety Update Reports of the Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities or as a simplified presentation.

(4) A minimal report should include the following sections containing any new information or changes beyond the most recent PSUR to which the Addendum Report refers:

a) Introduction (purpose; cross reference to most recent PSUR);

b) Changes to the Company Core Safety Information (CCSI) (including a copy of the most recent CCSI document if it differs from the one in the PSUR);

c) Significant regulatory actions bearing on safety;

d) Line listing(s) and/or summary tabulations;

e) Conclusions (brief overview of new information and any impact on the known safety profile).

II.6 Restarting the clock

Article 21. – For products in a long-term PSUR cycle, the return to 6-month or annual reporting could apply after important additions or changes in clinical use are first approved, such as:

a) A new therapeutic indication;

b) A previously unapproved use in a special patient population, such as children, pregnant women, or the elderly;

c) A new formulation or new route of administration.

Article 22. – The decision on restarting the clock clock should be discussed with the regulatory authority no later than the time of granting the relevant marketing authorisation (MA).

Article 23. – Even if the clock "restarts," the analyses in the PSUR should focus on the newly indicated population by identifying and characterizing any differences from the established safety profile in the previously indicated populations.

II.7 Time interval between the data lock point and PSUR submission

Article 24. – (1) PSUR are to be submitted within 60 days of the data lock point.

(2) To facilitate the preparation of both current and future PSURs, as well as safety reports outside of the PSUR, the regulatory authority will attempt to send comments to the MAH:

a) as rapidly as possible, if any issues of noncompliance with the ICH format and content of a PSUR are identified (particularly those that preclude review);

b) as rapidly as possible, if additional safety issues are identified that could prompt further evaluation by the MAH that should either be included in the next PSUR or provided as a separate stand-alone report;

c) before the next data lock point, if any additional analyses or issues of content are identified that should be included in the next PSUR.

II.8 Additional Time for Submissions

Article 25. – (1) in rare circumstances, an MAH can make a special request to the regulatory authority for 30 additional calendar days to submit a PSUR.

(2) Ideally, this request should be made before the data lock point.

(3) The regulatory authority will attempt to send response to MAH as rapidly as possible.

Article 26. –The basis of such a request should be justified and could include:

a) A large number of case reports for the reporting period, provided that there is no new significant safety concern;

b) Issues raised by regulatory authorities in the previous PSUR for which the MAH is preparing additional or further analysis in the next PSUR;

c) Issues identified by the MAH for additional or further analysis.

Article 27. – (1) The MAH should make such a request only for the single PSUR in question and not for subsequent PSURs.

(2) The regulatory authority will generally expect subsequent PSURs to be submitted on the appropriate date and to retain their original periodicity.

II.9 Reference Safety Information

Article 28. – It is important to highlight the differences between the CCSI and the local product information/local labelling in the cover letter accompanying the local submission of the PSUR (see section VIII.3.4 Changes to reference safety information of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities).

II.10 PSUR covering a period of 6 months or 1 year

Article 29. – For 6-month and annual reports, the version of the CCSI in effect at the beginning of the period covered by the report should be used as the reference.

II.11 PSUR covering a period of over 1 year

Article 30. – (1) When producing a longer duration PSUR or a summary bridging report, it is often impractical to base the analysis of listedness on the CCSI that was in effect at the beginning of the period covered.

(2) There can be considerable variation in listedness over the reporting period, depending on when the assessment of listedness is made (e.g., on an ongoing basis, such as at adverse event/adverse drug reaction (AE/ADR) case entry, or when a PSUR is compiled).

(3) The latest CCSI in effect at the end of the period can be used.

(4) The MAH should ensure that all changes to the CCSI made over the period covered by the PSUR are described in section VIII.3.4 Changes to reference safety information of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities.

Article 31. – (1) When listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the current version of the CCSI as the reference document, as long as that choice is made clear in the PSUR text.

(2) MAHs assessment of listedness at case entry or on an ongoing basis throughout the reporting period should include the current version of the CCSI and comment on the reasons for any changes in listedness assessment over time.

(3) in both cases, changes made to the CCSI since the previous PSUR should be explained in sections VIII.3.4 Changes to reference safety information and/or VIII.3.9 Overall safety evaluation of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities).

CHAPTER III
Model for a Periodic Safety Update Report (PSUR)

Article 32. – (1) PSURs contain proprietary information.

(2) Therefore, the title page of a PSUR should contain a statement on the confidentiality of the data and conclusions included in the report

Article 33. – (1) MAHs should prepare a brief overview, or executive summary, of each PSUR to provide the reader with a description of the most important information.

(2) This executive summary should be placed at the beginning of the PSUR immediately after the title page.

III.1 Patient exposure

Article 34. – Estimations of patient exposure takes into account provisions of section VIII.3.5 Patient exposure of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities.

Article 35. – (1) Estimations of patient exposure for marketed drugs often rely on gross approximations of sales data.

(2) This information is not always reliable or available for all products. For example, hospital-based (inpatient exposure) statistics from the major use-monitoring sources are frequently unavailable.

(3) It is also difficult to obtain accurate data for generics, non-prescription medicinal products or multiple drug therapeutic regimens.

Article 36. – (1) When exposure data are based on information from a period that does not fully cover the period of the PSUR, the MAH can make extrapolations using the available data.

(2) When this is done it should be clearly indicated what data were used and why it is valid to extrapolate for the PSUR period in question (e.g., stable sales over a long period of time, seasonal use of the product).

Article 37. – (1) The MAH should use a consistent method of calculation across PSURs for the same product.

(2) If a change in the method is appropriate, both previous and current methods and calculations should be shown in the PSUR introducing the change.

Article 38. –In summary bridging reports, recalculation of patient exposure data to cover the entire reporting period can be appropriate if the exposure periods used in the individual PSURs overlap.

Article 39. – As described in Chapter VIII Periodic Safety Update Reports of the Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities, when the pattern of reports indicate a potential safety problem, detailed presentation by clinical indication, approved or unapproved, should be provided when available.

III.2 Presentation of Individual Case Histories

Article 40. – Presentation of individual case report narratives takes into account provisions of section VIII.3.6 Presentation of individual case histories of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities)

Article 41. – (1) in Chapter VIII Periodic Safety Update Reports of the Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities there is no specific guidance on presentation of Individual Case Histories.

(2) As it is impractical to present all case reports for the reporting period in this chapter of the PSUR, a brief description of the criteria used to select cases for presentation should be given.

Article 42. –This chapter should contain a description and analysis of selected cases, including fatalities, presenting new and relevant safety information and grouped by medically relevant headings or system organ classes (SOCs).

III. 2.1 General Considerations

Article 43. – Provisions of section VIII.3.6.1 General considerations of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities must be taken into account.

III.2.1.1 Consumer and Other Non-healthcare Professional Reports

Article 44. – (1) MAHs should prepare standard line listings and tabulations that are considered acceptable by all regulatory authorities.

(2) To achieve this goal, MAHs should follow a consistent practice across all PSURs for all products by presenting consumer and other non-healthcare professional reports in separate line listings.

(3) When included in the analysis of safety issues in sections VIII.3.6 Presentation of individual case histories and VIII.3.9 Overall safety evaluation of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities, consumer reports should clearly be identified as such.

III.2.1.2 Presentation of the line listing

Article 45. – Presentation of the line listing takes into account provisions under section VIII.3.6.3 Presentation of the line listing of Guideline on procedure to be pursued by marketing authorisation holders in carrying out pharmacovigilance activities.

Article 46. – The “Comments” field should be used only for information that helps to clarify individual cases.

III.3 Studies

Article 47. – Only those company-sponsored studies and published safety studies, including epidemiology studies, that produce findings with potential impact on product safety information should be included with a discussion of any final or interim results.

III.4 Other Information

III.4.1 Risk management programmes

Article 48. – When an MAH has specific risk management programmes in place, they can be discussed in this section.

III.4.2 Benefit-risk analysis report

Article 49. – When a more comprehensive safety or benefit-risk analysis (e.g., all indications reviewed) has been conducted separately, a summary of the analysis should be included in this chapter.

III.5 Overall Safety Evaluation

Article 50. – (1) Discussion and analysis for the overall safety evaluation should be organized by SOC rather than by listedness or seriousness.

(2) Although related terms might be found in different SOCs, they should be reviewed together for clinical relevance.