famhp
federal agency for medicines and health products

DG POST authorisation/ Vigilance Division / pharmacovigilance (human)

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Circular No. 599
For the attention of holders of marketing authorisations or registrations of medicinal products for human use

Your letter from	Your reference	Our reference	Annex	Date
		567052		15.07.2013

New European legislation on pharmacovigilance for medicinal products for human use (national marketing authorisations and registrations) – national application

Dear Sir/Madam,

New European legislation on pharmacovigilance for medicinal products for human use, Directive 2010/84/EU[1] and Regulation 1235/2010[2], entered into force on 21 July 2012 and 2 July 2012, respectively. These new legal provisions change existing EU legislation included in Directive 2001/83/EC[3] and EC Regulation No. 726/2004[4].

Directive 2010/84/EU is transposed into Belgian legislation[5] by:
- the law of 3 August 2012 amending the law of 25 March 1964 on medicinal products, published on 11 September 2012 in the Belgian law gazette.
- the royal decree of 28 May 2013 amending the royal decree of 14 December 2006 on medicinal products for human and animal use, published on 10 June 2013 in the Belgian law gazette.

Implementing Regulation (EU) No. 520/2012[6] of 19 June 2012 completes this legal framework and adds technical details regarding the pharmacovigilance activities included in the directive and regulation.
The good pharmacovigilance practices (GVP)[7], published by EMA, are guidelines consisting of 16 modules that are to be applied by the marketing authorization and registration holders, EMA and the national competent authorities. These guidelines replace, upon approval and publication, the corresponding sections of Volume 9A of "the Rules Governing Medicinal Products in the EU".

The aim of this circular is to explain the new legal provisions for pharmacovigilance for medicinal products for human use (national marketing authorisations and registrations), more specifically its practical application by the famhp (federal agency for medicines and health products).

This circular replaces circulars Nos. 460, 490, 490 addendum, 476.

The requirements for the local persons responsible for pharmacovigilance and the system for pharmacovigilance are explained in circular No. 600.

We thank you for taking the time to read this circular,

Yours faithfully,

Xavier De Cuyper,
CEO

This document is a translation of the official and signed versions in Dutch and French

1. Reporting requirements for individual case safety reports (ICSRs) applicable to marketing authorisation and registration holders

Legislation

The legal requirements for the reporting of ICSRs (= individual case safety reports) are described in:

- the royal decree of 14 December 2006 on medicinal products for human and animal use (amended by the royal decree of 28 May 2013), art. 67 and the transitional measures in art. 22 § 3;
- the Implementing Regulation (EU) No. 520/2012 on the performance of pharmacovigilance activities, articles 27 to 29 and transitional measures in article 40;
- the "guideline on good pharmacovigilance practices (GVP)" - Module VI - Management and reporting of adverse reactions to medicinal products.

Suspected adverse reactions, occurring in the context of a clinical trial, shall be recorded and reported in accordance with the law of 7 May 2004 concerning experiments on the human person, as described in circular 586.

Transitional period

A transitional period applies to the electronic reporting of suspected adverse reactions to the EudraVigilance database until such time as the EMA can guarantee that EudraVigilance complies with agreed function specifications.

During the transitional period, the following provisions apply:

a) Adverse reactions occurring on Belgian territory:

   - ***Non-serious suspected adverse reactions*** need not be reported;
   - All ***serious suspected adverse reactions,*** reported by both healthcare professionals[a] and patients, must be reported.

   This pertains to:

   - Spontaneous reports, literature reports and other unsolicited reports, as specified in section VI.B.1.1 of GVP Module VI;
   - reports from non-interventional studies and other solicited reports, as specified in sections VI.B.1.2 and VI.C.1 of GVP Module VI.

b) Adverse reactions occurring outside of Belgian territory: see Appendix 3.1.1 of Module VI – Tables VI.4 and VI.5.

Reporting modalities

Serious suspected adverse reactions shall, within 15 days following the day on which the marketing authorisation or registration holder concerned gained knowledge of the event, be submitted to the EVPM-module (Post Marketing) electronically (E2B - format) with Receiver-ID "EVHUMAN" within the production environment of the European EudraVigilance database.

Following the transitional period, when EudraVigilance complies with the agreed functional specifications, all non-serious suspected adverse reactions occurring in the EU shall also be reported electronically to the

a healthcare professionals: the persons referred to in the royal decree No. 78 of 10 November 1967 on the practice of healthcare professions

EudraVigilance database within 90 days after following the day on which the marketing authorisation or registration holder concerned gained knowledge of the event. See Appendix 3.2.1 of GVP Module VI.

For more information on EudraVigilance, we would refer you to: http://EudraVigilance.ema.europa.eu.

2. Periodic safety update reports (PSURs)

Legislation

The legal requirements for the format and content of PSURs (periodic safety update reports), the electronic submission, the submission frequency and relevant assessment are described in:

- the royal decree of 14 December 2006 on medicinal products for human and animal use (amended by the royal decree of 28 May 2013), articles 68 to 68 quater and transitional measures in article 22 § 4;
- implementing regulation (EU) No. 520/2012 on the performance of pharmacovigilance activities, articles 34 and 35;
- the "guideline on good pharmacovigilance practices (GVP)" - Module VII – Periodic safety update reports.

Consequently, the requirement for a scientific assessment by the qualified person responsible for pharmacovigilance in Belgium, described in circular No. 490, hereby lapses.

Transitional period

New legislation states that marketing authorisation holders shall submit PSURs to the EMA.

However, there is a transitional period: until 12 months after the EMA PSUR repository is operational, PSURs shall be submitted electronically to the famhp, in agreement with the "National Competent Authorities (NCAs) and European Medicines Agency (EMA) requirements for submission of PSUR during the transitional period"[8], published by EMA. The same submission requirements apply to updates of the risk management plan (RMP), if an update of the RMP must be supplied together with a PSUR.

Content and format of PSUR

The new legislation changes the content and format of the PSURs and the emphasis is on the assessment of the benefit-risk balance of the medicine in question. PSURs should be written according to the new legal requirements set out in above mentioned Implementing Regulation (EU) No 520/2012 and GVP Module VII. PSURs shall be submitted within 70 or 90 days of the DLP (Data Lock Point), as defined in GVP module VII – PSURs.

Submission frequency

The submission frequency of PSURs is determined by the "List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)" ("EURD lijst")[9]. This list is published on the EMA webportal and applies from 1 April 2013. Any changes to the EURD list enter into force 6 months following the date of publication. Marketing authorisation holders shall follow the PSUR cycle, as defined in the EURD list.

The single assessment of PSURs for substances, for which only nationally authorised medicines (including

MRP / DCP) exist, will not start in 2013. Therefore, these active substances were temporarily removed from the EURD list. For these active substances, the "List of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronized"[10], published on the Heads of Medicines Agency, is applicable.

Medicinal products, containing an active substance not included in these lists, and for which the frequency and dates of submission of the PSURs are not laid down as a condition to the marketing authorisation will continue to follow the "routine" submission frequencies (6-monthly, annually, 3-yearly PSURs) (see also GVP VII). Marketing authorisation holders shall provide the minister, or his deputy, with PSURs at their request.

Derogation

From 21 July 2012, certain categories of medicinal products will be exempt from the obligation to submit PSURs routinely as mentioned above (i.e. 6-monthly, annually, 3-yearly), namely for:

- generics that are granted a marketing authorisation in agreement with article 6 bis, § 1, subparagraph 1 of the law of 25 March 1964 on medicinal products;[b]
- "well-established use" medicinal products that are granted a MA in agreement with article 6 bis, § 2 of the law of 25 March 1964 on medicinal products; [b]
- homeopathic medicinal products and herbal medicines that are registered in agreement with article 38 and 43 of the royal decree of 14 December 2006, respectively.

For these medicinal products, PSURs are only required in the following situations (see also GVP VII):

- when a marketing authorisation has been granted subject to the condition to submit PSURs;
- when requested by the minister, or his deputy, on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance after the marketing authorisation has been granted (article 68 of the royal decree of 14 December 2006);
- when the "EURD list" indicates that PSURs are required for generics, well-established use medicinal products, homeopathic medicinal products and herbal medicines.

3. Five-yearly renewal

Legislation:

The legal requirements for the five-yearly renewal are described in:

- the law of 25 March 1964 on medicinal products (amended by the law of 3 August 2012), art. 6 § 1 ter;
- the royal decree of 14 December 2006 on medicinal products for human and animal use (amended by the royal decree of 28 May 2013), art. 37;
- the "CMDh Best Practice Guide on the processing of renewals in mutual recognition and decentralised procedures"[11].

The application for the five-yearly renewal shall be submitted at least 9 months before the marketing authorisation ceases to be valid (previously 6 months).

[b] This PSUR derogation is also applicable to medicines, licensed on the basis of an equal legal basis, before the re-codification of the Directive 2001/83/EC, namely medicines registered in accordance with the provisions of article 2.8 a), second line and third line of the royal decree of 3 July 1969.

Submission requirements

The content requirements of the dossier for the five-yearly renewal application shall apply from the date on which the royal decree has been published. For more details, we would refer to the "CMDh Best Practice Guide on the processing of renewals in mutual recognition and decentralised procedures". The European application form[12] can be used for this purpose.

Applications to renew the marketing authorisation for medicinal products for human use shall be submitted to the Marketing Authorisation - Variations & Renewals Division.

The applications can be submitted by e-mail on the following e-mail address: dispatching@fagg-afmps.be

Dossiers on CD-rom or DVD should be sent to:

Famhp - Marketing Authorisation Division - Variations & Renewals

Dispatching unit

Eurostation II

Victor Hortaplein 40/40

1060 Brussels

From 1 July 2013 this will be submitted preferably via the Common European Submission Platform (CESP).

Applicants shall be sent confirmation of receipt by e-mail.

4. Post-authorisation safety / efficacy studies (PASS / PAES)

Legislation

The legal requirements for a post-authorisation safety study (PASS) and for a post-authorisation efficacy study (PAES) are described in:

- the royal decree of 14 December 2006 on medicinal products for human and animal use (amended by the royal decree of 28 May 2013), art. 65 ter §1-3, art. 72 to Art. 72 quinquies, and art. 73 – 73bis;
- the implementing regulation (EU) No. 520/2012 on the performance of pharmacovigilance activities, art. 36, 37 and 38 and transitional measures in art. 40;
- the "Guideline on good pharmacovigilance practices (GVP)" – Module VIII – Post-authorisation safety studies";
- the Annex to GVP module VIII – Post-authorisation safety studies – Member States' requirements for transmission of information on non-interventional post-authorisation safety studies (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129147.pdf).

This circular is without prejudice to other national requirements for ensuring the well-being and rights of participants in PASS/PAES.

Interventional trials are subject to the provisions of the law of 7 May 2004 concerning experiments on the human person (transposition of Directive 2001/20/EC) and of Volume 10 of "The Rules Governing Medicinal Products in the European Union".

Entry into force

The format and content of the study protocol, the final study report and the abstract of the final study report are described in Annex III of the Implementing Regulation (EU) No. 520/2012.

Submission requirements

a) PASS imposed by Belgium as competent authority with supervision on PASS by the famhp

If the minister, or his deputy, after a marketing authorisation has been granted, imposes a PASS and this study is only conducted in Belgium, the study should only be submitted to the Belgian competent authority, in this case the famhp.

For these studies, the study protocol, together with the cover letter, should be sent on CD-rom to:

famhp – R&D Division

Attn. Kristof Bonnarens

Eurostation II

Victor Hortaplein 40/40

1060 Brussels

Applicants will receive confirmation of receipt by e-mail.

Progress reports and the final study report (with the summary of the study results) should also be submitted to the famhp.

b) PASS imposed by a competent authority with supervision by the PRAC

If a PASS is imposed by a competent authority, with PRAC being responsible for supervision, the protocol and final study report must be submitted to the PRAC and the Member States where the study is conducted.

The Member States that act as rapporteur or RMS (Reference Member State) for the medicinal product in question, or where the product is authorised, but that are not rapporteur or RMS, receive the study protocols through the PRAC.

If a PASS is carried out in Belgium, the study protocol shall be submitted by e-mail or via Eudralink to the famhp, Vigilance Division – pharmacovigilance (human), via psurh@fagg.be. From 1 July 2013 this will be submitted preferably via the Common European Submission Platform (CESP).

Overview of procedures to be followed:

Table 1. Studies imposed by a competent authority with supervision by the PRAC

	Study protocols, updated study protocols following substantial amendments and final study reports[1]		Progress reports if requested[1]
	Direct transmission by the marketing authorisation holder to Belgium[2]	Transmission by the marketing authorisation holder to Belgium via PRAC[3]	Direct transmission by the marketing authorisation holder to Belgium [2]
Study conducted in Belgium	X		X
Belgium acts as rapporteur or RMS for the medicinal product*		X	X
Medicinal product is authorised in Belgium, but Belgium does not act as rapporteur or RMS for this medicinal product*		X	

[1] The study information should also be entered and updated in the EU PAS Register. As long as the EU PAS Register is not operational, this must be entered in the ENCePP Register (http://www.encepp.eu/encepp/studiesDatabase.jsp).

[2] Final study protocols, substantial changes to the study protocol, progress reports, abstracts of final study reports and final study reports to be transmitted by marketing authorisation holders to the Member States in accordance with national procedures.

[3] Information to be transmitted by marketing authorisation holders to the EMA and all PRAC members in the context of the oversight of PASS by the PRAC as described in Directive 2001/83/EC Art 107 n-p.

*even if the study is not conducted in Belgium

c) PASS initiated, managed or financed voluntarily by a marketing authorisation holder

Table 2. Studies initiated, managed or financed voluntarily by a marketing authorisation holder

	Study protocols, updated study protocols following substantial amendments, progress reports if requested and final study reports
	Transmission by the marketing authorisation holder via notification from EU PAS Register[4]
Study is conducted in Belgium	X
Belgium acting as rapporteur or RMS for the medicinal product*	X

Medicinal product is authorised in Belgium, but Belgium is not acting as rapporteur or RMS for this medicinal product*	X

[4] Notification message sent to all EU Member States with a link to the study record.

*even if the study is not conducted in Belgium

d) PAES

For post-authorisation efficacy studies, the delegated acts of the European Commission and the scientific guidance are yet to be drawn up.

5. Updates of the risk management plan

When an update of the risk management plan (RMP) should be submitted, outside of any marketing authorisation or variation application, the submission requirements that apply to PSURs also apply here: see “NCA requirements for PSUR submission during the transitional period”[8], published by the EMA.

6. Additional monitoring

From the autumn of 2013, the SPC and package leaflet of medicinal products under additional monitoring, shall contain a black inverted equilateral triangle, together with the sentence explaining what the symbol means: "This medicinal product is subject to additional monitoring.”

The current list of medicinal products under additional monitoring, is published on the website of the European Medicines Agency (EMA) and will also be published on the website of the famhp. The list is updated every month.

For new medicinal products authorised after 1 September 2013 and subject to additional monitoring, the black symbol should be included in the package leaflet and SPC when the medicinal product is put on the market in the EU.

The legislation applies to medicinal products authorised after 1 January, 2011 in the EU. For this reason, there is a transitional period for medicinal products authorised between January 2011 and August 2013, where updated product information leaflets gradually will replace the old stock on the European market.

For more information, see:

http://www.emea.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp&mid=WC0b01ac058067bfff

[1] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_nl.pdf

[2] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_nl.pdf

[3] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20110120:EN:PDF (consolidated version)

[4] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20120702:EN:PDF (consolidated version)

[5] http://www.ejustice.just.fgov.be/cgi/welcome.pl

[6] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF

[7] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

[8] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127656.pdf

[9] EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000361.jsp&mid=WC0b01ac058066f910#section2

[10] PSUR Work Sharing webpage, CMDh website: http://www.hma.eu/348.html

[11] http://www.hma.eu/95.html

[12] http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm#vol2c