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L.N. 373 of 2012

MEDICINES ACT
(CAP. 458)

Medicines (Marketing Authorisation) (Amendment) Regulations, 2012

IN exercise of the powers conferred by article 106 of the Medicines Act, the Minister of Health, the Elderly and Community Care, after consultation with the Licensing Authority, has made the following regulations:-

Citation, scope and coming into force.

1. (1) The title of these regulations is the Medicines (Marketing Authorisation) (Amendment) Regulations, 2012, and these regulations shall be read and construed as one with the Medicines (Marketing Authorisation) Regulations, hereinafter referred to as "the principal regulations".

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(2) The scope of these regulations is to transpose amendments to Directive 2001/83/EC on the Community code relating to medicinal products for human use, brought about by Directive 2010/84/EU, as regards pharmacovigilance and Directive 2011/62/EU, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.

(3) Paragraph (x) in the new regulation 5(1)(c) in regulation 5 hereof shall come into force on the 2nd January, 2013.

Amends regulation 2 of the principal regulations.

2. Sub-regulation (1) of regulation 2 of the principal regulations shall be amended as follows:

(a) immediately after the definition "Member State" there shall be added the following new definitions:

" "Pharmacovigilance system" means a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in these regulations and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance;

"Pharmacovigilance system master file" means a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products;

"post-authorisation safety study" means any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures;"; and

(b) immediately after the definition "risk-benefit plan" there shall be added the following new definitions:

" "risk management system" means a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions;

"Risk management plan" means a detailed description of the risk management system;".

Amends regulation 4 of the principal regulations.

3. Regulation 4 of the principal regulations shall be amended as follows:

(a) paragraph (g) of sub-regulation (1) thereof shall be substituted the following new paragraph:

"(g) The marketing authorisation holder shall be responsible for marketing the medicinal product and the designation of a representative shall not relieve the marketing authorisation holder of his legal responsibility. The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in Malta shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in Malta are covered."; and

(b) immediately at the end of paragraph (b) of sub-regulation (2) thereof, there shall be added the following new

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paragraph:

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"The Authority may decide that regulation 10(1) and (2) of the Medicinal Products (Labelling and Packaging) Regulations and Article 63(1) and (2) of Directive 2001/83/EC shall not apply to medicinal products authorised under paragraph (a).".

Substitutes regulation 5 of the principal regulations.

4. Regulation 5 of the principal regulations shall be substituted by the following new regulation:

"Grant or renewal of marketing authorisation.

5. (1) A marketing authorisation may only be granted or renewed if the general conditions applicable to authorisations and the conditions set out under Directive 2001/83/EC on the Community code relating to medicinal products for human use and subsequent amendments thereto, are fulfilled as follows:

(a) an application for marketing authorisation shall be made to the Licensing Authority which shall refer such application to the Authority for processing;

(b) a marketing authorisation may only be granted to an applicant established in the Community;

(c) the application shall be accompanied by the following documents and particulars to be submitted in accordance with Annex I:

(i) the name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer;

(ii) the name of the medicinal product;

(iii) qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the World Health Organisation, where an INN for the medicinal product exists, or a reference to the relevant chemical name;

(iv) evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged;

(v) a description of the manufacturing method;

(vi) therapeutic indications, contra-indications and adverse reactions;

(vii) posology, pharma-ceutical form, method and route of administration and expected shelf life;

(viii) reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment;

(ix) description of the control methods employed by the manufacturer;

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(x) a written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits, in accordance with regulation 5 of the Good Manufacturing Practice in respect of Medicinal Products, Active Substances and Investigational Medicinal Products for Human Use Regulations. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice;

(xi) results of pharmaceutical (physico-chemical, biological or microbiological) tests, pre-clinical (toxicological and pharmacological) tests, clinical trials;

(xii) a summary of the applicant's pharmacovigilance system which shall include the following elements:

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance,
- the Member States in which the qualified person resides and carries out his tasks,
- the contact details of the qualified person,

- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC as amended,

- a reference to the location where the pharmacovigilance system master file for the medicinal product is kept;

(xiii) the risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof of the risk management system which the applicant will introduce;

(xiv) a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of the Clinical Trials Regulations and of Directive 2001/20/EC of the European Parliament and of the Council of the 4th April, 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products on human use;

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(xv) a summary, in accordance with regulation 8, of the product characteristics, a mock-up of the outer packaging, containing the details provided for in the Medicinal Products (Labelling and Packaging) Regulations, and of the immediate packaging of the medicinal product, containing the details provided for in those regulations, together with a package leaflet in accordance with those same regulations;

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(xvi) a document showing that the manufacturer is authorised in his own country to produce medicinal products;

(xvii) copies of the following:

- any authorisation, obtained in another Member State or in a third country, to place the medicinal product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for authorisation submitted in accordance with the provisions of Directive 2001/83/EC, as amended, is under examination,

- the summary of the product characteristics proposed by the applicant in accordance with regulation 8 or approved by the competent authorities of the Member State in accordance with regulation 16 and the package leaflet proposed in accordance with the Medicinal Products (Labelling and Packaging) Regulations, or as approved by the competent authorities of the Member State in accordance with the Medicinal Products (Labelling and Packaging) Regulations,

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- details of any decision to refuse authorisation, whether in the Community or in a third country, and the reasons for such a decision;

(xviii) a copy of any designation of the medicinal product as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, accompanied by a copy of the relevant Agency opinion.

(2) The documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials referred to in sub-regulation (1)(c)(x) shall be accompanied by detailed summaries in accordance with regulation 9.

(3) The risk management system referred to in sub-regulation (1)(c)(xii) shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data.

(4) The information in sub-regulation (1) shall be updated where and when appropriate.".

5. Immediately after sub-regulation (2) of regulation 8 of the principal regulations, there shall be added the following new sub-regulation: Amends regulation 8 of the principal regulations.

"(3) For medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary of product characteristics shall include the statement: "This medicinal product is subject to additional monitoring". This statement shall be preceded by the black symbol referred to in Article 23 of Regulation (EC) No 726/2004 and followed by an appropriate standardised explanatory sentence.

For all medicinal products, a standard text shall be included expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system. Different ways of reporting, including electronic reporting, shall be available in compliance with the second subparagraph of Article 107a(1) of Directive 2001/83/EC as amended.".

6. Regulation 16 of the principal regulations shall be amended as follows: Amends regulation 16 of the principal regulations.

(a) sub-paragraphs (iii) and (iv) of paragraph (b) thereof shall be substituted by the following new sub-paragraphs:

"(iii) shall, without delay, make publicly available the marketing authorisation together with the package leaflet, the summary of the product characteristics and any conditions established in accordance with article 23 of the Cap. 458. Medicines Act and paragraph (c) and regulation 17(a) and (b), and together with any deadlines for the fulfilment of those conditions for each medicinal product which they have authorised;

(iv) shall draw up an assessment report and make comments on the file as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is important for the evaluation of the quality, safety or efficacy of the medicinal product concerned.";

(b) immediately at the end of paragraph (b) thereof, there shall be added the following:

"The Authority shall make the assessment report publicly accessible without delay, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each indication applied for.

The public assessment report shall include a summary written in a manner that is understandable to the public. The summary shall contain, in particular, a section relating to the conditions of use of the medicinal product."; and

(c) immediately after paragraph (b) thereof, there shall be added the following new paragraph:

"(c) In addition to the provisions laid down in regulation 15, a marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

(i) to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;

(ii) to conduct post-authorisation safety studies;

(iii) to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Title IX of Directive 2001/83/EC as amended;

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(iv) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;

(v) the existence of an adequate pharmacovigilance system;

(vi) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Regulation 17 of these regulations, while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC as amended.

The marketing authorisation shall lay down deadlines for the fulfilment of these conditions where necessary.".

Substitutes regulation 17 of the principal regulations.

7. Regulation 17 of the principal regulations shall be substituted by the following new regulation:

"17. (a) In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted subject to certain conditions, in particular relating to the safety of the medicinal product, notification to the Authority of any incident relating to its use, and action to be taken.

The marketing authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and it should be based on one of the grounds set out in Schedule I.

Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.

(b) After the granting of a marketing authorisation, the Licensing Authority may impose an obligation on the marketing authorisation holder:

(i) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than

one medicinal product, the Authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

(ii) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the guidelines or Regulations published by the Commission pursuant to Article 22b of Directive 2001/83/EC as amended, while taking into account the scientific guidance referred to in Article 108a of Directive 2001/83/EC as amended.

The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

The Authority shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within thirty days of receipt of the written notification of the obligation.

On the basis of the written observations submitted by the marketing authorisation holder, the Licensing Authority shall withdraw or confirm the obligation. Where the Licensing Authority confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

(c) The marketing authorisation holder shall incorporate any conditions referred to in paragraphs (a) and (b) and in regulation 16(b), in his risk management system.

(d) The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions pursuant to paragraphs (a) or (b) or in regulation 16(c).".

Substitutes regulation 18 of the principal regulations.

8. Regulation 18 of the principal regulations shall be substituted by the following new regulation:

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"18. (1) After a marketing authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in regulation 5(1)(c)(v) and (ix), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the Licensing Authority.

(2) The marketing authorisation holder shall forthwith provide the national competent authority with any new information which might entail the amendment of the particulars or documents referred to in regulation 5(1)(c), regulation 7(1), (2) and (3), and regulation 8 , or Article 32(5), or Annex I of Directive 2001/83/EC as amended.

In particular, the marketing authorisation holder shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

(3) The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.

(4) In order to be able to continuously assess the risk-benefit balance, the national competent authority may at any time ask the marketing authorisation holder to forward data demonstrating that the risk-benefit balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request.

The national competent authority may at any time ask the marketing authorisation holder to submit a copy of the

pharmacovigilance system master file. The marketing authorisation holder shall submit the copy at the latest seven days after receipt of the request.

(5) After a marketing authorisation has been granted, the holder of the authorisation shall inform the Authority of the date of actual marketing of the medicinal product for human use in Malta, taking into account the various presentations authorised. The holder shall also notify the Authority if the product ceases to be placed on the market in Malta, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than two months before the interruption in the placing on the market of the product.

(6) Upon request by the Authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide it with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions.".

Substitutes regulation 19 of the principal regulations.

9. Regulation 19 of the principal regulations shall be substituted by the following new regulation:

"19. (1) Without prejudice to sub-regulations (5) and (6), a marketing authorisation shall be valid for five years.

(2) The marketing authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the Authority.

(3) To this end, the marketing authorisation holder shall provide the Authority with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in suspected adverse reactions reports and periodic safety update reports submitted in accordance with Title IX of Directive 2001/83/EC as amended, and information on all variations introduced since the marketing authorisation was granted, at least nine months before the marketing authorisation ceases to be valid in accordance with sub-regulation (1).

(4) Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the national competent Authority decides, on justified grounds relating to pharmacovigilance, including exposure of an insufficient number of patients to the medicinal product concerned, to

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proceed with one additional five-year renewal in accordance with sub-regulation (2).

(5) Any authorisation granted by the Authority which within three years of its granting is not followed by the actual placing on the market of the authorised product in Malta shall cease to be valid.

(6) When an authorised product previously placed on the market in Malta is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid.

(7) The Authority may, in exceptional circumstances and on public health grounds, grant exemptions from sub-regulations (4) and (5) provided that such exemptions are duly justified.".

Amends regulation 23 of the principal regulations.

10. Sub-regulation (4) of regulation 23 of the principal regulations shall be substituted by the following new sub-regulation:

"(4) The Member States, the Commission, the applicant or the marketing authorisation holder shall, in specific cases where the interests of the European Union are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC as amended before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation which appears necessary.

Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 107j(2) of Directive 2001/83/EC may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 32 of Directive 2001/83/EC as amended. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in regulation 65 of the Pharmacovigilance Regulations, 2012, shall apply.

However, where urgent action is considered necessary, the procedure laid down in regulations 60 and 65 of the Pharmacovigilance Regulations, 2012, shall apply.".

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Amends regulation 24 of the principal regulations.

11. Sub-regulation (2) of regulation 24 of the principal regulations shall be deleted and sub-regulation (1) thereof shall be renumbered as the whole regulation.

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