DECISION

No. 4/27.03.2009

on approval of the Guideline on change of classification for supply of a medicinal product for human use

The Scientific Council of the National Medicines Agency, set up in based on Order of the minister of health No. 1027/22.05.2008, reunited on summons of the National Medicines Agency President in the ordinary meeting of 27.03.2009, according to Article of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002 as amended, hereby adopts the following

DECISION

Single article. - Is approved Guideline on change of classification for supply of a medicinal product for human use according to the Annex, which are integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE ON CHANGE OF CLASSIFICATION FOR SUPPLY OF A MEDICINAL PRODUCT FOR HUMAN USE

CHAPTER I
General principles

Art. 1. – (1) This guideline is a translation into Romanian and an adaptation of the Guideline included in Notice to Applicants, Volume 2C, the version revised in January 2006.

(2) The updated version of the guideline includes two new parts (chapter VI and chapter VII), in order to reflect the provisions set out by Directive 2001/83/EC as amended by Directive 2004/27/EC and the requirements for Article 74a.

(3) Chapters IV and V of the guideline are unchanged except of the references to the new legislation. The necessary update of chapters IV and V in respect to the technical and scientific progress will be started within the coming year.

CHAPTER II
Legal framework

Art. 2. – Recital 32 of Directive 2001/83/EC refers to ”It is appropriate, as an initial step, to harmonise the basic principles applicable to the classification for the supply of medicinal products in the Community or in the Member States concerned, while taking as a starting point the principles already established on this subject by the Council of Europe as well as the work of harmonisation completed within the framework of the United Nations, concerning narcotic and psychotic substances.”

Art. 3. – Article 780 of Title XVII - The medicinal product, of Law no. 95/2006 on healthcare reform, as amended, transposing Article 70 of Directive 2001/83/CE, provides two classifications for the supply of medicinal products for human use:

- ”medicinal products subject to medical prescription”
- ”medicinal products not subject to medical prescription”

Art. 4. – Article 781 of Title XVII - The medicinal product, transposing Article 71 of Directive 2001/83/CE, provides the criteria for classifying a medicinal product as subject to medical prescription. Thus a medicinal product which meets these criteria is subject to a medical prescription and a medicinal product which does not meet these criteria is not subject to a medical prescription, as stated in Article 782 of Title XVII - The medicinal product transposing Article 72 of Directive 2001/83/CE.

Art. 5. – Article 785 of Title XVII - The medicinal product, transposing Article 74a of Directive 2001/83/CE states that "Where a change of classification of a medicinal product has been authorised on the basis of significant preclinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation (MAH) for a change of classification of the same substance for one year after the initial change was authorised".

Art. 6. – This guideline does not address the subcategories of classifications which may be available for medicinal products not subject to a medical prescription at Member State level, such as: available in pharmacies only following initial medical diagnosis or available on general sale, as the case may be.

CHAPTER III
SCOPE

Art.7. – This guideline is for use by MAHs applying to change the classification for supply of a medicinal product. The guideline applies to all marketing authorisation granted in the Community. It is also for use by competent authorities to facilitate harmonisation, within the Community, of medicinal products restricted to medical prescription and of medicinal products available without a medical prescription.

Art. 8. – This guideline includes four important chapters:

- Chapter IV concerns the criteria for classifying a medicinal product as subject to medical prescription or not;
- Chapter V outlines the data requirements for an application to change the classification for the supply of a medicinal product from subject to a medical prescription to not subject to a medical prescription;
- Chapter VI outlines definition for the data exclusivity for data provided in a 'switch' application to describe the extent of data exclusivity in relation to significant pre-clinical tests or clinical trials according to Article 785 of Title XVII - The medicinal product transposing Article 74a of Directive 2001/83/CE;
- Chapter VII outlines the principles and procedure to claim for one-year data exclusivity based on Article 785 of Title XVII - The medicinal product transposing Article 74a of Directive 2001/83/CE.

CHAPTER IV
Criteria for classifying a medicinal product as subject to a medical prescription or not and how to determine if a medicinal product

CHAPTER IV.1
The first criterion

Art. 9. – Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision.

CHAPTER IV.1.1
Direct danger/safety profile

Art. 10. – (1) A direct danger, when the product is used correctly, (according to the patient information), encompasses toxicity, interactions and adverse reactions.

(2) A medicinal product not subject to a medical prescription should have:

a) low general toxicity and no relevant reproductive toxicity, genotoxic or carcinogenic properties;

b) low risk of serious type A adverse reactions in the general population (resulting from exaggeration of a medicinal product expected pharmacological actions when given in the usual therapeutic dose – normally, dose-dependent adverse reactions);

c) very low risk of serious type B reactions (representing a novel response not expected from known pharmacological action);

d) no interactions with commonly used medicines which can produce serious adverse reactions (also refer to Article 23);

Art. 11. – The criterion of danger can take account of the possibility of preventive action. For example, serious type A reactions can be acceptable if there is a clear identifiable risk group that can be excluded even in the absence of medical supervision.

Art. 12. – The safety of a medicinal product is relative to that of the alternative treatment.

CHAPTER IV.1.2
Indirect danger/safety profile

Art. 13. – (1) An example of indirect danger, even when the product is used correctly, that is to say used according to the patient information, would be where symptomatic treatment might mask/hide an underlying condition requiring medical attention and supervision. Use of the medicine might delay diagnosis and definitive treatment and jeopardise the chance of more successful therapy.

(2) Package leaflet and or label warnings may be necessary to prevent treatment from ”masking” the development of a serious disorder. Therefore, such warnings should indicate a time limit beyond which, if symptoms persist, medical advice should be sought.

(3) Medicinal products not subject to a medical prescription (Over-the-Counter = OTC) should be approved primarily for short term treatment, e.g. when the possibility of ”masking” could occur.

Art. 14. – An indirect danger is also present if wider use of a medicinal product would increase the risk of resistance to the product, in particular in the general population, to such an extent that the usefulness of any medicinal product is likely to be compromised.

Art. 15. – An additional example of indirect danger is when the symptom is commonly the outward manifestation of a diverse range of underlying pathologies and the patient cannot easily discern the underlying disease

CHAPTER IV.1.3
Self-assessment

Art. 16. – (1) It is important that the condition or symptoms, for which a medicinal product not subject to a medical prescription is indicated, can be correctly assessed by the patient and that the product can be used without medical supervision.

(2) This means that the patient should be capable of excluding conditions which could appear to be similar to the indications but unsuitable for treatment with the medicine in question.

(3) Account may be taken of the availability of appropriate information sources that would assist the patient in achieving this, including written information or the advice of pharmacist and other healthcare professionals.

Art. 17. – The natural course of the disease, the condition, the duration of symptoms and their reoccurrence and consequences due to this should be correctly self-assessable.

Art. 18. – Contraindications, interactions, warnings and precautions should be those which can be understood by the patient.

CHAPTER IV.1.4
Risk and consequences of incorrect use

Art. 19. – (1) A high incidence of conditions listed as contraindications, precautions or warnings, or a high rate of usage of interacting products in the population, in case of patients likely to use the medicine, may increase the incidence and risk of misuse (see Chapter IV.1.5 *Patient information*).

(2) It is important that the danger to health is small, if the patient uses the product where it is not indicated, uses it for a longer period than recommended**,** exceeds the recommended dose or fails to heed warnings or contraindications.

Art. 20. – Consideration of the consequences of misuse is an important component of the overall safety profile of the medicinal product which should be reflected in the label (as provided for in Article 763, (g) and (n) of Title XVII - The medicinal product transposing Article 54 lit. g) and lit. n) of Directive 2001/83/CE) and/or the package leaflet.

CHAPTER IV.1.5
Patient information

Art. 21. – (1) The way in which a medicinal product not subject to medical prescription is used is likely to differ from the way the same product was used when available only on prescription, even when the indications are the same or in the same therapeutic area.

(2) There is also the risk that the patient will consider the medicinal product not subject to a medical prescription as being less dangerous than when the same product is subject to a medical prescription. This should be taken into consideration.

Art. 22. – (1) The written information (package leaflet and label) must contribute effectively to safe and effective use of the medicine. The correct use of the medicine should be explained in the information.

(2) It is necessary to consider if the information is clear enough for the patients to use the medicine appropriately. This information should be sufficient so that it substitutes for the absence of medical supervision.

Art. 23. – The written information supplied with the medicine, in addition to the supervision of the pharmacist when applicable, should be adequate to guard against a risk of using the product where it is contraindicated or unsafe. Contraindications, interactions, warnings and precautions need to be clearly described in layman's terms and prominently presented in the leaflet. Also see the guideline on the readability of the label and package leaflet.

Art. 24. – (1) In order to minimise risk and maximise benefit, the leaflet and the label should describe the situations where the product should not be used, in at least as much detail and prominence as to when it may be used (see Chapter IV.1.4 *Risk and consequences of incorrect use*), and in accordance with the summary of product characteristics [SPC].

(2) The patient is likely to need guidance on action to take if the medicine does not have the desired effect or cause an adverse effect. The product information (package leaflet and label) should in such cases recommend appropriate action e.g. consulting a doctor or a pharmacist within the time stated in the label/package leaflet.

CHAPTER IV.2
The second criterion

Art. 25. – (1) Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health.

(2) In considering whether this criterion applies, the following factor should be addressed.

CHAPTER IV.2.1
Known incorrect use

Art. 26. – Known incorrect use for products not subject to a medical prescription (e.g. used for the purpose of increasing the effects of alcohol), could lead to restrictions on the product or reclassification for supply subject to a medical prescription (also see Chapter IV.6 *Other Considerations*). Under such circumstances, classifying the medicinal product as not subject to a medical prescription should not be considered.

CHAPTER IV.3
The third criterion

Art. 27. – (1) Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side-effects of which require further investigation.

(2) In considering whether this criterion applies, the following factors should be addressed.

CHAPTER IV.3.1
Recent authorisation/limited experience

Art. 28. – (1) Further investigation may be necessary when a medicinal product has only recently been granted a marketing authorisation or because of limited experience/use of the product e.g. low sales.

(2) Experience in other EU Member States and in other markets, which have sufficient post marketing surveillance, should be taken into consideration.

Art. 29. – (1) Even if clinical trial data are extensive and reassuring, it is important to have post-marketing experience in the general population, that is evidence of safety when the product is being used without the exclusion of certain groups of patients, which may be imposed by the design of clinical trials e.g. the elderly, children, certain racial or phenotypic groups and those having certain medical conditions.

(2) Products which have different safety or efficacy profiles in different racial or phenotypic groups may need special warnings.

CHAPTER IV.3.2
New strength, dose, route of administration, indication, new age group or combination of substances

Art. 30. – (1) Further investigation is likely to be necessary when it is proposed that the medicinal product will be available without prescription in a new strength, at a new dose, using a new route of administration, new age group or for a new indication particularly when the indication has not previously been authorised for a medicinal product not subject to a medical prescription.

(2) A lower dose or a lower strength does not necessarily render further investigation necessary, but it is necessary to confirm that the reduced dose retains the efficacy.

Art. 31. – (1) Even though the safety profile of the medicinal product while it was subject to a medical prescription is relevant, a re-evaluation of the risk to benefit ratio is necessary.

(2) However, this may be difficult because the product will not have been widely available for the new indication or new dosage. It may, nevertheless, be possible to extrapolate from the safety of the existing prescription product. This is particularly true if there are few side-effects and/or when doses proposed for supply without a prescription are lower and the population is a sub-group of the patient group treated while the medicinal product was subject to medical prescription.

Art. 32. – A medicinal product containing a combination of two active substances, which are available in two separate medicinal products, both of which are not subject to a medical prescription, would not automatically be classified for supply not subject to a medical prescription, but would be evaluated in line with the „Guideline on Fixed-combination products" (Rules governing medicinal products Volume 3C)

CHAPTER IV.4
The fourth criterion

Art. 33. – (1) Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally.

(2) In considering whether this criterion applies, the following factor should be addressed:

- Parenteral products should normally be subject to a medical prescription, because of the additional risks and complexity of the route of administration.

CHAPTER IV.5
Criteria in Articles 781 and 697 c) of Title XVII - The medicinal product transposing Article 71 and Article 3.3 of Directive 2001/83/CE

Art. 34. – As provide din Articles 781 and 697 c) of Title XVII - The medicinal product transposing Article 71 and Article 3.3 of Directive 2001/83/CE, Classification of a medicinal product as not subject to a medical prescription should not be considered whenever these criteria apply (see Article 35).

CHAPTER IV.6
Other considerations

Art. 35. – In line with provisions in Article 781 of Title XVII - The medicinal product transposing Article 71(4) of Directive 2001/83/CE, a medicinal product, which meets any of the criteria for supply subject to medical prescription, may be classified for supply not subject to medical prescription if: the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging and/or other circumstances of use, can make supply without appropriate medical prescription.

CHAPTER IV.6.1
Pack size and package form

Art. 36. – (1) The pack size should be decided in relation to the intended length of the treatment.

(2) Restricting the availability of a medicinal product to a small pack size is a possible safeguard against misuse, particularly overdose, or a delay in seeking medical attention.

Art. 37. – Medicinal products should have a container which as far as possible prevents children gaining access to the medicine, if they get hold of the container.

CHAPTER IV.6.2
Maximum dose, maximum daily dose

Art. 38. – (1) Restricting the maximum dose or maximum daily dose may protect against potential danger whether the medicine is used correctly or incorrectly.

(2) However it is necessary to confirm that the reduced dose retains the efficacy.

CHAPTER V
The data requirements

Art. 39. – The documentation concerning safety and efficacy in support of an application for a change in the classification for the supply will depend on the nature of the active substance and the extent of any changes to the MA. In order to facilitate the evaluation of safety in relation to benefit it should be presented in a logical and concise manner.

CHAPTER V.1

Non-clinical and/or clinical overview (Expert Reports)

Art. 40. – (1) In all cases, a *non-clinical and/or clinical overview (expert reports)* should be provided. The expert should provide a critical analysis of the proposed availability of the product without a medical prescription with the dose and indications as stated in the application. The expert is expected to take a clear position, defend the proposal in light of current scientific knowledge and demonstrate why none of the criteria that determine classification for supply subject to a medical prescription apply to the product.

(2) Advice on the format of *non-clinical and/or clinical overview (expert reports)* can be found in Volume IIB of the „Notice to Applicants for Marketing Authorisations for Medicinal Products for Human Use in the Member States of the European Community".

(3) All of the points in Part 1 of this guideline should be addressed and supporting documentation submitted, when applicable. Some of these points are commented on below.

CHAPTER V.2
Non-clinical and/or clinical safety

Art. 41. – A pre-clinical and/or clinical overview and the non-clinical and/or clinical summaries of, or references to, animal studies or studies on humans that show low general toxicity and no relevant reproductive toxicity, genotoxic or carcinogenic properties relevant to the experience/exposure of the medicinal product should be given.

Art. 42. – (1) Experience in terms of patient exposure to the substance needs to be considerable and should be outlined. Normally, active substances which are suitable for supply without a medical prescription will have been in widespread use for five years, in medicinal products subject to a medical prescription.

(2) However, provided enough data is available, this does not exclude the possibility of an authority accepting a shorter time; for instance, if the active substance has been in use, other than in a medicinal product (e.g. in a foodstuff or as a metabolite of a known active substance).

(3) Adverse reactions related to the pharmaceutical form and/or posology and strength proposed for supply not subject to a medical prescription should in normal conditions be minor and should cease on discontinuing therapy.

(4) Information on adverse reactions should be provided, including experience of use without medical supervision, for example in another Member State or in a third country.

(5) Variables such as numbers of patients treated, demographic details, indications for use and dose should be provided and taken into account in providing and interpreting the data.

Art. 43. – (1) The safety profile should be summarised according to EU guidelines, including reports of and data from post-marketing surveillance studies, clinical trials and published literature presenting the issue of drug safety. Information concerning serious type A and type B reactions should be given and discussed.

(2) The problems of extrapolating data from the population, using the active substance supplied only on a medical prescription, to the population using it without a medical prescription should be presented and discussed.

Art. 44. – The application should consider the potential for and consequences of drug interactions, in particular with commonly prescribed medicinal products.

Art. 45. – The application should consider the consequences concerning misuse, e.g. use for longer periods than recommended, as well as accidental or intended overdose and the use of higher doses, should be discussed.

Art. 46. – The application should consider the consequences of the use of the product by a patient who has incorrectly assessed his condition or symptoms.

Art. 47. – The application should consider the consequences of incorrect or delayed diagnosis of a patient's condition or symptoms due to self medication with the medicinal product.

CHAPTER V.3
Clinical efficacy

Art. 48. – (1) Evidence of the medicinal product's efficacy is not normally considered in the application for changing the classification for supply, unless this application also includes changes to the indications or posology.

(2) If other parts of the dossier are changed, e.g. indication, posology or strength, then supporting data should be provided.

(3) A suitable time-period for treatment of the suggested indication(s) should be justified and given together with a proposed pack size.

CHAPTER V.4

Product information

Art. 49. – (1) For a medicinal product classified for supply without a medical prescription, the proposed labelling and package leaflet are important elements of the application and will be closely examined for comprehensive information and effectiveness in protecting patients from any safety hazards.

(2) Package leaflets should provide information on/appropriately describe the use of the product and the circumstances when referral for medical advice is appropriate.

(3) The outer packaging or, where there is no outer carton, the immediate packaging should include instructions for use in the case of non-prescription medicinal products, as required by Article 763 (n) of Title XVII - The medicinal product transposing Article 54 n) of Directive 2001/83/CE.

(4) Contraindications and warnings, such as advice limiting duration of treatment or the need to consult a doctor in certain situations, should be provided as appropriate.

(5) This product information, on the label and in the leaflet, should be readable, see the *guideline on the readability of the label and package leaflet*.

CHAPTER V.5
Other

Art. 50. – A related change of container or packaging material should be discussed when applicable, together with necessary documentation.

CHAPTER VI
Data Exclusivity for data submitted for a 'switch' of the legal status of a medicinal product from prescription to non-prescription (change in classification)

Art. 51. – This guidance should be read in conjunction with Chapter 1 of the Notice to Applicants.

Art. 52. – (1) Article 785 of Title XVII - The medicinal product, transposing Article 74a of Directive 2001/83/CE as amended by Directive 2004/27/CE provides that: „Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised".

(2) This provision can be used within the already given marketing authorisation or as a separate stand alone application providing information is submitted which demonstrates that the medicinal product does no longer meet the criteria for classification of a medicinal product as subject to medical prescription as given in Article 781 of Title XVII - The medicinal product transposing Article 71 of Directive 2001/83/CE.

CHAPTER VI.1
Significant pre-clinical tests and clinical trials

Art. 53. – (1) Pre-clinical tests and/or clinical trials are significant if they are related to a new strength/posology, using a new route of administration, new pharmaceutical form or for a new indication particularly one not previously authorised for a medicinal product not subject to medical prescription or a subpopulations (e.g. elderly, children, certain racial groups and those having certain medical conditions).

(2) For a lower strength/posology studies are significant if it is necessary to confirm that the reduced strength/posology retains the efficacy.

(3) For a new indication, confirmatory clinical trial(s) are very likely to be necessary and significant.

(4) Similarly, if duration or modalities of treatment are changed, new non-clinical and/or clinical studies may become necessary and would be subject to protection.

Art. 54. – (1) Where the safety/efficacy profile of a medicinal product requires confirmation either within the prescription setting or within the envisioned non-prescription environment, resulting in the generation of new safety/efficacy data (e.g. actual use studies), such data are likely to be eligible for exclusivity.

(2) The significance of the new pre-clinical tests and/or clinical trials will be evaluated by the competent authorities/the Committee for Medicinal Products for Human Use of the European Medicines Agency (CHMP - EMEA). In accordance with Article 785 of Title XVII - The medicinal product transposing Article 74a of Directive 2001/83/CE, It is recommended that the marketing authorisation holder request scientific advice from competent authorities/EMEA-CHMP, at an appropriate time, when designing tests and/or trials expected to benefit from one-year data exclusivity.

(3) To be considered „significant”, the pre-clinical tests and/or clinical trials must be relevant and necessary to the change in classification.

CHAPTER VI.2

Data exclusivity

Art. 55. – Under Article 785 of Title XVII - The medicinal product transposing Article 74a of Directive 2001/83/CE, the one-year data exclusivity period is a standalone period of protection, which covers only the data provided to substantiate the change of classification. As a standalone protection, it can be granted independently and at any time after the initial protection period has expired (i.e. irrespective of whether the product benefited or not from other data exclusivity periods as set out in Article 704 (1) and (5) of Title XVII - The medicinal product transposing Article 10(1) or 10(5) of Directive 2001/83/CE, as amended and in Article 14(11) of Regulation no. 726/2004/EC.

CHAPTER VII
Principles and procedures for data submitted for a 'switch' of the legal status of a medicinal product from prescription to non-prescription (change in classification)

CHAPTER VII.1
Principles and procedures

Art. 56. – (1) It is to the applicant to claim the one-year data exclusivity at the time of the application for the change of classification. The submission can be both within or separate from an existing marketing authorisation.

(2) The applicant shall support its claim by providing a report justifying that its application includes significant preclinical tests or clinical trials which have been carried out in relation to this change of classification in accordance with Article 74a of Directive 2001/83/CE and this Guideline provisions.

(2) a) Such documentation should be submitted in Module 1 of the application for a variation or extension application to an existing marketing authorisation or for a standalone for marketing authorisation.

(2) b) Related study reports and literature references shall be placed in relevant Modules of the dossier and thus cross-referred to accordingly.

CHAPTER VII.2
Aspects related to national/mutual recognition/decentralised procedure only

Art. 57. – It is expected that data exclusivity would be applied by each competent authority, irrespective of whether the data was common to more than one application.

Art. 58. – (1) For marketing authorisations processed through the mutual recognition or decentralised procedures each competent authority will take its own decision as to whether the one-year data exclusivity period is to be granted.

(2) Nevertheless, in the view of harmonising medicinal products throughout the Community and to keep the already reached harmonisation in a mutual recognition or decentralised procedure it is recommended to the competent authorities of the Member States to use their best endeavours to reach agreement on the legal status of a medicinal product and on the one-year data exclusivity.

(3) The decision of each competent authority authorising the change will contain a clear statement of whether the change in classification is based on significant pre-clinical tests or clinical trials.

CHAPTER VII.3
Aspects related to centralised procedure only

Art. 59. – (1) Where the change in classification is submitted within an existing Marketing authorisation, the change requires the submission of a Type II variation application, unless it introduces the need for an extension application e.g. a new strength, pharmaceutical form, route of administration or any other. Alternatively a separate standalone application for marketing authorisation could be submitted.

(2) The CHMP will assess the pre-clinical or clinical trials and issue a single opinion for the change of the classification. A Commission Decision will authorise the change in classification including a clear statement of whether the change in classification is based on significant pre-clinical tests or clinical trials.

CHAPTER VIII
Name of the Medicinal Product

Art. 60. – It is to the applicant in the case of a switch from ‘prescription’ to ‘non-prescription’ status of an already authorised medicinal product to choose whether to retain the same invented name or to choose a new invented name.