Regulations whose amendment is included in updated form

Type	Number	Date of issuance	Date of enforcement	Approved / Rejected
Order	212	13.02.2018	19.02.2018	

ORDER no. 1.018*)
of 3 September 2014

Ministry of Health

on approval of the conditions for authorisation of the use of a medicinal product for human use to be available for use in last-resort treatments, in line with the provisions of Art. 83 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

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***) Note:**
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Order no. 212/13.02.2018 Published in the Official Gazette of Romania no. 153/19.02.2018

On seeing the report for approval No. NB 7.069/2014 of the Medicinal Product and Medical Device Policy Directorate and Notification no. 51.568E of 24 July 2014 of the National Agency for Medicines and Medical Devices, registered at the Ministry of Health with no. 45.390 of 24 July 2014,

taking into account the provisions of Art. 4 (2) a) of Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, as further amended and supplemented,

pursuant to Article 7 (4) of Government Decision no. 144/2010 on the organisation and operation of the Ministry of Health, as further amended and supplemented,

the minister of health hereby issues the following order:

Art. 1 - The conditions for authorisation of the use of a medicinal product for human use to be available for use in last-resort treatments, in line with the provisions of Art. 83 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, are approved, in line with the provisions of Art. 83 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, in line

with the Annex which is an integral part of this Order.

Art. 2 - This Order shall be published in the Official Gazette of Romania, Part I.

On behalf of the Minister of Health,
Dorel Săndesc,
Secretary of state

Annex

CONDITIONS
for authorisation of the use of a medicinal product for human use to be available for use in last-resort treatments, in line with the provisions of Art. 83 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

Art. 1 - The terms used in this Order have the following meanings:

a) ***the competent authority for the assessment and authorisation of medicinal products for human use to be available for use in last-resort treatments*** – the National Agency for Medicines and Medical Devices;

b) ***use in last-resort treatments*** - a medicinal product for human use unauthorised for being placed on the market in Romania or another EU member state, which meets the conditions set out in this Annex, becomes available, for humanitarian reasons, to a group of patients suffering from disabling, chronic or serious diseases or diseases which are considered life-threatening and which cannot be satisfactorily treated with the help of an authorised medicinal product;

c) ***group of patients who cannot be treated satisfactorily*** - patients whose disease does not respond to or relapse to existing available treatments and who cannot be enrolled in ongoing clinical trials;

d) ***medicinal product authorised for marketing*** - medicinal product for human use which has been issued a marketing authorisation in Romania, in accordance with the law;

e) ***conditions of use*** - the recommendations for medical specialists on how to administer and use the medicinal product under safe and effective conditions. These recommendations include relevant information about the clinical, pharmacological and pharmaceutical properties of the medicinal product and about patient monitoring conditions;

f) ***manufacturing company*** - the manufacturer or its legal representative in Romania.

Art. 2 - (1) The medicinal product for human use for which the authorisation for use in last-resort treatments is requested must be the subject of an application for marketing authorisation through the centralised procedure or be in the clinical trial stage in which they have accumulated evidence in support of the efficacy and safety of administration in the proposed use, in at least one of the EU member states.

(2) The following categories of medicinal products may be subject to an application for authorisation for use in last-resort treatments:

a) medicinal products for human use manufactured through one of the following biotechnological processes:

1. recombinant DNA technology;

2. controlled expression of genes encoding biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells;

3. methods based on hybridomas and monoclonal antibodies;

b) medicinal products for human use containing a new active substance which has not been authorised in the EU and for which the therapeutic indication is the treatment of any of the following diseases:

1. acquired immunodeficiency syndrome;

2. cancer;
3. neurodegenerative diseases;
4. diabetes;
5. autoimmune diseases and other immune dysfunctions;
6. viral diseases;

c) medicinal products for human use designated as an orphan medicinal product in line with Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products;

d) medicinal products for advanced therapies.

Art. 3 - (1) The manufacturing company requests authorisation to use the medicinal product in last-resort treatments.

(2) For authorisation, the manufacturing company submits an application to the NAMMD headquarters, accompanied by the following information and documents, in Romanian or English, as appropriate:

1. the name and address of the medical specialist(s) who support(s) the need to authorise the use of the medicinal product for human use, in order to be available for use in last-resort treatments and who apply this treatment;

2. name or code of the medicinal product, name of the active substance(s) depending on type and quantity, other components (excipients), pharmaceutical form, doses, route of administration and treatment regimen;

3. the physician’s request, which shall include:

a) patient identification data;

b) description of the disease from which the patients suffer, which causes severe/serious disability or is life-threatening and for which the last-resort is intended;

c) the reasons why these patients cannot be satisfactorily treated with the authorised medicinal product(s) and the justification for using the last-resort treatment;

d) the reasons why patients cannot be enrolled in an ongoing clinical trial, if applicable;

e) presentation of medical facilities and qualification of personnel to ensure correct administration and storage of the medicinal product in accordance with the information in the investigator's brochure, as appropriate;

f) agreement of the healthcare unit for application of last-resort treatments with the medicinal product for human use for which authorisation for use is requested;

4. evidence which includes information supporting the quality of the medicinal product to be administered, in accordance with the pharmaceutical regulations in force, as well as the qualified person's declaration regarding the manufacture of the medicinal product in accordance with the legislation in force, such as, but not limited to: qualitative and quantitative composition of the product, analysis reports, copy of the manufacturer's Good Manufacturing Practice (GMP) certificate, place of batch release, GMP certificates for the packaging site, storage conditions, shape and size of the packaging, shelf life;

5. the opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency or of another competent authority in a Member State, as appropriate;

6. additional details concerning:

a) authorised clinical trials of the medicinal product in the targeted therapeutic area, mentioning the EudraCT number;

b) the current investigator's brochure made available to investigators involved in clinical trials or the proposed draft summary of product characteristics included in the marketing authorisation application;

a) the information and documents which shall be handed to patients, in Romanian; description of the informed consent procedure, after training by the medical specialist under whose care the patient is admitted, the informed consent form;

b) information on safe storage, handling and use conditions.

(3) The NAMMD may request any other information deemed useful for the authorisation of the use of a medicinal product for human use in last-resort treatments.

(4) The NAMMD shall issue the authorisation for the use of a medicinal product in last - resort treatments within maximum of 60 days from submission of all the documents and information provided for in this article.

Art. 4 - The decision as to whether a group of patients are eligible for treatment with last-resort medicinal products and whether the treatment cannot be satisfied by medicinal products authorised for marketing belongs to the medical specialist(s) under whose care the respective patients are.

Art. 5 - The NAMMD requests the specialised Commission of the Ministry of Health with competence in the therapeutic area of the medicinal product, for which authorisation for use as a last-resort treatment is requested, to issue a recommendation on the appropriateness of its use, when there is no opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency.

Art. 6 - (1) The authorisation is granted for a period of 6 months of use and may be renewed or modified, as the case may be.

(2) The application for renewal of the authorisation referred to in paragraph (1) shall be submitted 30 days before its expiration.

Art. 7 - The authorisation may be suspended or withdrawn if it is found that the conditions under which it was granted are no longer met.

Art. 8 - The manufacturing company must comply with the following obligations:

a) to ensure the financing of the last-resort treatment, including the cost of the expertise in order to obtain the opinion of the European Medicines Agency, as appropriate;

b) to ensure that the manufacturing, import and batch release take place in accordance with the regulations in force;

c) to ensure that the secondary packaging contains at least the following information, in Romanian or an internationally spoken language (English or French):

1. name, name of active substance(s) (if established) or the medicinal product’s code;
2. batch identification;
3. route of administration;
4. expiry date;
5. storage conditions;

d) not to advertise the medicinal product for human use authorised to be available for use in last-resort treatments;

e) to keep specific records regarding the administration of the medicinal product authorised to be available for use in last-resort treatments;

f) to notify the NAMMD of the effective commencement of use of the medicinal product for human use authorised to be available for use in last-resort treatments;

g) to immediately inform the NAMMD of any safety or quality issues;

h) to ensure that the medicinal product for human use authorised to be available for use in last-resort treatments is used only on the Romanian territory;

i) not to market the medicinal product;

j) to document all cases of serious adverse reactions reported by the physician who supported the authorisation for use and who applies the last-resort treatment, or reported by the patient/relatives, and to forward them to the database and the computer network mentioned in art. 24 of Regulation (EC) no. 726/2004, hereinafter referred to as the EudraVigilance database, at the latest within a period of 15 days;

k) to document all cases of non-serious adverse reactions reported by the physician who supported authorisation of the use and who applies the last-resort treatment, or reported by the patient/relatives, and to forward them to the EudraVigilance database, at the latest within a period of 90 days;

l) immediately inform the NAMMD of any change in the information on the authorised medicinal product and submit the relevant documents;

m) immediately inform the NAMMD and justify the decision to prematurely cease the availability/use of the authorised medicinal product for use in last-resort treatments;

n) submit to the NAMMD a report on the safety of the use of the medicinal product for human use in the last-resort treatment, after expiry of the period for which the authorisation was issued;

o) to keep all documents related to the medicinal product, doctors and patient or group of patients for a period of 10 years from completion of the programme;

p) to allow inspections by the competent authority from which it received approval for the conduct of the last-resort treatment;

q) to ensure that any change in the risk/benefit ratio is reported immediately to the NAMMD, so that the necessary measures to prevent risks can be taken without delay.

Art. 9 - The last-resort treatment shall be completed within one year at the latest from the date of authorisation by the NAMMD or upon marketing authorisation of the medicinal product, whichever occurs sooner.

Art. 10 - The duties of the medical specialist who uses the last-resort treatment are:

a) to ensure that the last-resort treatment is carried out appropriately, in accordance with the NAMMD approval;

b) to ensure that all measures and restrictions regarding the safe and effective use of the medicinal product are respected, and that the persons involved receive the necessary information for this purpose;

c) to immediately inform the NAMMD of any safety or quality issues;

d) not to advertise the programme;

e) to keep specific records regarding the administration of the medicinal product in the programme;

f) *to document all cases of adverse reactions identified or reported by patients or relatives and to inform the manufacturing company or the NAMMD no later than 15 days for non-serious adverse reactions and no later than 7 days for serious adverse reactions;*

g) to establish whether there is a causal relationship between the adverse reaction and the administration of the last-resort medicinal product;

h) to administer the medicinal product in accordance with the conditions of use provided by the company and which are an integral part of the scientific file submitted to the competent authority for assessment of the application for last-resort treatment;

i) to stop the administration of the medicinal product at the request of the NAMMD or the manufacturing company, if applicable;

j) to obtain informed consent forms from patients, prior to initiation of treatment, documented by their signature;

k) to obtain the agreement of the healthcare facility (where the last-resort treatment is carried out);

l) to store the medicinal product in accordance with the storage conditions of the product, provided by the manufacturing company;

m) to keep all documents related to the medicinal product and the patient or group of patients for a period of 10 years from completion of the programme;

n) to allow inspections carried out by the competent authority and the manufacturing

company which has received approval for the last-resort treatment;

o) to keep strict a strict inventory of administration of the medicinal product (quantities, doses) to patients;

p) not to market the medicinal product.

Art. 11 - Changes of therapeutic indication, strength or pharmaceutical form of the medicinal product for last-resort treatment, as well as changes likely to impact patient safety can only be operated after grant of a new authorisation.

Art. 12 - Essential documents pertaining to last-resort treatment are retained for minimum 10 years; this does not conflict with other regulations regarding the archiving of medical documents.

Art. 13 - The manufacturing company provides patients who have benefited from last-resort treatment with the new medicinal product, between its authorisation and its actual placement on the market.

Art. 14 - NAMMD authorisation for use of last-resort treatments does not pre-empt civil or criminal liability of the manufacturing company.

Art. 15 - The forms used for authorisation of medicinal products use as last-resort treatment shall be published on the NAMMD website in 30 days as of publication of the Order.