ORDER no. 1018 of 3 September 2014
on approval of Conditions for authorisation of human medicinal products for compassionate use, in accordance with provisions of Article 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

ISSUED: THE MINISTRY OF HEALTH

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On seeing Approval Report no. NB. 7.069/2014 of the Medicinal Product and Medical Device Policy Directorate and Notification no. 51.568E of the National Agency for Medicines and Medical Devices of 24 July 2014, under Ministry of Health no. 45.390,

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

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

the minister of health hereby issues the following Order:

ARTICLE 1

The Conditions for authorisation of human medicinal products for compassionate use, in accordance with provisions of Article 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 accordance with the Annex, which is integral part of this Order.

ARTICLE 2

This Order is to be published in the Official Journal of Romania, Part I.

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

Bucharest, 3 September 2014.
No. 1.018.

ANNEX 1

CONDITIONS

for authorisation of human medicinal products for compassionate use, in accordance with provisions of Article 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

ARTICLE 1

For the purposes of this Order, terms used shall have the following meaning:

a) ***competent authority for assessment and authorisation of human medicinal products for compassionate use*** – the National Agency for Medicines and Medical Devices (***NAMMD***);

b) ***medicinal products for compassionate use*** – medicinal products for human use not authorised for marketing in Romania or another Member State, meeting conditions mentioned in this Annex, made available, for humanitarian reasons, to a group of patients with invalidating, chronic, severe or life-threatening diseases, whose proper therapy is not feasible using authorised products;

c) ***group of patients whose proper therapy is not feasible*** - patients who do not respond to or relapse on available existing treatments, also ineligible for enrolment in ongoing clinical trials;

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

e) ***conditions for use*** – recommendations for specialist physicians concerning the manner of administration and safe and effective use of the medicinal product. Such recommendations include relevant information about clinical, pharmacological and pharmaceutical properties of the medicinal product as well as on conditions for patient monitoring;

f) ***manufacturing company*** – the manufacturer or their legal representative in Romania.

ARTICLE 2

(1) The human medicinal product for which authorisation is sought for compassionate use must be either the object of an application for marketing authorisation through centralised procedure or be included in a clinical trial phase allowing for accumulation of sufficient evidence in support of its administration under conditions of efficacy and safety for the proposed use, in at least one Member State.

(2) The following categories of medicinal products may be subject to an application for authorisation for compassionate use:

a) medicinal products for human use manufactured using one of the following biotechnological procedures:

1. recombinant DNA technology;

2. controlled expression of gene coding for biologically active proteins in prokaryotes and eukaryotes, including mammalian cell transformation;
3. methods based on hybridomas and monoclonal antibodies;
b) medicinal products for human use containing a new active substance not yet authorised in the EU and whose therapeutic indication is a treatment for each of the following diseases:
1. acquired immunodeficiency syndrome;
2. cancer;
3. neurodegenerative diseases;
4. diabetes;
5. autoimmune diseases and other malfunctions of the immune system;
6. viral diseases;
c) medicinal product for human use designated as an orphan medicinal product in line with provisions of Regulation (EC) no. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products;
d) advanced therapy medicinal product.

ARTICLE 3

(1) The manufacturing company applies for authorisation for use of the medicinal product for compassionate use.
(2) For authorisation purposes, the manufacturing company submits an application for authorisation at the NAMMD offices, accompanied by the following information and documents, in Romanian or English, as required:
1. name and address of the specialist physician(s) who support the need for authorisation for use of the human medicinal product for compassionate use and are to implement the respective therapy;
2. name or code of the medicinal product, name(s) of active substance(s) depending on type and quantity, other ingredients (excipients), pharmaceutical form, dosage, manner of administration and treatment schedule;
3. The physician’s request, including:
a) patient identification data;
b) description of patients’ disease, leading to severe/serious disability or is life-threatening, for which compassionate use is intended;
c) reasons for which proper care may not be provided to patients using the authorised medicinal product(s) and rationale for use of the medicinal product for compassionate use;
d) reasons for which patients cannot be enrolled in ongoing clinical trials, as required;
e) description of medical facilities and staff qualifications to ensure proper administration and keeping of the product in accordance with the information provided in the investigator’s brochure, as required;
f) agreement of the healthcare unit regarding application of compassionate use therapies involving the medicinal product for which authorisation for use is sought;

4. proof including information substantiating the quality of the medicinal product to be administered, in accordance with pharmaceutical regulations in force, and a statement by the qualified person concerning medicinal product manufacturing in compliance with legislation in force, in relation with but not limited to such issues as: medicinal product qualitative and quantitative composition, test bulletins, copy of the manufacturer's Good Manufacturing Practice (***GMP***) Certificate, batch release site, GMP certificates for the packaging site, storage conditions, packaging shape and size, shelf life;
5. approval of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency or a different competent authority in a Member State, as required;
6. additional details on:
a) authorised clinical trials on the medicinal product within the concerned therapeutic field, with mention of the EudraCT number;
b) the current investigator's brochure made available for investigators involved in clinical trials or the proposed Summary of Product Characteristics (SmPC) draft included in the application for marketing authorisation;
c) information and documents to be handed to patients, in Romanian; description of the informed consent procedure, following training by the specialist physician providing care to the respective patient, the informed consent form;
d) information on conditions for keeping, storage and safe use.
(3) The NAMMD may require any other information deemed useful for authorisation of a human medicinal product for compassionate use.
(4) The NAMMD issues the authorisation of a medicinal product for compassionate use within 60 days after submission of all documents and information provided for in this Article.

ARTICLE 4

The decision on a group of patients' eligibility for compassionate use and on unsuitability of regular authorised medicinal products to ensure proper treatment lies with the specialist physician(s) caring for the respective patients.

ARTICLE 5

In the absence of CHMP approval, the NAMMD shall require a recommendation from the Specialist Commission of the Ministry of Health specialised in the therapeutic area including the product for which authorisation for compassionate use is sought, concerning its suitability for use.

ARTICLE 6

(1) The authorisation is valid for 6 months and may be renewed or changed, as required.
(2) The application for renewal of authorisation as per paragraph (1) shall be submitted 30 days prior to its expiry.

ARTICLE 7

The authorisation may be suspended or revoked when conditions for its grant are no longer met.

ARTICLE 8

The manufacturing company must comply with the following obligations:

a) to ensure funding of the compassionate use therapy, including costs of expertise for obtaining EMA approval, as required;

b) to ensure compliance with regulations in force on manufacturing, import and batch release;

c) to ensure that the secondary packaging contains at least the following information, in Romanian or a different language of international use (English or French):

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

d) not to advertise the medicinal product for human use authorised for compassionate use;

e) to keep specific records concerning administration of the medicinal product authorised for compassionate use;

f) to notify the NAMMD on actual beginning of the use of the medicinal product authorised for compassionate use;

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

h) to ensure that the medicinal product authorised for compassionate use is solely used in Romania;

i) not to market the medicinal product;

j) within 15 days, to document all cases of severe adverse reactions reported by the physician who had supported authorisation for compassionate use and currently applies the respective therapy or by the patient/caregivers, and report them to the database and information network provided under Article 24 of Regulation (EC) no. 726/2004, hereinafter referred to as Eudravigilance;

k) within 90 days, to document all cases of non-serious adverse reactions reported by the physician who had supported authorisation for compassionate use and currently applies the respective therapy or by the patient/caregivers, and report them to the Eudravigilance;

l) to immediately inform the NAMMD about any change in information concerning the authorised medicinal product and submit all appropriate documents;

m) to immediately inform the NAMMD and provide the grounds for the decision on early discontinuation of the use/availability of the medicinal product authorised for compassionate use;

n) to submit a report to the NAMMD on the safe use of the respective medicinal product for compassionate use, after expiry of the authorisation validity;

o) to archive all documents referring to the medicinal product, physicians and patient/group of patients for 10 years after completion of the programme;

p) to allow for inspections conducted by the competent authority granting authorisation for compassionate use;
q) to ensure immediate reporting to the NAMMD of any changes in the risk/benefit ratio, enabling prompt measures for risk prevention.

ARTICLE 9

Compassionate use shall be completed within one year since the date of authorisation by the NAMMD or at the same time as grant of a marketing authorisation for the respective product, whichever comes first.

ARTICLE 10

The duties of the specialist physician applying compassionate use therapies are as follows:
a) to ensure that compassionate use is carried out appropriately, in accordance with NAMMD approval;
b) to ensure that all measures and restrictions concerning the safe and effective use of the medicinal product are observed, and that all persons involved receive all necessary information in this respect;
c) to immediately inform the NAMMD about safety or quality issues;
d) not to advertise the program;
e) to keep specific records on administration of the medicinal product included in the programme;
f) to document all cases of adverse reactions identified or reported by the patient or caregivers and inform the manufacturer or the NAMMD thereof within 15 days (non-serious adverse reactions) and within a week (serious adverse reactions);
g) to establish causality between the occurrence of the adverse reaction and administration of a medicinal product for compassionate use;
h) to administer the medicinal product in accordance with conditions for use provided for by the company, which are integral part of the scientific dossier submitted to the competent authority for assessment of the application for compassionate use;
i) to stop medicinal product administration upon request by the NAMMD or the manufacturing company, if necessary;
j) to obtain forms for patients' informed consent, prior to treatment initiation, documented by signature thereof;
k) to obtain consent of the healthcare unit (where the respective compassionate use therapy is conducted);
l) to keep the medicinal product in accordance with the product's storage conditions, as provided for by the manufacturing company;
m) to keep all documents related to the medicinal product and patient/patient group for 10 years after completion of the programme;
n) to allow for inspections from the competent authority and the manufacturing company granted approval for conduct of compassionate use;
o) to keep a strict record of product administration to patients (quantities, dosage);
p) not to market the medicinal product.

ARTICLE 11

Changes of therapeutic indication, strength or pharmaceutical form of the medicinal product for compassionate use, as well as changes likely to impact patient safety can only be made after grant of a new authorisation.

ARTICLE 12

Notwithstanding regulations concerning archiving of medical records, key documents related to compassionate use shall be archived for minimum 10 years.

ARTICLE 13

Provision of the new medicinal product between authorisation and its actual placement on the market shall be ensured by the manufacturing company.

ARTICLE 14

NAMMD authorisation for compassionate use does not exclude civil or criminal liability of the manufacturing company.

ARTICLE 15

The forms used for authorisation of medicinal products for compassionate use shall be published on the NAMMD website within 30 days as of publication of the Order.