Ministerial Decision No. DYG3a/G.P. 85037/10

Terms, conditions and procedure for granting temporary approval for early access to medicines for human use ("compassionate use")

THE MINISTER
OF HEALTH AND SOCIAL SOLIDARITY

Having regard to:
1. the provisions of:
A) Articles 2(1), (2) and (5) of Law 1316/83 (Government Gazette A 3), as replaced by the provisions of Article 1 of Law 1965/91 (GG A 146) re: "Amendments to legislation on the National Organisation for Medicines (EOF), and other provisions", Article 3(5) and Article 6(10), as amended by Article 25 of Law 3730/2008 (GG A 262), Article 14 (4) and Article 31 of the same law;

B) Article 90 of Presidential Decree 63/2005 "Consolidation of legislation on government and government bodies" (GG A 98);

C) Ministerial Decision DYG3a/G.P. 86209/1.10.2009 re: "Terms, conditions and procedure for granting temporary approval for early access to medicines for human use ("compassionate use") (GG B 2157/2009);

D) Article 20 of Law 2690/1999 re: "Code of Administrative Procedures";

2. Decision-Proposal No. 48143/7.7.2010 of the chairman of the Board of EOF;

3. Regulation (EC) 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" (OJ L 136/30.4.2004);

4. Joint Ministerial Decision No. DYG3(a)/83657/2005 of the Minister of Finance and the Minister of Health and Social Solidarity (GG B 59/2006);

5. Joint Ministerial Decision DYG3/89292/2003 re: “Harmonisation of Greek legislation with Directive 2001/20/EC of 4 April 2001 on the approximation of 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 for human use” (GG B 1973) and relevant Joint Ministerial Decisions DYG3(a)69150/2004 (GG B 1503) and DYG3a/79602/2007 (GG B 64);

6. the fact that the provisions of this Decision shall not result in expenditure out of the State Budget;

We hereby decide as follows:

Article 1

Purpose

This Decision lays down provisions specifying the terms, conditions and procedures for the granting by EOF of temporary approval for early access to medicines for human use, by way of exemption from Article 7 of Joint Ministerial Decision DYG3(a)/83657/2005 (GG B 59/24.1.2006).

Article 2

Definitions

1. “Early access” to medicinal products for human use (“compassionate use”) shall mean making available, on humanitarian grounds, to a group of patients with a chronically or seriously debilitating or life threatening disease that cannot be treated satisfactorily by an authorised medicinal product, a medicinal product belonging to the categories referred to in Article 3(1) and (2) of Regulation (EC) 26/2004 or in the categories referred to in Article 2 of Joint Ministerial Decision DYG3 (a)/83657/2005 (GG B 59/24.1.2006) which is the subject of a marketing authorisation application in accordance with the procedures laid down in the aforementioned Regulation or Ministerial Decision or is undergoing clinical trials, in particular clinical data analysis study, showing, in principle, positive results, in accordance with the provisions of Joint Ministerial Decision DYG3/89292/2003 on clinical trials on medicinal products for human use (GG B 1973) and the related Joint Ministerial Decisions

DYG3(a)/69150/2004 (GG B 1503) and DYG3a/79602/2007 (GG B 64). The administration of an early-access medicinal product shall not constitute a clinical trial.

2. A "collective early access programme" may be implemented following approval by EOF, under the terms and conditions laid down herein for a specific group or sub-group of patients as part of an overall collective treatment and monitoring programme, based on the detailed criteria specified in an approved therapeutic protocol for the compassionate use of the medicinal product concerned, provided that available data suggest that the potential benefit outweighs the potential risk of using the treatment.

3. "Person responsible for a collective early access programme" shall mean the applicant for marketing authorisation or, as appropriate, the sponsor of the clinical trial, as defined in Article 2 point (e) of Joint Ministerial Decision DYG3/89292/2003, who bears full responsibility for the development, implementation and compliance of the early access programme, for record keeping, as well as for any consequences of the use of the medicinal product.

4. "Individual approval of early access to a medicinal product" may be granted, under the terms and conditions hereof, to a named patient in exceptional and fully justified cases, at the request and under the sole and unlimited responsibility of the attendant physician, where available data suggest that the potential benefit outweighs the potential risk of using the treatment and where available epidemiological data on the prevalence and incidence of the disease among the population of the European Union show this to be a rare disease requiring treatment by an orphan medicinal product in accordance with the relevant provisions or an extremely urgent case in which it is considered that any delay in giving appropriate treatment would cause the patient's death or seriously and irreversibly impair his health.

5. "Person responsible for individual approval of early access to a medicinal product" shall only be the attending physician who applies for, and justifies the necessity of, the administration of the medicinal product to a specific patient.

Procedure and requirements for early access to medicinal products for human use

Article 3

Early access programme

1. The person responsible for a collective early access programme shall develop and set up a “collective early access programme” either on his own initiative or at the request of a physician, taking the needs of patients into consideration.

2. The person responsible for a collective early access programme shall, before the launch of the programme, submit to EOF: a) a document containing a description of the collective early access programme, the criteria for inclusion of the specific patients in the programme, the intended indication of the medicinal product, the duration of the programme, a statement of the company’s commitment to fully cover the cost of supplying and administering the product, the fate of any unused stocks of the product, a statement of commitment to report any serious adverse reaction and to submit regular adverse reaction reports according to the duration of the programme, the nature of the treatment and the associated risks, and the data of the proposed Summary of Product Characteristics (SPC) and, where applicable, any SOC approved in another Member State; b) an “informed consent form” , which shall be provided to patients participating in the programme by the attendant physician in charge, under his care and responsibility; c) a copy of the submitted marketing authorisation application, along with the proposed Summary of Product Characteristics (SPC) and Package Leaflet (PL) in the Greek language, and summaries of all clinical studies submitted to support the marketing authorisation application and relating to the disease or, if the medicinal product is undergoing clinical studies, a summary of the results of clinical studies conducted on the disease and showing in principle that the potential benefit outweighs the potential risk of using the treatment; d) a model of the product’s labelling for use in the context of a collective early access programme, in accordance with the provisions of paragraph 9 of this article; e) compliance with the latest version of the detailed European Commission guidelines on early access to medicinal products; f) a solemn statement by a relevant specialist doctor that existing therapy options have been exhausted or it is certain that they will be exhausted; g) if the medicinal product is undergoing clinical trials, such trials must be at a final stage and preliminary results must be available that are favourable for the targeted patients. In this case, the person responsible for early access shall commit himself in writing to

submit a marketing authorisation application in the near future and in any event no later than seven months of the request for temporary approval of early access to the medicinal product; h) any available information on the product's quality, safety efficacy and conditions for safe use; i) any positive assessment by the European Medicines Agency or the competent authority of another Member State and detailed information according to Article 83(2) of Regulation 726/2004/EC and relevant EU guidelines; j) a solemn declaration by the person responsible for early access that there has been no rejection of a relevant request nor a negative opinion from the European Medicines Agency or the Committee for Medicinal Products for Human Use (CHMP) or another Member State; k) in general, any available information that is likely to enable the evaluation of the safety and efficacy of the medicinal product for the group or sub-group of patients participating in the early access programme and to provide a sound basis for the application.

3. The early access indication must: be based on solid scientific data; focus on diseases for which treatments do not exist or have been exhausted; be justified by unsatisfactory results of treatments already used and the expected benefits of the new treatment; and coincide with the indication for which clinical trials are being conducted or for which a marketing authorisation application has been submitted.

4. When an application with a complete dossier is submitted, EOF shall assess the submitted data and decide to grant, or not, the requested temporary approval.

5. Such approval is always granted for a specific indication for a defined group of patients and for a fixed period of no more than one year, which can be renewed provided that the circumstances underlying the original approval continue to exist and subject to the provisions of Article 5(2) hereof. In any event, EOF may set additional requirements, commitments and conditions, suspend or revoke at any time the temporary approval for grounds of public health or when the circumstances underlying the approval no longer exist or it is established that the terms of the approval are not complied with.

6. The person responsible for early access shall inform physicians of the availability of a collective early access programme and of the modalities of its implementation.

7. The person responsible for early access shall forthwith notify EOF of the names of the public hospitals, attending doctors and, on a quarterly basis, the patients included in the approved “collective early access programme”, forwarding at the same time the written concurrent opinions of the Scientific Council of each hospital and of the head of the relevant hospital department.

8. A medicinal product which is the subject of a temporary approval of early access shall be dispensed under the responsibility of the hospital pharmacist.

9. The labelling of medicinal products administered following approval of early access shall include:
a) name or, where applicable, code name of the medicinal product and the active substance(s);
b) name or company name, as appropriate, location, phone number and other details of the person responsible for the programme;
c) pharmaceutical form and route of administration;
d) lot number and expiry date;
e) storage conditions;
f) directions for use (reference may be made to the leaflet or other explanatory document);
g) the words “Early access medicine - not for sale” '

10. EOF shall publish on its website a list of medicinal products that are the subject of collective early access programmes.

Article 4

Inclusion of patients in a collective early access programme

1. Responsibility for the inclusion or non-inclusion of individual patients in a collective early access programme shall lie with the person responsible for early access, at the request of the attending physician.

2. The attending physician’s application to the person responsible for the collective early access programme must be in writing and specific to each individual patient as

identified only by the initials of his/her name, or any other code enabling identification if necessary, and shall contain the following warranties:

a) that the attending physician is fully aware of the personal responsibility assumed for administering an as yet unauthorised medicine;

b) that the patients to whom the medicine is to be administered suffer from a chronically or severely debilitating or life-threatening disease and cannot be satisfactorily treated by medicinal products authorised in Greece, along with a description of the disease concerned and the treatments already used;

c) that the attending physician will fully and properly explain to the patient or, in case of incapacity, the patient's legal representative, the significance, implications and risks of using the medicine in question;

d) that the attending physician will not administer the medicine to a patient unless the patient or, in case of incapacity, the patient's legal representative has previously signed and delivered an informed consent form.

3. The person responsible for the collective early access programme shall examine each application to decide the inclusion or non-inclusion of each individual patient and shall inform the attending physician of the outcome. If he accepts the inclusion of the patient, he shall make the medicine available to the attending physician in accordance with the specified terms and conditions for its use. Where the inclusion of an individual patient in the programme is rejected, the grounds justifying such rejection shall be specifically explained.

Article 5

Duration of the collective early access programme

1. The duration of a collective early access programme shall be fixed and shall not exceed one year. An extension can be considered where it is adequately justified on public health grounds, provided that the circumstances underlying the approval continue to exist. The application for extension shall be submitted with a full dossier,

together with a copy of the submitted marketing authorisation application, at least two months prior to the expiry of the granted temporary approval.

2. Once the medicine is granted marketing authorisation, the temporary approval of early access shall be cancelled and the person responsible for early access shall forthwith advise the attending physician and participating patients thereof, such patients shall henceforth use the medicine under the terms and conditions specified in the marketing authorisation.

3. If the marketing authorisation application is rejected on substantive grounds, the temporary approval of early access shall automatically be cancelled; if it is rejected for formal grounds, the provisions of paragraph 1 of this article shall apply.

Article 6

Modifications

Any material modification of the programme shall be resubmitted to EOF for approval. “Material” shall mean any change which is relevant for the physical or mental integrity or safety of the subjects participating in the programme, the progress of the programme, the quality, safety or efficacy of the medicine in the light of its early use. Any other modification shall be communicated immediately to EOF, along with the relevant decision of the Scientific Council of the Hospital and the concurrent opinion of the head of the relevant hospital department, where modification consists in an addition or replacement of a hospital or of an attending physician.

With regard to putting the intended modifications into effect, the provisions of Articles 3 and 4 hereof shall apply *mutatis mutandis*.

Article 7

Other obligations of the person responsible for early access

In addition to the obligations specified in individual provisions, the person responsible for early access shall:

1. ensure the administration of the early access medicine free of charge to patients, and without any cost to the State Budget or social security funds, unless special

reimbursement arrangements have been put in place, in which case a relevant certificate from the competent fund shall be submitted;

2. keep for a period of fifteen (15) years full records of the early access programme implemented. The records shall be detailed and include all relevant information about early access to the medicine, in particular the patient's name, gender and age, the course of the disease and any possible connection with the use of the medicine, the attending physician, hospital, tests run on the patient and any adverse reactions. These data shall be readily available to EOF at any time, enabling to ascertain compliance with the terms and conditions of early access. The above period may be extended should any relevant issue arise and until final judgment thereon;

3. immediately inform EOF of any serious adverse reaction and submit regular adverse reaction reports, according to the time frame of the collective early access programme or as determined by EOF;

4. not advertise the early access medicines;

5. not use the early access procedure in the dossier submitted for the marketing authorisation of the medicine;

6. not use, himself or the attending physicians involved in the programme, any information or data relating to the administration of the early access medicine in any publication or scientific conference, before the medicinal product concerned is granted a marketing authorisation.

Article 8

Individual approval of early access to a medicinal product

1. Notwithstanding the above, in exceptional and specifically justified cases of patients, in accordance with the provisions of Article 2(4) and Article 3(3) hereof, EOF may grant a temporary approval for early access to a medicinal product following a reasoned request by the attending physician and with a view to meeting the needs of the specific patient, under the following terms and conditions.

2. To obtain a temporary individual approval of early access, the attending physician shall submit to EOF:

a) an application, making a strong case that the requirements of the preceding paragraph 2 of this article are met;

b) a written statement whereby the applicant for approval or the sponsor of the clinical trial, as appropriate, shall commit to administer the medicinal product and to assume all pharmacovigilance obligations. The above commitment shall also include the free supply of the medicine or, if it is reimbursed by a social security organisation, fund, or an agency in general, a relevant certificate by the reimbursing entity shall ne submitted;

c) an informed consent form signed by the patient. Specifically, before the use of the medicine, the attending physician shall fully and accurately explain to the patient or, in case of incapacity, the patient's legal representative, the risks and consequences, and shall not administer the medicine prior to obtaining a signed informed consent as above;

d) communication to the Scientific Council of the hospital where the medicinal product will be administered and the concurrent opinion of the head of the relevant department of the hospital;

e) the recommended dosage, route of administration and duration of treatment;

f) all information available to the applicant and likely to support the application;

g) the statement referred to in point (a) of Article 4(2) hereof.

3. In assessing the physician's application, EOF shall require from the applicant or the sponsor of the clinical trial, as appropriate, the data referred to in Article 3 (2), points (c), (d), (g), (h), (i), (j) and (k). EOF shall preserve the commercial and industrial secrecy of such data vis-à-vis any third party. EOF shall also require a model of the early access labelling including the following:

a) name of the medicine or, if applicable, a code name and active substance(s);

b) lot number and expiry date;

c) storage conditions;

d) instructions for use (reference may be made to the leaflet or other explanatory document)

e) the words “early access medicine” with the initials of the name of the patient or other code enabling the identification of the patient.

4. For the granting of a temporary approval for early access, the procedure of Article 3(3) and (4) shall apply.

5. The individual temporary approval for early access shall determine the terms and conditions on which it is granted, any special commitments and requirements and shall be specific and not exceed one year, with a possibility of renewal or extension, provided that the circumstances underlying the approval continue to exist, at the request of the attending physician to EOF. In any event, the temporary approval shall expire once the medicine is granted a marketing authorisation, whereupon the patients who used the medicine under an individual temporary approval shall use it according to the terms and conditions of the marketing authorisation.

6. In all other respects, the provisions of Article 3(8) and (10), Article 5(3) and (6) and Article 7 hereinabove, as well as the provisions of the following articles, shall apply.

Article 9

Public service obligations

In line with scientific and technological advances and provided that the European Medicines Agency (EMEA) has delivered a positive opinion, EOF may, based on strictly scientific criteria and in the public interest, in exceptional cases that require the protection of public health, require from the persons responsible for early access, as defined in Article 2 hereof, to develop an early access programme for a group or sub-group of patients or for extremely urgent individual cases. The person responsible for early access may only refuse for specific and fully explained reasons relating to the safety and efficacy of the medicine, otherwise the sanctions provided for in Article 11(2) hereof shall apply.

Article 10

Civil and criminal liability

No provision hereof shall affect the civil and/or criminal liability of the person responsible for the early access programme and of the attending physician, both of whom shall be held solely responsible.

Article 11

Sanctions

1. Without prejudice to the provisions of the following paragraph, non-compliance with this Decision shall be punished by the sanctions provided for in Article 19(1) and (2) of Legislative Decree 96/73, as replaced by Article 33(1) of Law 1316/83 and adjusted by Article 152(1) of Joint Ministerial Decision DYG3(a)/83657/2005 (GG B 59/2006), namely a financial penalty of up to EUR 44,000.00 for violations of paragraph 1 and up EUR 13,200.00 for violations of paragraph 2.

2. Notwithstanding the provisions of the preceding paragraph, non-compliance with the provisions of Article 9 hereof shall be punished by the sanctions of Article 19(5A) of Legislative Decree 96/73, as inserted by Article 33(4) of Law 1316/83 and adjusted by Article 152(2) (c) of Joint Ministerial Decision DYG3(a)/83657/2005 (GG B 59/2006), namely a financial penalty of up to EUR 22,000.00, for obstructing the work of EOF.

Article 12

Decisions of EOF shall determine all necessary details regarding the implementation hereof.

Article 13

Transitional provisions

As from the entry into force hereof, any contrary provision or procedure shall be repealed. Any treatments that, at the time of publication hereof, are being conducted on a compassionate basis shall be subject to the framework for early access to medicinal products for human use under the terms and conditions hereof, and the relevant application shall be submitted to EOF within a strict period of two months of the entry into force hereof, otherwise they shall be deemed to be conducted without approval, in which case the sanctions provided for herein shall apply.

Article 14

Repealed provisions -- Entry into force

1. As from the entry into force hereof, Ministerial Decision No. DYG3a/G.P. 86209/1.10.2009 re: “Terms, conditions and procedure for granting a temporary approval for early access to medicines for human use (“compassionate use”)” (GG B 2157/2009) shall be repealed.

2. This Decision shall enter into force as from its publication in the Government Gazette.

We order that this Decision be published in the Government Gazette.

Athens, 16 March 2011

THE MINISTER

ANDREAS LOVERDOS