01.02.2009

GUIDELINE ON THE COMPASSIONATE USE PROGRAM

1. Objective

This program is an arrangement that aims to provide free of charge drugs, which are not registered in our country and are or are not registered in other countries, to patients whose treatment in Turkey has failed with the existing accessible products registered by the Ministry and who suffer from a serious or urgent and life-threatening disease and have not been included into scope of the clinical trials conducted in this field.

2. Patients to be Covered by the Program

As specified in the "Objective" section, this program shall encompass patients whose treatment with the medicinal products available in our country has failed, who are urgently exposed to a life-threatening disease or a disease that leads to a sequel, and who are not included into the scope of the clinical trials conducted in this field, whose disease has been diagnosed by a physician who made a written commitment for assuming the responsibility of including the patient to the treatment within the scope of the program and who have been reported to the Pharmaceutical General Directorate.

3. Scope of the Program

Except for scientifically justifiable and very rare exceptional cases, drugs for which at least Phase II studies have been completed and Phase III studies have been initiated across the world, are included into the program. It is not necessary for Phase studies to have been conducted in Turkey in order for a drug to be included into this program.

This program is not a clinical drug trial. The physician(s) conducting the program shall not receive any payment under any name.

This program shall not aim to collect information about the effectiveness of the drug and even if such information is collected, they will not be used in the procedures relating to the registration of the drug by the Ministry of Health.

4. Method for Receiving Permit

The physician envisaging to use the relevant drug, shall apply to the Pharmaceutical General Directorate with the dossier content indicated in Annex 1.

5. Mode of Conduct of the Program

This program shall be applied on a "patient" basis.

This program may be applied in training and research hospitals as well as public hospitals and private hospitals whose adequacy in terms of the place where application will be made is approved. However, it shall not be applied in outpatient services, private surgeries, health clinics and dispensaries.

Adverse effects arising during the treatment shall be reported to the Pharmaceutical General Directorate upon completing the adverse effect notification form within the timeframes indicated in the effective legislation. Deaths occurring in patients where the drug is used during the application (whether these are related with the program drug or not) and serious adverse events shall be reported to the Pharmaceutical General Directorate within eight days.

Besides for the routine analyses to be made during the administration of the drug, none of the analysis fees shall be paid by the patient or the reimbursement institute. This should be indicated in the letter of commitment presented in Annex 2.

Information on whether the patient undergoing therapy has benefited from the therapy and the adverse effects shall be reported to the Pharmaceutical General Directorate in the form a ranking list (Annex 3) once every three months.

The form presented in Annex 4 shall be submitted to the Pharmaceutical General Directorate once every six months.

The company shall not prohibit the physician from making publications. However, the physician shall inform the relevant company one month before the publication. The publication to be made on the efficacy and/or safety of the drug should explicitly include the statement that the data belong to the compassionate use program and do not reflect the phase study data.

In relation with the drug of the patient included into the compassionate use program, the physician shall not simultaneously apply to another unit of the Pharmaceutical General Directorate within the framework of the off-label use of the drug and on a prescription basis during the conduct of this program and will have to commit that he/she shall not do so.

Correspondences relating to the application can be made by the applicant physician or company.

6. Report to be Submitted at the End of the Program

A report shall be submitted to the Pharmaceutical General Directorate at the end of the program. The report will contain the following:

1. In relation with the patient to be encompassed by the program and his/her disease:
   - Initials of the name and surname of the patient,
   - Age,
   - Gender,
   - Weight,
   - Diagnosis (diagnosis of the patient's disease),
   - Stage of the disease,
   - Therapies previously applied to the patient,
   - Drugs used and their amount,
   - Stage of the disease when the drug begins to be used,
   - Whether there have been any benefits of the drug (where possible, the benefits should be expressed with comprehensible clinical, radiological and laboratory parameters such as "improvement in laboratory findings, shrinking of lesions, relative improvement in the patient's quality of life),
2. Summarized chart indicating the adverse events ranking list (Annex-3),
3. General opinion on whether conduct of the program provides any benefit to the patient,
4. Outcome, observations and proposals relating to the program.

7. Termination of the Program

The therapeutic program where the physician has indicated that it provides benefit to the patient cannot be terminated unilaterally by the company. The company shall be responsible for procuring the drug until it receives registration in Turkey. In case it is requested by the company and approved by the Pharmaceutical General Directorate, the relevant company may continue to procure the drug until it is included into the reimbursement list.

In case a negative opinion is established regarding the benefit/risk ratio of the safety of the drug, the implementation shall be terminated by the physician and/or the Pharmaceutical General Directorate.

The company shall procure the drug of the patients designated by the Pharmaceutical General Directorate to be benefiting from the program until the therapy is completed.

8. Revoked Arrangements

The Circular Regarding the Program on the Compassionate Use Program dated 20.07.2006, with No. 2006/86 has been revoked.

9. Enforcement

This guideline shall become effective as of 01.01.2009.

ANNEX - 1
Information and Documents Required in the Application to the Compassionate Use Program

1. Name of Program,
2. Justification for Using the Drug on the Patient within the Scope of the Referred Program,
3. Patient Epicrisis,
4. Amount of Drug to Be Used,
5. Recently Signed Curriculum Vitae of the Physician (original version),
6. If the Drug is Being Used in a "Compassionate Program" Abroad, Information About Such Use,
7. Sponsoring Organization/Company's Name and Title,
8. Notary-Public Certified Circular of Signatures of the Relevant Company,
9. Contact Person of the Program,
10. Envisaged Duration of the Program,
11. Location where the Program will Be Conducted,
12. Mode of Conduct of the Program,
13. Detailed List Approved/Signed by the Physician Regarding the Routine Analyses tı be Conducted on the Patient,
14. Formulation of the Drug,
15. Mode of Action of the Drug,
16. Label Sample of the Drug,
17. Preclinical and Clinical Studies Conducted So Far Regarding the Drug,
18. Dose of the Envisaged Drug,
19. Conditions for the Storage of the Drug,
20. The Interaction of the Drug with Other Drugs, Nutrients, Chemical Substances and Laboratory Analysis Methods,
21. Information Regarding the Safety of the Drug,
22. Sample Patient Consent Form (Annex 7),
23. Sample Adverse Effect Monitoring Form,
24. Commitment Document Indicating the Responsibilities of the Physician and the Rules He/She Shall Comply With (Annex-2),
25. Document Indicating the Distribution of Responsibilities Between the Sponsoring Organization and the Physician,

NB: The aspects indicated in articles 6,7,8,14,15,16,17,19,20,21,23 shall only be submitted in the first application pertaining to the program, but in case of a change in this information and documents, the application shall be re-submitted and the information indicating that these changes will be submitted shall be committed by the relevant company.

ANNEX - 2
Sample Commitment for the Compassionate Use Program

I hereby declare and confirm to be participating in the "Compassionate Use Program entitled ..... and commit that;

1. I shall fulfill the requirements of the final text of the Declaration of Helsinki, Compassionate Use Program and the Regulation on Patients' Rights,

2. I shall comply with the principle of confidentiality of the personal data of the patients included into the program,

3. The analysis fees, other than the routine analyses to be conducted during the use of the drug, shall not be paid by the patient or the reimbursement institutes,

4. I shall not request for prescription approval for the relevant drug for its off-label use during the treatment of the patients included into the program of the prescription.

The Physician's;

Name/Surname/Title:

Institute :

Date :

Signature :

ANNEX - 3
Adverse Events' Ranking List

The Patient's:

1. Age,
2. Gender,
3. Country,
4. Daily dose administered (mg/day),

Relating to the adverse effect:

1. Starting date or the period elapsed until the onset of the effect,
2. Treatment dates or duration of the treatment,
3. Definition of the effect,
4. Result,
5. Remarks relating to the result.

Annex- 4
Biannual Notification Form of the Compassionate Use Program

1. Name of Program,
2. List of Physician Included into the Program (Name/Title of the Responsible Physicians, Name of Medical Institution Where They Work, First Two Letters of the Name and Surname of the Patient They Are Following),
3. List of Healthcare Institutions Included into the Program,
4. Number of Patients Included into the Program,
5. Dates on which the Patients Have Been Included into the Program,
6. Number of Patients Continuing with the Program,
7. Information on the Current Status of the Patients Continuing with the Program,
8. Amount of Drugs Imported within the Framework of the Program.
9. Whether the patients have benefited from the drug (where possible, the benefits should be expressed with comprehensible clinical, radiological and laboratory parameters such as "improvement in laboratory findings, shrinking of lesions, relative improvement in the patient's quality of life)
10. Summarized chart of adverse events' ranking list
11. General opinion on whether the conduct of the program provides any benefit to the patient,
12. Observations and proposals relating to the program

Annex - 5
Sample Patient Epicrisis

Initials of the Patient	as XX.YY.

Gender:	□ Male □ Female
Date of Birth:	as XX/YY/ZZZZ
Age of the Patient:	Weight of the Patient:

Name of Responsible Physician:	
Name of Institute/Hospital where the Physician Works:	
Address (Street, City, County)	

Current Diagnosis:
Date of First Diagnosis:
Total number of drugs to be used on the patient:
Phase of the disease:

Therapeutic methods previously applied on the patient:

Past Therapies:

Therapy	Dose	Date on Initiation	Termination Date	Adverse Events

Medical history of the patient, other co-existing conditions: (Document any organ discomfort in organs such as in the GI system, kidneys, etc.)

Other Drugs Used by the Patient: 1. 2. 3. 4. 5. Other:

Test Results: It is obligatory to indicate the latest results of below-mentioned tests. The results may be recorded on the form or annexed as separate documents.

Laboratory Findings:

Hematological Tests: Biochemical Tests:

Tumor Markers:

Cytogenetic Tests:

Bone Marrow Biopsy:

BT:

MR:

Scintigraphy:

US:

Bcr-Abl Levels

ECG:

Mutation Analysis:

1) In order to receive fast response, make sure that you have responded to all questions.
2) We kindly ask you to annex the patient's all current laboratory results to this form.
3) Abovementioned articles may be modified according to the disease.
4) **Please include the name, stamp and signature of the responsible physician in the section indicated below.**

Responsible Physician:

Signature:
Date:

Annex- 6
Sample List for Routine Analyses

1) Physical Examination; vital findings,
   (General appearance, skin, neck including the thyroid, eyes, ears, nose, throat, lungs, heart, back, lymphatic nodules, extremities, neurological investigation, body temperature, weight, pulse, blood pressure, height, etc.)
2) Hematological Tests
   (Complete blood count)
3) Biochemical Tests
   (Fasting blood glucose, urea, BUN, creatinine, LDH, total protein, phosphorus, serum-adjusted calcium, electrolytes (sodium, potassium, magnesium, chloride, etc.), total bilirubin, GGT, albumin, alkaline phosphatase, AST (SGOT), ALT (SGPT), uric acid, etc.)
4) Urinalysis
   Microscopic investigation (WBC/HPF, RBC HPF and cylinders)
   Macroscopic investigation (specific weight, pH, protein, glucose, bilirubin, ketones, blood cells and leukocytes)
5) Coagulation Panel
6) Electrocardiogram
   (Standard 12 lead ECG)
7) Radiological Tests:
   - X-Ray
   - BT
   - MR
   - US
   -Other
8) Scintigraphy:
9) Bone Marrow Analysis:
10) Cytogenetic Investigation
11) Pregnancy Test:
   (In women with potential of giving birth to a child, a serum pregnancy test should be made within 14 days prior to the administration of the study drug.)

1) Please annex the patient's all current laboratory results (obtained in the last one month) to this form.
2) Abovementioned articles may be modified according to the disease.
3) Please include the name, stamp and signature of the responsible physician in the section indicated below.

Responsible Physician: Signature:
Date:

Annex - 7
Sample Patient Consent Form for the Compassionate Use Program

Name of Program:
Program Code:
Responsible Physician's; (This section shall be filled by the physician)

Name & Surname **Signature** **Date**

Please Read Carefully!
You have been invited to participate in this program. Before accepting to participate in this program, you should understand the purpose for the conduct of this program and take your decision freely upon receiving this information. Please read carefully this information which has been prepared specifically for you.

- **What is the Purpose of the Program?**
- **What are the Participation Requirements?**
- **What type of an administration will it involve?**
  (The patient will be informed on the frequency and dosage at which the drug will be used per day and the analyses to be made (blood, urine, imaging methods, biopsy where necessary, etc.)
- **What are my Responsibilities?**
  (Visit frequencies, etc.)
- **What is the number of participants?**
- **What will be the duration of my participation?**
- **What are the potential benefits of participating in the program?**
- **What are the expected potential risks and discomforts of participating in the program?**
  (The potential harms of the drugs should be clearly described starting with the most widespread down to the most rarely observed harm; it should also be mentioned that it should not be used in patients with sensitivity to the substance in question or any of its other components and the results of animal studies, if any, should be declared.)
- **What are the alternative therapeutic methods?**
  (All alternative transactions or therapeutic cures that may be suitable/advantageous for the patient, their significant potential benefits and risks should be described to the patient by the responsible physician.)
- **Information Regarding Use During Pregnancy and Breastfeeding**
- **What are the drugs/nutrients known to be inconvenient if used concomitantly during the program?**
- **What are the storage conditions of the drug?**
- **Under what conditions will I be excluded from the program?**
- **New findings**
  (In case of any development related with the treatment/administration conducted during the program, it should be indicated that the patient will be informed about it.)
- **Whom can I call for any problems to arise during the program?**
  (It is necessary to provide a mobile phone number that the patient can reach 24 hours a day.)

- **Are there any organizations sponsoring the program?**
- **Will I receive any payment due to my participation in the program?**
  (It should be indicated that no payment will be made.)

- **What should I do in case I refuse to participate in the program or wish to quit the program?**
- **Confidentiality**

The Patient's;

Name & Surname: Signature: Date:

Address: Telephone:

For those under guardianship, the parent's or guardian's;

Name & Surname: Signature: Date:

Address: Telephone:

The following information relating to the person who has witnessed to the consent receipt process from the beginning until the end and is not included into the team encompassed by the referred program;

Name & Surname: Signature: Duty: Date: