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CLINICAL PRACTICE GUIDELINE KAD-KLVZ-30

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SECTION ONE

Introductory Provisions

Purpose

ARTICLE 1- (1) The purpose of this guideline is to establish the procedures and principles for clinical practices (trials) to be carried out with the aims of ensuring accessibility to regenerative medicine practices that may be performed with advanced therapy medicinal products, enabling the use of advanced therapy medicinal products in our country for the benefit of patients in need, in line with scientific and technological developments worldwide, and laying the groundwork for the emergence of new industrial products. Scope

ARTICLE 2- (1) This guideline covers clinical practices (trials) in which advanced therapy medicinal products manufactured in our country are used. (2) This guideline does not cover clinical trials of tissue and cell products and advanced therapy medicinal products. Legal Basis

ARTICLE 3- (1) This guideline has been prepared based on the Regulation on Products Obtained from Human Tissues and Cells and Centres Related to These Products, published in the Official Gazette No. 33007 dated 04.09.2025. Definitions

ARTICLE 4- (1) In this Guideline; a) Ministry: the Ministry of Health, b) Tissue: the parts constituting the human body that are composed of cells and extracellular elements and that do not have the property of being transplanted as an organ, c) Tissue and cell product: tissues and cells that are not classified as an advanced therapy medicinal product, have not undergone substantial manipulation, do not exert their effect through a systemic mode of action, and have been processed for homologous use in the clinical setting, ç) Homolog use: the use of a tissue or cell, when transplanted to the recipient, for the purpose of performing the same essential functions as in the donor, d) Non-homologous use: the use of a tissue or cell, when transplanted to the recipient, for the purpose of performing functions other than those in the donor, e) Cell: a single human cell or a collection of human cells, not accompanied by any connective tissue, f) Advanced therapy medicinal product: products that carry at least one of the criteria of substantial manipulation, systemic effect, or non-homologous use in cases where tissue and cells are used as starting material, g) Legal representative: the person who is authorized, in accordance with the legislation in force, to give consent on behalf of the patient for the performance of a clinical application (testing) on the patient, ğ) Clinical application (testing): the use of an advanced therapy medicinal product not yet licensed in our country; prepared in a non-routine manner in accordance with specific quality standards, specifically for a certain number of patients, and at human application centers authorized by the Ministry, in accordance with an individual medical prescription, under the exclusive professional responsibility of a medical doctor who has completed specialization in the relevant field,

h) Agency: the Turkish Medicines and Medical Devices Agency (TİTCK), ı) TÜSEB: the Health Institutes of Türkiye, i) Manufacturing License: the authorization granted by the Agency for the manufacturing in our country of advanced therapy medicinal products to be used for the purpose of clinical application (testing), j) Donor: the person from whom tissue and cells are obtained, for autologous application, allogeneic application, and as a donor, for one or more of these, shall mean. (2) The term "clinical application (testing)" used in this Guideline is used as the equivalent, limited to the scope of application of this Guideline, of the concepts of "clinical experimental study and treatment trial" set forth in the Regulation on Products Obtained from Human Tissues and Cells and on Centers Related to These Products, dated 04.09.2025 and numbered 33007. (3) The term "clinical application (testing)" used in this Guideline is used as the equivalent of the concept of "hospital exemption" set forth in the Directives of the European Parliament and of the Council.

SECTION TWO General Principles General Principles

ARTICLE 5- (1) Clinical applications (tests) are carried out with the permission of the Agency in cases where there are unmet medical needs and where the industrial/commercial development of the advanced therapy medicinal product in question is not possible in line with current scientific and technological data, or where licensed advanced therapy medicinal products for the relevant indication are not available in our country, or where an adequate response cannot be obtained with the treatment options approved in our country for the relevant indication, with the aim of ensuring access to innovative treatments.

(2) Permission shall not be granted for clinical application (test) applications if there is an ongoing clinical trial in our country with the same advanced therapy medicinal product, in the same indication and patient population, to which the patient could be enrolled.

(3) For diseases that are treatable within the relevant indication in our country, the use of advanced therapy medicinal products within the scope of a clinical application (test) shall only be taken into evaluation by the Agency where such products constitute treatment options providing a distinct advantage in accordance with evidence-based medicine.

(4), Each application shall be evaluated by the Agency on a case-by-case basis in accordance with scientific and ethical requirements.

(5) The clinical application (test) permission is personal (on a patient basis) and is granted for the specific clinical condition of the patient. Any permission granted for a patient shall neither constitute a precedent for other patients with a similar diagnosis but a different clinical presentation or clinical course, nor reflect the general health strategy of the Agency.

(6) A product must be prepared exclusively for a certain number of patients in compliance with an individual medical prescription and must be used only for the patient for whom the clinical application (test) has been approved.

(7) The Agency may carry out an evaluation, in accordance with the relevant legislation, regarding the continuation, modification (dose, frequency of administration, duration, etc.) or termination of the clinical application (test) permission in question, based on changes occurring in the patient's clinical condition, new scientific data emerging regarding the product, and evidence-based medicine.

(8) Clinical applications (tests) may only be performed at human application centers authorized by the Ministry.

(9) Clinical applications (tests) may only be performed by physicians who are responsible for the medical treatment of the patient, who are from the relevant specialty field, and who hold a "clinical application certificate".

(10) The medical and legal liability regarding clinical applications (tests) lies with the physician responsible for the medical treatment of the patient.

(11) The characteristics of the advanced therapy medicinal product to be used in the clinical application (test) (type, quantity, etc.) and its mode of administration (route of administration) must have been included in a previously conducted clinical study in the same indication and patient population as the patient for whom the clinical application (test) will be performed, or the data prior to the clinical application (test) (preclinical data) must have provided a sufficient level of evidence for the clinical application of this administration. The systematic clinical and preclinical data that will form the scientific basis for the clinical application (test) must be presented in the application file. Depending on the nature of the product, these systematic data, preclinical/clinical review findings, and scientific publications (congress abstracts, full-text research articles, thesis studies) must be included in the application annex in pdf format. Literature published in journals indexed in SCI/SCIE is considered by the Agency to constitute high-level evidence.

(12) Since this practice, organized by the Agency by prioritizing patient safety and treatment, constitutes an exceptional treatment option, the patient data (reports) obtained as a result of the administration of the products in question must be submitted to the Agency and TÜSEB in accordance with the periods determined by this guideline. The threshold value for the number of

clinical application (test) permissions to be granted by the Agency is determined by the scientific commission through an evaluation based on the incidence of the disease and the nature of the product.

(13) In cases where the reports for the periods determined for each application are not submitted to the Agency, or depending on the decision formed as a result of the evaluation of the reports regarding the findings obtained from the relevant clinical applications (tests) concerning the efficacy and safety profile of the product, the Agency has the authority to modify its decision to grant permission for the clinical application (test), and to terminate and suspend the permissions. The modification of the decision to grant permission for the clinical application (test), and the additional procedures for the termination and suspension of permissions also apply to those who fail to fulfill the requirements specified in the Pharmacovigilance/Biovigilance Section of this guideline.

(14) The data obtained as a result of clinical applications (tests) cannot be used as the sole source of evidence in the licensing of the advanced therapy medicinal product in question; for data supporting the license, the submission of data obtained from the clinical trials of these products is also mandatory.

(15) Matters relating to the licensing of the advanced therapy medicinal product that is the subject of the clinical application (test) are subject to the provisions of the Regulation on the Licensing of Advanced Therapy Medicinal Products published in the Official Gazette No. 32203 dated 27.05.2023. In this context, clinical trials that meet the scientific and ethical requirements determined by the Regulation on Clinical Trials of Medicinal Products for Human Use published in the Official Gazette No. 32203 dated 27.05.2023 must be conducted.

(16) The safety and efficacy data obtained from clinical applications (tests), long-term patient follow-up results, and pharmacovigilance/biovigilance reports are submitted to TÜSEB simultaneously with the notifications made to the Agency within the periods determined by this guideline. These reports are subjected to scientific and strategic evaluation by TÜSEB. As a result of the evaluation, in line with national planning, clinical applications (tests) relating to advanced therapy medicinal products identified as having high added value and public benefit are evaluated by TÜSEB in accordance with the relevant Regulation.

(17) No advertising or promotional activities may be carried out regarding clinical applications (tests); through means of communication such as television, newspapers, and social media, no promising or misleading statements that are not based on scientific data may be made regarding these applications.

SECTION THREE Procedures and Principles Regarding Clinical Application (Test) Applications
Persons Who May Apply for a Clinical Application (Test) and the Form of Application

ARTICLE 6- (1) The clinical use (trial) application shall be made by the physician responsible for the patient's medical treatment. Applications may not be made by the patient, the patient's relatives, the pharmacist, manufacturers, centres or other persons. (2) The clinical use (trial) application shall be submitted to the Agency electronically or by post. (3) Provided that the other requirements specified in this guideline are fulfilled, the minimum information required to be included in the clinical use (trial) application file is as follows: a) A signed petition of application, addressed to the Agency, containing a brief summary of the clinical use (trial) and indicating the request for the clinical use (trial), b) The Clinical Use Application Form (ANNEX-1), c) The use protocol containing the details of the clinical use (trial) to be performed (information on the human use centre where the use will be carried out and on the physician responsible for the patient's medical treatment, the termination criteria of the clinical use (trial), a brief description of the donor source, cell type, dose to be administered, route of administration, number and frequency of administrations, etc.), ç) Systematic clinical and preclinical data constituting the scientific basis for the clinical use (trial) (depending on the nature of the product, preclinical/clinical study findings; a Reference List concerning scientific publications (congress abstracts, full-text research articles, thesis studies), summaries of the references, and all

references in the reference list shall be included in the application annex in pdf format), d) The discharge summary containing the treatments received by the patient, the responses obtained from these treatments and current laboratory values related to the diagnosis, e) The Informed Patient Consent Form (ANNEX-2) obtained from the patient or his/her legal representative, f) The curriculum vitae of the physician responsible for the patient's medical treatment, who will conduct the clinical use (trial), and his/her "clinical use certificate", g) The signed business protocol regulating the mutual duties and responsibilities of the parties to the clinical use (trial),

ğ) Pharmacovigilance/biovigilance standard operating procedures covering the processes of review, reporting and recording of safety notifications, h) Regarding the manufacturing, quality, storage and distribution information of the advanced therapy medicinal product to be used within the scope of the clinical use (trial): 1) The name, address and responsibility of the manufacturer(s) and manufacturing site(s)/facility(ies) responsible for the manufacturing, testing and batch release of the finished product, 2) A copy of the tissue and cell processing-manufacturing centre licence belonging to the centre(s) where the manufacturing will be carried out for all manufacturing steps of the finished product, 3) A letter of commitment, signed by the centre responsible person of the licensed tissue and cell processing-manufacturing centre where the manufacturing is carried out, undertaking that all processes that may affect the quality and safety of the product, including donor selection, medical evaluation of the donor, laboratory tests, procurement of tissues and cells, processing-manufacturing, and the systems relating to traceability are conducted in compliance with the provisions of the Regulation on Products Obtained from Human Tissues and Cells and Centres Related to These Products, 4) The qualitative and quantitative composition of all active substance(s) and excipients contained in the finished product, 5) A description of the manufacturing process of the finished product, 6) The specifications, tests and acceptance criteria specified in national/international guidelines and pharmacopoeias regarding the specific characteristics of the finished product and quality characteristics that may have been affected by the formulation steps, 7) Information on the storage temperature and storage period of the finished product and supporting information thereof, 8) In cases where the storage/distribution of the advanced therapy medicinal product to be used in the clinical use (trial) is in question, a copy of the tissue and cell storage/distribution centre licence belonging to the relevant centre. (4) Applications shall bear the signature, stamp or electronic signature of the physician responsible for the patient's medical treatment.

Evaluation of the Clinical Use (Trial) Application

ARTICLE 7- (1) Applications shall be evaluated by the Agency in accordance with the requirements set out in this guideline. (2) The evaluation of the applications by the Agency shall be carried out in the order of the application date. (3) The Agency may request additional information and documents, within the scope determined by the relevant national and international legislation and pharmacopoeias relating to the product concerned, by applying a risk-based approach according to the type of advanced therapy medicinal product to be used in the clinical use (trial). (4) The Agency may request additional information or documents, including, where necessary depending on the nature of the requested clinical use (trial), the results of specific laboratory investigations performed in relation to the disease. (5) Ethics committee approval shall not be required for applications. However, where deemed necessary by the Agency, the submission of an ethics committee approval obtained from an authorised ethics committee may be requested. (6) The result of the evaluation shall be notified to the applicant by the Agency by means of an official letter.

(7) The clinical use (trial) may be carried out, after permission is obtained from the Agency, under the full medical and legal responsibility of the physician responsible for the patient's medical treatment. (8) For applications found unsuitable, where there are scientifically valid objections submitted by the physician making the application, the application may be re-evaluated by the Agency on one occasion only.

SECTION FOUR Ethical Requirements Ethics Committee Decision

ARTICLE 8- (1) For applications approved by the Agency, there is no requirement to additionally obtain ethics committee approval for the conduct of the clinical use (trial). (2) Where retrospective studies of the data obtained as a result of the use are in question, approval shall be obtained from the relevant ethics committee. Informed Patient Consent

ARTICLE 9- (1) The patient wishing to participate in the clinical use (trial), or his/her legal representative, shall be informed before the use, sufficiently and in a manner that he/she can understand, by the physician responsible for his/her follow-up and treatment, about the purpose and methodology of the use, the fact that there is not yet a sufficient level of evidence regarding its efficacy and safety, the expected benefits, foreseeable risks and discomforts, aspects that are unsuitable in terms of the patient's health and personal characteristics, the conditions under which the clinical use (trial) will be performed and continued, and the fact that the patient has the right to terminate the clinical use (trial) at any time he/she wishes. (2) The consent of the patient shall be obtained entirely of his/her own free will, and this shall be documented by means of the Informed Patient Consent Form. In cases where the patient is unable to give informed consent, his/her legal representative shall be informed about all aspects of the clinical use (trial), consent shall be obtained and documented.

SECTION FIVE Labelling Labelling of the Primary/Secondary Packaging

ARTICLE 10- (1) Manufacturers of advanced therapy medicinal products to be used within the scope of clinical application (trial) shall be obliged to provide at least the following information on the label of the said products: a) The name of the advanced therapy medicinal product and, where applicable, the information indicating whether it is intended for infants, children or adults, b) The qualitative and quantitative description of the active substance(s); where the product contains cells or tissues, a brief description of the said cells or tissues and information on their specific source, together with the statement "This product contains human/animal [whichever is applicable] origin cells", and in the case of non-human origin, the specification of the animal species, c) The pharmaceutical form, route of administration and, where applicable, the content of the product in terms of mass, volume or number of doses,

ç) The list of excipients, including preservatives, d) Instructions for use, administration/implantation and route of administration, e) Where applicable, a blank space to allow the prescribed dose to be indicated, f) The special warning "Keep out of the sight and reach of children and store in its packaging.", g) Where applicable, special warnings or precautions for use relating to the product; ğ) Storage conditions and expiry date (month and year, including the day if necessary), h) Special precautions for the disposal of unused medicinal products or waste derived from medicinal products, ı) The name and address of the holder of the "Manufacturing License", i) The authorization number of the manufacturing site, j) The product serial number, donor and product code; k) For advanced therapy medicinal products manufactured for autologous use, the "Patient Identifier Statement" and the statement "For Autologous Use Only".

SECTION SIX Conduct of the Clinical Application (Trial) and Post-Application Follow-up Certificate of Analysis of the Finished Product

ARTICLE 11- (1) The manufacturer responsible for batch release of the advanced therapy medicinal product to be used within the scope of the clinical application (trial) shall be obliged to submit to the physician responsible for the medical treatment of the patient and/or the centre director of the human application centre the certificate of analysis of the finished product, containing the tests demonstrating conformity with the approved specifications of the product, acceptance limits and analysis results. (2) Unless otherwise justified, the finished product specifications shall include: a) Identification, assay, potency and purity tests, b) Sterility and endotoxin tests for sterile products, c) For gene therapy medicinal products, in addition; where non-replicative viruses are used, tests for the detection of replication-competent viruses, ç) For cell therapy medicinal products, in addition; cell viability, total cell count and mycoplasma tests,

together with acceptance criteria and test results. (3) The selection of tests shall be product-specific, and additional requirements may be requested for different product types in line with national/international regulations and pharmacopoeias. (4) In cases where comprehensive release testing cannot be performed on the finished product (for example, where sampling is not possible or the quantity of the product is limited), this situation shall be explained on the basis of scientific and technical justifications; the specifications shall be established in such a way as to include the applicable tests, taking the said limitations into consideration, and the relevant matter shall be clearly stated in the clinical application (trial) application dossier submitted to the Agency and Agency approval shall be obtained.

(5) In cases where the clinical application of the finished product is required before the results of all tests included in the approved specifications have been obtained, this situation shall be justified in light of scientific data. In this case; a) The essential tests of critical nature that can be performed within a limited period of time prior to the clinical application (trial) of the product shall be defined and the selection of these tests shall be explained with scientific justifications, b) The procedures to be followed in the event that out-of-limit results are obtained following the clinical application of the product shall be defined in a clear and detailed manner, c) An explanation of the risk analysis and risk mitigation measures shall be provided, and the relevant matter shall be clearly stated in the clinical application (trial) application dossier submitted to the Agency and Agency approval shall be obtained. (6) Records relating to the certificate of analysis of the finished product shall be retained by the manufacturer and the physician responsible for the follow-up and treatment of the patient and/or the centre director of the human application centre for a period of 30 years. Conduct of the Clinical Application (Trial)

ARTICLE 12- (1) The advanced therapy medicinal product to be used within the scope of the clinical application (trial) may be administered to the patient only; following the examination of the certificate of analysis of the finished product, containing the tests demonstrating conformity with its approved specifications, acceptance limits and analysis results, and the confirmation of its conformity. (2) The obligation relating to the examination and confirmation of the conformity of the certificate of analysis of the finished product specified in the first paragraph shall rest with the physician responsible for the medical treatment of the patient and/or the centre director of the human application centre. (3) Clinical applications (trials) shall be carried out only by physicians holding a "clinical application certificate", from the relevant specialty, responsible for the medical treatment of the patient. Post-Clinical Application (Trial) Follow-up

ARTICLE 13 (1) Reports, including also the audit results relating to clinical applications (trials), shall be submitted by the physician responsible for the follow-up and treatment of the patient and/or the centre director of the human application centre to the Agency and TÜSEB at the 1st month, 3rd month, 6th month, 1st year and 5th year following the completion of the application protocol. The relevant reports shall include the opinion of the physician regarding the clinical course of the patient. In addition; the certificate of analysis of the finished product, containing the tests demonstrating conformity of the advanced therapy medicinal product used in the clinical application (trial) with its approved specifications, its limits and results, shall be included in the relevant reports (ANNEX-3). (2) For those who fail to provide feedback on the determined reporting periods, the evaluation processes relating to their applications shall be suspended until the deficiencies regarding their reporting obligations are remedied. (3) The tissue and cell centre and the human application centre shall record all information relating to the advanced therapy medicinal product used in the clinical application (trial) and to the patient on whom the clinical application (trial) was performed in a manner ensuring traceability, shall retain the records for a period of 30 years, and shall submit them to the Agency and TÜSEB upon request.

(4) The physician responsible for the medical treatment of the patient, the physician performing the clinical application (trial) and the human application centre may conduct retrospective scientific studies using the data obtained from the application. The relevant publications shall be notified to the Agency and TÜSEB. Matters relating to the observance of

intellectual property rights in this process are not addressed within the scope of this guideline and are subject to the relevant legislative provisions. (5) In the disposal of advanced therapy medicinal products within the scope of the clinical application (trial), the provisions of the Regulation on the Control of Medical Wastes, published in the Official Gazette No. 29959 dated 25.01.2017, and the other relevant legislative provisions shall apply. Pharmacovigilance/Biovigilance

ARTICLE 14- (1) The physician responsible for the follow-up and treatment of the patient and/or the head of the human application centre are obliged to record all adverse events/reactions and to notify the manufacturer within the shortest possible time. (2) The physician responsible for the follow-up and treatment of the patient and/or the head of the human application centre are obliged to notify all serious adverse reactions and deaths to the Agency, TÜSEB and the manufacturer within 7 days of the occurrence of the event (ANNEX-3). (3) In cases requiring the termination of treatment, written information shall be provided, together with the justification, to the Agency, TÜSEB and the manufacturer by the physician responsible for the follow-up and treatment of the patient and/or the head of the human application centre within 7 days at the latest. (4) Serious adverse reactions and deaths occurring during the clinical application (trial) shall be notified, in compliance with the legislation on the protection of personal data, by the manufacturer within 7 days of being notified of the event, to the other human application centres where the said advanced therapy medicinal product is used within the scope of the clinical application (trial) and to the physicians performing the application. (5) Where the Agency deems it necessary, it may request the manufacturer to submit a risk management plan at the time of application or at any stage of the clinical application (trial) process. The risk management plan shall contain details of the methods used for the identification, characterisation and minimisation of the risks related to the product.

SECTION SEVEN Principles Regarding Inspection Inspection, Administrative Sanctions and Penal Provisions

ARTICLE 15- (1) In accordance with this guideline, the Agency and the General Directorate of Health Services shall inspect — with or without prior notice — clinical applications (trials), the centres where clinical applications (trials) are conducted, the physicians performing the clinical application (trial), the supply, processing-manufacturing, storage/distribution centres of the products used in clinical applications (trials), the laboratories where analyses related to the clinical application (trial) are performed, and all persons and places related to the clinical application (trial), with respect to compliance with this guideline and other relevant legislative provisions. (2) Inspections to be carried out by the Agency with respect to compliance with this guideline and other relevant legislative provisions shall be conducted by Agency inspectors; inspections to be carried out by the General Directorate of Health Services shall be conducted by the relevant inspection units.

(3) During the inspections they conduct, the inspectors are authorised to request, examine and, where deemed necessary, obtain copies approved by the competent authorities of any files and documents they deem necessary from the public or private institutions and organisations they inspect and from the persons concerned, unless there is a legal impediment; to conduct counts and investigations; to take samples and, where necessary, seal them; to place products in custody, to collect or have them collected; to request any kind of assistance and information from authorised persons and concerned parties at every level on these matters; and to carry out the necessary correspondence. The inspectors are obliged to protect the confidentiality of the information obtained during the inspection. (4) Administrative penalties shall be imposed, in accordance with the relevant legislative provisions, on persons and institutions who act contrary to the matters specified in this guideline and who fail to act in accordance with the matters declared at the time of application for clinical applications (trials), and where deemed necessary, a criminal complaint shall be filed. (5) Action shall be taken, in accordance with the relevant legislative provisions, against those who fail to comply with the confidentiality principles.

SECTION EIGHT General and Final Provisions Miscellaneous and Final Provisions

ARTICLE 16- (1) Clinical trials of advanced therapy medicinal products are subject to the provisions of the Regulation on Clinical Trials of Medicinal Products for Human Use published in the Official Gazette No. 32203 dated 27.05.2023. (2) Clinical trials of tissue and cell products are evaluated within the scope of "Non-Medicinal Clinical Trials". (3) As of the date of entry into force of this guideline, the "Research Projects" that have been authorised by the General Directorate of Health Services and are still ongoing shall, within one year of the date of entry into force of the said Regulation, convert these projects into clinical trials meeting the requirements of the Regulation on Clinical Trials of Medicinal Products for Human Use published in the Official Gazette No. 32203 dated 27.05.2023. At the end of the period specified, research projects that fail to meet the requirements of the Regulation on Clinical Trials of Medicinal Products for Human Use published in the Official Gazette No. 32203 dated 27.05.2023 shall be terminated. Transitional Provisions

ARTICLE 17- (1) Until the authorisation of human application centres by the Ministry is completed, clinical applications (trials) may be performed only in universities, training and research hospitals, and secondary and tertiary private hospitals. (2) Until the first "clinical application certified training programme" to be opened by the Ministry is completed, clinical applications (trials) shall be carried out only under the responsibility of the physician from the relevant specialty field responsible for the medical treatment of the patient. (3) For the advanced therapy medicinal product manufactured, within the scope stated in the licence, at centres that already hold a Tissue Cell Processing-Manufacturing Centre licence issued by the Agency as of the date of publication of this guideline, an application for a clinical application (trial) permit may be made until 01.01.2029. The information and documents to be submitted in the application regarding the manufacturing and quality aspects of the advanced therapy medicinal products to be used within this scope shall be evaluated in accordance with the provisions of Article 6 of this Guideline.

(4) In order to make a clinical application (trial) application for the advanced therapy medicinal product to be manufactured at centres that do not hold a Tissue Cell Processing-Manufacturing Centre licence issued by the Agency as of the date of publication of this guideline, a Tissue Cell Processing-Manufacturing Centre licence and a Manufacturing Licence for the said advanced therapy medicinal product issued by the Agency must be available. (5) As of 01.01.2029, in clinical application (trial) applications, a Tissue Cell Processing-Manufacturing Centre licence/permit and a Manufacturing Licence issued by the Agency must be available for all of the advanced therapy medicinal products to be used within this scope. Entry into Force

ARTICLE 18- (1) This Guideline shall enter into force as of its date of publication. Enforcement

ARTICLE 19- (1) The President of the Agency shall execute the provisions of this Guideline.

ANNEX-1 CLINICAL IMPLEMENTATION APPLICATION FORM

Patient Identification Information:

Name and Surname: T.R. ID No:

Date of Birth: Gender:

File No:

Address:

Condition/Justification for Which the Clinical Implementation Is Requested

Medical Condition or Disease of the Patient to Whom the Implementation Will Be Applied

Diagnosis: Date of diagnosis: Specify the medical condition(s) or disease(s) (as free text): Brief clinical summary and examination findings: Brief laboratory summary: All treatments the patient has received to date related to the diagnosis and the observed responses: Specify the therapeutic area (e.g., oncology, hematology): Purpose of the implementation: Primary purpose: Secondary purposes: Is there a substudy related to the implementation? Yes No If your answer is yes, specify the full title, date, version, and relevant objectives of the substudies:

Description of the Product to Be Applied Product name: Specify the pharmaceutical form (content and manufacturing method): Specify, according to the protocol, the duration of treatment to be applied to the patient: Specify the dose to be applied according to the protocol (daily or total dose): Specify the route of administration (use standard expressions): Will the product to be applied be administered to humans for the first time? Yes No If your answer is yes, have any risk factors been identified? Yes No If your answer is yes, specify the identified risk factors: If the product to be applied has previously been administered to humans, summarize the implementations performed and their results: Specify the mechanism of action (as free text):

Category: Gene Therapy Medicinal Product Somatic Cell Therapy Medicinal Product Tissue Engineered Product

Combined Advanced Therapy Medicinal Product Yes No

Source of Cells: Autologous Allogeneic Xenogeneic

Specify the Criteria for Initiating the Implementation (List as Items):

Specify the Criteria for Terminating the Implementation (List as Items):

Specify the tests, care, and treatment planned to be performed on the patient during the implementation (Free Text):

Specify the tests, care, and treatment planned to be performed on the patient after the completion of the implementation (Free Text):

Human Implementation Center: Head of the Human Implementation Center Name and Surname: Title (Dr., ...): Specialty area: Center address: License No of the Center: E-mail address: Telephone number: T.R. ID No: Signature: Physician Responsible for the Clinical Implementation (Physician Responsible for the Medical Treatment of the Patient) Name and Surname: Title (Dr., ...): Specialty area: Work address: E-mail address: Telephone number: T.R. ID No: Role in the implementation: Signature Physician Who Will Perform the Implementation (Repeat this section if necessary) Name and Surname: Title (Dr., ...): Specialty area: Work address: E-mail address: Telephone number: T.R. ID No: Role in the implementation: Signature Head of the Licensed Tissue and Cell Center for Processing-Manufacturing Name and Surname: Title (Dr., ...): Specialty area: Center address: License No of the Center:

E-mail address: Telephone number: T.R. ID No: Signature: Other Physicians or Responsible Personnel Included in the Clinical Implementation Team (Repeat this section if necessary) Name and Surname: Title (Dr., ...): Specialty area: Work address: E-mail address: Telephone number: T.R. ID No: Role in the implementation: Signature: By means of this application form (please cross out any invalid statements, adding the date and initials next to them): • The information provided in the application is accurate, • The implementation will be carried out in accordance with the protocol, the relevant legislation, the current Declaration of Helsinki, and the Good Clinical Practice principles, • The product to be applied has been manufactured in accordance with the Good Manufacturing Practice rules, • I have provided training to the clinical implementation team (such as laboratory team, nurses) regarding the implementation and have concluded a contract, • The proposed clinical implementation is feasible, • I will submit the reports on efficacy and safety within the specified periods, I acknowledge and undertake. Applicant (Physician Responsible for the Clinical Implementation (Physician Responsible for the Medical Treatment of the Patient)

Name and surname: Date (as day/month/year): Signature:

ANNEX-2

INFORMED PATIENT CONSENT FORM

I have been sufficiently informed by the physician
..... that I have been diagnosed with; that there is not yet a sufficient level of evidence regarding the purpose, methodology, efficacy, and safety of the clinical implementation to be performed; its expected benefits, foreseeable risks, and difficulties; aspects unsuitable for my health and personal characteristics; the conditions under which the clinical implementation will be performed and continued; and that I have the right to terminate the clinical implementation at any time I wish.

NOTE: The informed patient consent form must be completed in full by the physician responsible for the medical treatment of the patient.

Patient's: Physician's Stamp Name and Surname: Signature: Signature: Date: Date:

ANNEX-3

EFFICACY AND SAFETY NOTIFICATION FORM *The physician responsible for the follow-up and treatment of the patient and/or the head of the human implementation center is obliged to record all adverse events/reactions and to report them to the manufacturer as soon as possible. The physician responsible for the follow-up and treatment of the patient and/or the head of the human implementation center is obliged to report all serious adverse reactions and deaths to the Agency, TÜSEB, and the manufacturer within 7 days of the occurrence of the event. In cases requiring the termination of treatment, the physician responsible for the follow-up and treatment of the patient and/or the head of the human implementation center must provide written information, together with the justification, to the Agency, TÜSEB, and the manufacturer within 7 days at the latest. Reports concerning clinical implementations (trials), including audit results, shall be submitted by the physician responsible for the follow-up and treatment of the patient and/or the head of the human implementation center to the Agency and TÜSEB at the end of the 1st month, 3rd month, 6th month, 1st year, and 5th year following the completion of the implementation protocol. The relevant reports must include the physician's opinion on the clinical course of the patient. In addition, the relevant reports must include the certificate of analysis of the finished product containing the tests, limits, and results demonstrating that the advanced therapy medicinal product used in the clinical implementation conforms to its approved specifications.

Purpose of Submission: Periodic Reporting Reporting Period: Safety Notification

Patient Information: Name-Surname: T.R. ID No: Diagnosis: Date of Diagnosis: Age/Gender:

Advanced Therapy Medicinal Product Used: Name (Active substance/dose/route of administration): Frequency and duration of administration:

Where the Clinical Implementation Was Performed: Human implementation center:

Which of the following is consistent with the response observed in the patient after administration? a. Complete clinical response b. Partial objective response c. Subjective response ç. Stable disease d. Disease progression e. Other:

Serious Adverse Reactions and Deaths Observed:

Declared by

Physician Responsible for the Patient's Medical Treatment Head of the Human Application Centre

I declare that the information above is accurate and accept responsibility for any possible medical/ethical/legal/financial proceedings in case of the contrary.

....../....../20.... (Name, Surname, Signature)

Annexes*: 1. Reports including the audit results relating to clinical applications (trials) 2. Statement reporting the physician's opinion on the patient's clinical course 3. Certificate of analysis

of the finished advanced therapy medicinal product used in the clinical application * Must be submitted in Periodic Reports.

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