REGULATION ON THE LICENSING OF ADVANCED THERAPY MEDICINAL PRODUCTS

Saturday, 27 May 2023 OFFICIAL GAZETTE Issue No.: 32203 REGULATION From the Turkish Medicines and Medical Devices Agency: REGULATION ON THE LICENSING OF ADVANCED THERAPY MEDICINAL PRODUCTS

PART ONE Preliminary Provisions Objective

ARTICLE 1- (1) The objective of this Regulation is to set out the procedures and principles to be applied in the licensing and pharmacovigilance of advanced therapy medicinal products in order to ensure that advanced therapy medicinal products have the desired efficacy and safety and the requisite quality, as well as the practices concerning licensed advanced therapy medicinal products. Scope

ARTICLE 2- (1) This Regulation covers advanced therapy medicinal products that are industrially prepared or manufactured by a method involving an industrial process, as well as natural and legal persons who have applied or been granted a licence for such products. (2) For combined advanced therapy medicinal products containing viable cells or tissues, irrespective of the role of the medical device, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered to be the principal mode of action of the combined product, and such combined products shall therefore always be regulated under this Regulation. (3) Procedures and practices concerning advanced therapy medicinal products which are prepared on a non-routine basis, in accordance with specific quality standards, for an individual patient following a prescription given by a medical practitioner under his/her professional responsibility in a hospital, are outside the scope of this Regulation, without prejudice to the legislation on quality and safety. (4) This Regulation does not cover products that do not contain viable cells or tissues and that do not act principally by pharmacological, metabolic or immunological means; or that contain, or consist exclusively of, non-viable human or animal cells or tissues. (5) This Regulation does not cover vaccines developed against infectious diseases. Legal Basis

ARTICLE 3- (1) This Regulation has been prepared on the basis of the provisions of the Pharmacy and Medicinal Preparations Law No. 1262 dated 14/5/1928, subparagraph (k) of the first paragraph of Article 3 of the Fundamental Law on Health Services No. 3359 dated 7/5/1987, Article 6 of the Blood and Blood Products Law No. 5624 dated 11/4/2007, and Articles 508 and 796 of the Presidential Decree No. 4 on the Organisation of Ministries and Affiliated, Related and Associated Institutions and Organisations and Other Institutions and Organisations. Definitions

ARTICLE 4- (1) In this Regulation; a) Adverse reaction/suspected adverse reaction: a harmful and unintended response to an advanced therapy medicinal product, b) Active device: the definition of active device set out in the Medical Device Regulation published in the Official Gazette No. 31499 duplicated (mükerrer) dated 2/6/2021, c) Allogeneic use: the application of tissues or cells taken from one person to another person, ç) Bioengineering product: cells or tissues which have undergone significant manipulation in order to obtain the biological characteristics, physiological functions or structural features relevant to the intended regeneration, repair or replacement, or which are not intended to be used in the recipient for the same essential function or functions as in the donor, it being understood that the manipulations listed in Annex-1 are not considered significant manipulations; 1) cells or tissues that have undergone significant manipulation in order to obtain the biological characteristics, physiological functions or structural features relevant to the intended regeneration, repair or replacement, 2) cells or tissues that are not intended to be used in the recipient for the same essential function or functions as in the donor, d) Serious adverse reaction: an adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect, e) Tissue engineered product: a product which contains or consists of bioengineering product cells or tissues, and which is presented as having properties for, or is used in or administered to, human beings with a view to regenerating, repairing or replacing a human tissue, excluding products that

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contain or consist exclusively of non-viable human or animal cells or tissues, that do not contain any viable cells or tissues, and that do not act principally by pharmacological, immunological or metabolic means; 1) containing or consisting of bioengineering product cells or tissues, 2) presented as having properties for, or used in or administered to, human beings with a view to regenerating, repairing or replacing a human tissue, f) Gene therapy medicinal product: the medicinal product defined in Annex-5, g) Hospital exemption: the clinical trial authorisations granted by the Ministry for advanced therapy medicinal products which are prepared on a basis that has not yet reached the stage of routine medical practice, in accordance with specific quality standards, for an individual patient following a prescription given by a medical practitioner under his/her professional responsibility in a hospital, ğ) Advanced therapy medicinal product: any of the following medicinal products for human use: 1) gene therapy medicinal product, 2) somatic cell therapy medicinal product, 3) tissue engineered product, h) Implantable device: the definition of implantable device set out in the Medical Device Regulation,

ı) Combined advanced therapy medicinal product: an advanced therapy medicinal product which, as an integral part of the product, contains one or more medical devices as defined in subparagraph (eee) of the first paragraph of Article 3 of the Medical Device Regulation, and in which: 1) the cell or tissue part contains viable cells or tissues, 2) the cell or tissue part containing non-viable cells or non-viable tissues, or the part containing non-viable cells or tissues, is deemed to be liable to act on the human body with an action that can be considered primary in relation to that of the device referred to, i) Xenogeneic use: the transplantation of tissues or cells between species, j) Agency: the Turkish Medicines and Medical Devices Agency, k) Autologous use: the application of tissues or cells to the person from whom they were taken, l) Priority Assessment Board: the Priority Assessment Board for Medicinal Products for Human Use of the Turkish Medicines and Medical Devices Agency, m) Somatic cell therapy medicinal product: the medicinal product defined in Annex-5, n) Medical device: the definition of medical device set out in the Medical Device Regulation, o) Excipient: any constituents of the advanced therapy medicinal product other than the active substance(s) and the packaging material, shall be meant. PART TWO General Principles General principles

ARTICLE 5- (1) A tissue engineered product may contain human or animal cells or tissues. The cells or tissues may be viable or non-viable. Cellular products may also contain additional ingredients such as bio-molecules, biomaterials, chemical substances, scaffolds or matrices. (2) Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered to be the principal mode of action of the product. (3) An advanced therapy medicinal product containing both autologous and allogeneic cells or tissues shall be assessed as being intended for allogeneic use. (4) A product that meets both the definition of a somatic cell therapy medicinal product and that of a tissue engineered product shall be assessed as a tissue engineered product. (5) A product that falls within the definition of a somatic cell therapy medicinal product or a tissue engineered product but that also meets the definition of a gene therapy medicinal product shall be assessed as a gene therapy medicinal product. PART THREE Licensing Application and Its Assessment Licensing obligation

ARTICLE 6- (1) No advanced therapy medicinal product that has not been licensed by the Agency in accordance with the provisions of this Regulation may be placed on the market. Persons who may apply for a licence

ARTICLE 7- (1) Pursuant to Article 5 of Law No. 1262, persons who wish to obtain a licence in order to place an advanced therapy medicinal product on the market must: a) for natural persons: have graduated from one of the schools providing education in the fields of pharmacy, medicine or chemistry and be authorised to practise their profession in Türkiye; b) for legal persons: employ, as the authorised person, a person possessing the qualifications specified in subparagraph (a) of the first paragraph. (2) Natural persons who are members of the dental profession and who are authorised to practise their profession in Türkiye shall also have the right to apply for a licence for advanced therapy medicinal products used in dentistry. Licensing application and the form of

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application

ARTICLE 8- (1) Natural or legal persons established in Türkiye shall apply to the Agency for a licence in order to place an advanced therapy medicinal product on the market, in accordance with Annex-5 and Annex-1 to the Regulation on the Licensing of Medicinal Products for Human Use published in the Official Gazette No. 31686 dated 11/12/2021. (2) Except in cases deemed necessary by the Agency, cases of force majeure or compulsory situations; licensing applications shall be accepted only electronically, and all correspondence during the licensing process shall be conducted exclusively in the electronic environment. Scientific advice

ARTICLE 9- (1) Upon request, the Agency may provide scientific advice to the applicant prior to the licensing application or during the licensing process, subject to a fee set out in the schedule of fees. (2) Prior to an application, separate scientific advice may be sought from the Agency on the classification of the advanced therapy medicinal product for each product and each requested indication. (3) Where the product has more than one presentation, a single application shall be made for the advice on classification covering all presentations. (4) Applications for scientific advice shall be assessed by the Agency within sixty days, and the outcome shall be notified to the applicant. Information and documents to be submitted in a licensing application

İleri Tedavi Tıbbi Ürünleri Ruhsatlandırma Yönetmeliği

MADDE 10- (1) Real or legal persons wishing to obtain a license for an advanced therapy medicinal product shall apply to the Agency together with documents prepared in accordance with Annex-5 and Annex-1 of the Regulation on Licensing of Medicinal Products for Human Use and containing the following matters:

a) The diploma of the applicant demonstrating membership in one of the professions specified in Article 7, or its notarized copy, or the graduation certificate obtained from the Council of Higher Education.

b) A certified document demonstrating that the applicant is authorized to make the application.

c) In the event the applicant is a legal person, the Turkish Trade Registry Gazette indicating the partners of the company and the duties and titles of the responsible persons.

ç) The name or trade name of the applicant, permanent address, registered electronic mail (KEP) address, telephone and fax numbers.

d) The name, permanent address, telephone number and fax number of the manufacturing site/sites for all manufacturing steps.

e) The name of the advanced therapy medicinal product.

f) A statement of all active substance/substances and excipients contained in the advanced therapy medicinal product, qualitatively and quantitatively, using the common names of the active substance/substances.

g) A description of the manufacturing method.

ğ) Therapeutic indications, contraindications and adverse reactions.

h) Posology, pharmaceutical form, method and route of administration, shelf life, package size.

ı) Taking into consideration the potential risks posed to the environment by the advanced therapy medicinal product in question, the measures and safety precautions to be taken regarding the storage of the advanced therapy medicinal product, its administration to patients, and the disposal of waste products in accordance with the provisions of the Waste Management Regulation published in the Official Gazette dated 2/4/2015 and numbered 29314.

j) A description of the control methods used by the manufacturer, where applicable, presented in accordance with the pharmacopoeia (where deemed appropriate by the Agency, some of these analyses, tests and controls listed on a product basis may be waived, provided that quality, efficacy and safety are not affected.).

k) The results of pharmaceutical tests consisting of physicochemical, biological or microbiological tests.

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l) The results of preclinical tests consisting of toxicological and pharmacological tests.

m) In the event the clinical trials are conducted in Türkiye; information or documentation that the Agency has granted a research permit for the clinical trials in question, and in the event they are conducted outside Türkiye;

1) The statement of the applicant containing an explanation that the clinical trials comply with the scientific and ethical requirements regulated in the Regulation on Clinical Trials of Medicinal Products for Human Use.

2) For clinical trials authorized by the Agency, the Australian Therapeutic Goods Administration (TGA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), or competent authorities that are founding or permanent members of the International Council for Harmonisation (ICH); information or documentation that the research permit for the clinical trials in question has been granted by the Agency, the Australian Therapeutic Goods Administration (TGA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), or competent authorities that are founding or permanent members of the International Council for Harmonisation (ICH).

3) For clinical trials authorized by health authorities other than the Agency, the Australian Therapeutic Goods Administration (TGA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), or competent authorities that are founding or permanent members of the International Council for Harmonisation (ICH); a Good Clinical Practice (GCP) inspection report demonstrating that the clinical trials in question are appropriate, conducted in accordance with the relevant guideline requirements by the Agency, the Australian Therapeutic Goods Administration (TGA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), or competent authorities that are founding or permanent members of the International Council for Harmonisation (ICH).

n) In the event of importation of the advanced therapy medicinal product, a document issued by the licensor company demonstrating that the real or legal person performing the importation is the sole authorized representative for the importation of the product in question into Türkiye, its licensing and sale in Türkiye.

o) In the event the advanced therapy medicinal product is manufactured under license, a document issued by the licensor company demonstrating that the real or legal person performing the manufacturing is the sole authorized representative for the licensing, manufacturing and sale of the product in question in Türkiye.

ö) In the event the applicant is not the manufacturer for advanced therapy medicinal products to be manufactured in Türkiye, the contract manufacturing agreement concluded with a manufacturer possessing the conditions specified in the Regulation on Manufacturing Sites of Medicinal Products for Human Use published in the Official Gazette dated 21/10/2017 and numbered 30217, and the registry certificates of the parties.

p) For the imported product or product manufactured under license for which an application is made, the list of other country/countries where a licensing application has been filed, and prior to the issuance of the license in Türkiye, a certified copy of the license approved by the health authority of one of the countries on the list, or a Certificate of a Pharmaceutical Product, or in cases where these documents are not issued, information or documentation accepted by the Agency demonstrating that the licensing of the product by the relevant authority has been approved.

r) In the event that, for the advanced therapy medicinal product for which an application is made, the licensing application has been rejected by the competent authority of other countries or has been withdrawn by the applicant, or the licensed product has been withdrawn or its license has been suspended, the list of these countries, together with the name of the advanced therapy medicinal product in the country in question, and the date and justification of the procedures carried out.

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s) The summary of product characteristics prepared in accordance with Article 32, and the patient information leaflet prepared in accordance with the Regulation on Package Information, Patient Information Leaflet and Tracking of Medicinal Products for Human Use published in the Official Gazette dated 25/4/2017 and numbered 30048, and samples of packaging in the size and design in which the advanced therapy medicinal product will be placed on the market; and in the event of importation or licensed manufacturing of the advanced therapy medicinal product, additionally, where available, the summary of product characteristics, patient information leaflet and packaging samples of the current reference medicinal product of the product, approved by the competent authorities of the other country or countries where the product is placed on the market and indicating the date of approval, if available.

ş) The pharmacovigilance-related documents required to be submitted during the licensing application in accordance with the Regulation on the Safety of Medicines published in the Official Gazette dated 15/4/2014 and numbered 28973.

t) Within the scope of the Regulation on Promotional Activities of Medicinal Products for Human Use published in the Official Gazette dated 3/7/2015 and numbered 29405, the document describing the scientific service and the address, KEP address, telephone and fax numbers of this service.

u) An assessment of the potential environmental risks posed by the advanced therapy medicinal product.

ü) Where applicable; documents demonstrating that the advanced therapy medicinal product for which a licensing application is filed complies with the requirements specified in Article 33 or Article 36 of the Regulation on Licensing of Medicinal Products for Human Use.

v) Regarding the active substance manufacturing sites of advanced therapy medicinal products, in addition to the written declaration submitted in accordance with the second paragraph of Article 14 of the Regulation on Manufacturing Sites of Medicinal Products for Human Use; for active substance/substances included in the scope of inspection by the Agency, except for products deemed appropriate to be submitted after the licensing application in the assessment made by the Priority Assessment Board, a document issued by the Agency for the active substance manufacturing site/sites demonstrating that manufacturing is carried out in accordance with internationally accepted good manufacturing practice guidelines; for manufacturing steps for which no document is issued by the Agency, a document accepted by the Agency, issued by an authorized health authority, demonstrating that manufacturing is carried out in accordance with internationally accepted good manufacturing practice guidelines; or, for active substance manufacturing site/sites operating in Türkiye, a Manufacturing Site Licence Certificate;

For active substances not included in the scope of inspection by the Agency and, where applicable, for the manufacturing site/sites of the intermediate products used in the manufacturing process of the active substance, respectively;

1) A document issued by an authorized health authority for these sites, demonstrating that the active substance/substances and, where applicable, the intermediate product/products used in the manufacturing process of the active substance are manufactured in accordance with internationally accepted good manufacturing practices. In cases where this document is not physically issued, information or documentation accepted by the Agency demonstrating that the active substance/substances are manufactured in accordance with internationally accepted good manufacturing practices.

2) In cases where it is evidenced that the documents specified in subitem (1) cannot be submitted, an inspection report issued as a result of the inspection conducted in accordance with the second paragraph of Article 14 of the Regulation on Manufacturing Sites of Medicinal Products for Human Use for the active substance/substances, by the responsible manager of the finished product manufacturing site, and a declaration accepted by the Agency.

3) For the manufacturing site/sites of intermediate products used in the manufacturing process of the active substance, in cases where the documents specified in subitem (1) cannot be

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submitted, a declaration, issued on the basis of the inspection conducted by the active substance manufacturer, that manufacturing is carried out in accordance with good manufacturing practices, and, if requested by the Agency, the inspection report.

y) Except for those deemed appropriate to be submitted after the licensing application in the assessment made by the Priority Assessment Board, for advanced therapy medicinal products, for all manufacturing steps of the finished product, the document belonging to the manufacturing site; a document issued by the Agency or, for manufacturing steps for which no document is issued by the Agency, a document accepted by the Agency, issued by an authorized health authority, demonstrating that manufacturing is carried out in accordance with internationally accepted good manufacturing practice guidelines; or in cases where this document is not physically issued, information or documentation accepted by the Agency demonstrating that manufacturing is carried out in accordance with internationally accepted good manufacturing practice guidelines; or a document issued by the official authorities of countries having a mutual recognition agreement with our country, demonstrating that manufacturing can be carried out within the framework of good manufacturing practices; or a manufacturing site licence certificate for advanced therapy medicinal products to be manufactured in Türkiye.

(2) In addition to the requirements specified in the first paragraph, in the licensing application for an advanced therapy medicinal product containing a medical device, biomaterials, scaffolds or matrices, a description of the physical characteristics and performance of the product and of the product design methods shall be submitted in accordance with Annex-1 of the Regulation on Licensing of Medicinal Products for Human Use.

(3) All official documents obtained from abroad must bear an apostille annotation or consular approval. While the submission of all documents in Turkish is the rule, the parts deemed appropriate by the Agency may be submitted in English. However, it is mandatory to submit those prepared in languages other than English together with their sworn Turkish translation. In cases where the sworn translation cannot be performed in our country, a sworn translation certificate translated into Turkish or English in another country may be accepted.

(4) Detailed summaries of the documents concerning the results of physicochemical, biological or microbiological tests, preclinical tests and clinical trials specified in subitems (j), (k) and (l) of the first paragraph, prepared in accordance with Article 11 of the Regulation on Licensing of Medicinal Products for Human Use, must be submitted.

(5) It is mandatory to notify the Agency of any updated information among the information contained in this Article.

Preliminary evaluation of the licensing application

ARTICLE 11- (1) Marketing authorization applications may be submitted by applicants throughout the year. (2) Whether the application dossier submitted to the Agency for the purpose of obtaining a marketing authorization for an advanced therapy medicinal product constitutes a complete application with respect to the documents required to be submitted in accordance with the nature of the application and the electronic marketing authorization application requirements shall be examined by the Agency subject to a preliminary assessment. This assessment shall be carried out in the order of the application date. However, the preliminary assessment procedures for applications deemed appropriate by the Agency Priority Assessment Board to be evaluated as priority or high priority in marketing authorization procedures shall be carried out on a priority basis. (3) The necessary assessment shall be carried out within thirty days of the application dossier reaching the Agency, and the result shall be notified to the applicant. In the event that the application is found to be incomplete, the applicant shall complete the deficiencies within thirty days. The second preliminary assessment to be carried out after the completion of the deficiencies and their submission to the Agency shall also be concluded within thirty days.

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Rejection of the application on procedural grounds

ARTICLE 12- (1) In the following circumstances, the application shall be rejected on procedural grounds and returned to its owner: a) Failure to submit a second application within the specified period by completing the deficiencies identified in the first preliminary assessment carried out by the Agency under Article 11, or failure to complete the deficiencies related to the first preliminary assessment in the second preliminary assessment application. b) Failure to pay the authorization fee within sixty days following the date on which the applicant is officially notified that the marketing authorization procedure has been completed.

c) Failure to submit to the Agency, at the latest within thirty days, the information and documents requested by the Agency outside the preliminary assessment procedure, or the necessary explanation regarding the inability to submit such information and documents together with the date information on which they will be submitted. ç) Failure to submit the required information and documents to the Agency by the end of the period specified in the second paragraph. (2) The date information submitted for the information and documents to be submitted to the Agency pursuant to paragraph (c) of the first paragraph must be found appropriate by the Agency with respect to current scientific requirements and must not exceed three years. The Agency may apply an exception to this matter for conditional marketing authorization applications made within the scope of Article 33 of the Regulation on Licensing of Human Medicinal Products. (3) In the event that a new marketing authorization application is made for advanced therapy medicinal products whose application has been rejected on procedural grounds pursuant to paragraph (c) of the first paragraph, for the priority decisions given by the Priority Assessment Board, if any, in marketing authorization or inspection procedures for the products in question, and for the analyses conducted by the Department of Analysis and Control Laboratories; if the analysis reports prepared regarding the concluded and ongoing analyses are found appropriate, they shall be deemed valid and the marketing authorization procedures for the relevant products shall be initiated directly. (4) In the event that a new marketing authorization application is made for advanced therapy medicinal products whose application has been rejected on procedural grounds pursuant to paragraph (c) of the first paragraph, the current dossier reflecting the changes approved by the Agency and a commitment letter stating that the changes have been reflected shall be submitted in the dossier.

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Marketing authorization period

ARTICLE 13- (1) During the preliminary assessment, the Agency examines the marketing authorization application in accordance with the marketing authorization criteria and officially notifies the applicant of the acceptance or rejection of the application. The notification of acceptance of the application shall not be considered as the commencement of the marketing authorization procedure. For complete marketing authorization applications whose assessment has been completed and accepted, the applicant shall be additionally notified by the Agency that the marketing authorization procedure has commenced. The date of this notification shall be considered as the marketing authorization procedure commencement date. The marketing authorization procedure shall be concluded within the following two hundred and ten days. In addition, the period elapsed for the advanced therapy medicinal product to be tested in the Agency's laboratory or in a laboratory accepted by the Agency for this purpose, in order for the Agency to determine the declared accuracy of the control methods described in the documents submitted in the application pursuant to subparagraphs (i) and (j) of the first paragraph of Article 10 by the manufacturer and used in the manufacture of the advanced therapy medicinal product; the period elapsed for assessments by external organizations; the period elapsed for official holidays excluding weekend holidays and the period elapsed for states of emergency shall not be included in the marketing authorization period. (2) For advanced therapy medicinal products for which a marketing authorization application is made pursuant to Article 38, the marketing authorization period of two hundred and ten days shall be ninety days. (3) In cases where additional information and documents are requested from the applicant by the Agency during the marketing authorization procedure under Articles 10, 31, and 38, and Articles 33 and 36 of the Regulation on Licensing of Human Medicinal Products, where necessary, the marketing authorization period shall be suspended until the relevant information and documents are obtained.

Prioritization in marketing authorization procedures

ARTICLE 14- (1) Marketing authorization procedures shall be carried out through electronic systems in accordance with the marketing authorization procedure commencement date. However, applications for products applied for pursuant to Articles 9 and 38 and Articles 33 or 36 of the Regulation on Licensing of Human Medicinal Products, which are deemed appropriate by the Agency Priority Assessment Board, shall be evaluated on a priority basis in marketing authorization procedures. (2) The marketing authorization procedures for products in this situation shall be completed within the periods specified in the relevant guidelines published by the Agency. (3) The provisions of the first and third paragraphs of Article 13 regarding the suspension of the period shall also apply to the advanced therapy medicinal products designated within the scope of this Article.

Marketing authorization criteria

ARTICLE 15- (1) In granting a marketing authorization for an advanced therapy medicinal product, the criteria to be taken into consideration by the Agency regarding the product are as follows: a) Quality being demonstrated by appropriate technological and pharmaceutical characteristics. b) Efficacy being proven under the proposed conditions of use. c) Safety being proven.

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Assessment of the application

ARTICLE 16- (1) In assessing applications, at minimum the following matters shall be taken into consideration: a) Scientific and technological examination of the documents proving the efficacy and safety of a product and demonstrating its quality. b) Performance of the analysis of the advanced therapy medicinal product with respect to the quality control of the finished product specifications using internationally accepted analytical methods or the quality control method proposed by the company as the basis for the product's marketing authorization. c) Performance of the analyses specified in subparagraph (b), on a per-application basis, in the Agency's laboratories or in laboratories deemed appropriate by the Agency for this purpose, in order to be decided upon by the Agency. ç) Where applicable, the control tests conducted to determine whether microbial contamination is present proving the safety of the product, and the declaration of the source from which the plasma used in the preparation of these products is obtained, and the submission of the certificates of analysis. d) If the product contains materials of animal origin, the submission of the applicant's declaration that there is no risk of causing Transmissible Spongiform Encephalopathy (TSE) and, if available, the official authority letter; if the product contains blood and plasma products, the submission of viral contamination tests.

Rejection of the application on substantive grounds

ARTICLE 17- (1) The advanced therapy medicinal product for which a marketing authorization application has been submitted shall be subjected to analysis. In the event that nonconformity is found in the first analysis, a corrected sample shall be requested from the company and the analysis shall be repeated. In the event that nonconformity is also found in the second analysis, an assessment meeting shall be held with company representatives regarding the analytical method, the analytical method for the new sample shall be determined, and the analysis shall be carried out. In the event that nonconformity is also found in the third analysis, a final assessment meeting shall be held with company representatives, the analytical nonconformity shall be described, and a new analytical method shall be determined and the analysis shall be conducted for the last time. Notwithstanding the completion of the specified analysis steps, in cases where it is determined that the qualitative and quantitative formulation is nonconforming and that the declared specifications are outside the acceptable limits, the marketing authorization application shall be rejected on substantive grounds. (2) In the process of assessing the application made to the Agency for the marketing authorization of an advanced therapy medicinal product, for each of the circumstances specified below, after the applicant is granted a maximum of three written and two oral rights of reply, and as a result of the assessment of the documents and information submitted, in cases where it is determined that the product's: a) Potential risk under normal conditions of use exceeds the beneficial effect of the treatment, or b) Therapeutic effect is insufficient, or its therapeutic effect cannot be adequately proven, or c) Qualitative and quantitative formulation and data relating to the quality of the product are nonconforming, the marketing authorization application shall be rejected on substantive grounds. (3) Information regarding the assessment of marketing authorization applications rejected within the scope of this Article shall not be published.

Notification of rejection of the application on substantive grounds and appeal

ARTICLE 18- (1) In the event of rejection of the marketing authorization application on substantive grounds, the decision shall be notified to the applicant with its reasoning, or if notification cannot be made, it may be announced on the Agency's website. The applicant has the right to appeal to the Agency within forty-five days from the date of notification or announcement of the decision. If no appeal is made within forty-five days, the application documents shall be returned to the owner. In the event that the applicant does not take delivery of the documents; the provisions of the Regulation on State Archive Services published in the Official Gazette dated 18/10/2019 and numbered 30922 shall apply. (2) The appeal shall be assessed by the Agency within ninety days and the result shall be notified to the applicant. During the assessment of the

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appeal, if deemed necessary, the applicant shall be granted the right to oral explanation and defense. (3) The decision resulting from the assessment of the appeal shall be final, and no appeal may be made to the Agency regarding the said decision. (4) The rejection of the application shall not prevent the applicant from making a new marketing authorization application.

Granting of the marketing authorization

ARTICLE 19- (1) Upon examination and evaluation of the documents submitted to the Agency by the applicant, a marketing authorization shall be issued for the advanced therapy medicinal product found to be in compliance with the provisions set forth in the Regulation, and the applicant shall be informed thereof. (2) Except for variation applications within the scope of the Regulation on Variations to Licensed Human Medicinal Products published in the Official Gazette dated 18/12/2021 and numbered 31693; a second marketing authorization shall not be issued to the same company for products having the same qualitative and quantitative composition, the same indication, and the same route of administration as an advanced therapy medicinal product licensed by the Agency. However, applications concerning advanced therapy medicinal products that are scientifically and technologically demonstrated to have superiority over a licensed advanced therapy medicinal product shall be separately evaluated by the Agency. (3) The same natural or legal person may not use a different trade name for advanced therapy medicinal products containing the same active substance(s) and having the same indication, for different strengths, routes of administration, or pharmaceutical forms. (4) A marketing authorization may not be granted to an advanced therapy medicinal product under the same name as a human medicinal product, traditional herbal medicinal product, medical device, or homeopathic medicinal product. (5) Licenses, certificates, and other internationally valid documents may also be prepared by the Agency as physical documents. (6) The list of advanced therapy medicinal products licensed by the Agency shall be published on the official website of the Agency and, once a year, in the Official Gazette. (7) The Agency may prepare a public assessment report that does not contain commercially confidential information regarding pharmaceutical and non-clinical tests, clinical trials, risk management system, and pharmacovigilance system of the relevant advanced therapy medicinal product. This assessment report shall be updated when new information that is important for the evaluation of the quality, safety, or efficacy of the relevant advanced therapy medicinal product is obtained. The public assessment report shall include a summary containing, in particular, a section related to the conditions of use of the advanced therapy medicinal product.

Validity Period of the Marketing Authorization

ARTICLE 20- (1) The evaluation regarding the renewal of the marketing authorization shall be carried out by the Agency five years after the date of issuance, taking into account the benefit/risk balance. The marketing authorization holder shall submit to the Agency, nine months before the expiration of the five-year period, a file containing all current information on efficacy, safety, and quality, including the evaluation of suspected adverse reaction reports and periodic benefit/risk evaluation reports in accordance with the provisions of the Regulation on the Safety of Medicines, as well as information regarding all variations made since the licensing of the product. (2) Once the marketing authorization has been renewed once, the marketing authorization shall remain valid indefinitely, unless the Agency decides to conduct an additional five-year renewal evaluation for the relevant advanced therapy medicinal product for pharmacovigilance-related reasons, including insufficient exposure of patients to the product. (3) In cases where five-year pharmacovigilance data for the product cannot be submitted due to the product not having been placed on the market, the evaluation regarding the validity of the marketing authorization shall be carried out after the available pharmacovigilance data is prepared and submitted in accordance with the relevant legislative provisions.

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Suspension of the Marketing Authorization

ARTICLE 21- (1) In relation to a licensed product; a) The emergence of harmful effects under normal conditions of use, b) The determination that the product has no therapeutic effect or that its therapeutic effect is insufficient, c) The production of the product with a formula different from the formula on which the marketing authorization was based, ç) The making of changes to the formula, strength, pharmaceutical form, packaging, and summary of product characteristics on which the marketing authorization was based, without the knowledge and/or approval of the Agency, d) The failure of the marketing authorization holder to take into account scientific and technical progress in terms of manufacturing and control methods and the failure to make the necessary changes to ensure that the advanced therapy medicinal product is manufactured and controlled in accordance with generally accepted scientific methods, or the failure to submit such changes to the approval of the Agency if changes have been made, e) The failure to take into account the warning issued for products found to be defective as a result of market surveillance and the continuation of defective production, f) The determination that the manufacturing method and the control methods used by the manufacturer specified in subparagraphs (g) and (i) of the first paragraph of Article 10 are not applied as stated, g) Non-compliance with the legislative provisions regarding packaging information and patient information leaflet, ğ) The failure to make and/or notify the necessary updates in the summary of product characteristics and the patient information leaflet, h) The failure of the marketing authorization holder to respond to Agency instructions regarding the advanced therapy medicinal product within the period determined by the Agency, ı) The determination that the documents submitted in an application made for an advanced therapy medicinal product in accordance with the provisions of this Regulation contain errors that would affect the quality, efficacy, or safety of the product, or the loss of validity of the submitted documents, i) The decision to suspend the marketing authorization as a result of the benefit/risk evaluation made by the Agency for notifications received within the framework of pharmacovigilance practices, j) The determination of circumstances requiring the suspension of the marketing authorization in accordance with the provisions of the Regulation on the Safety of Medicines, k) In the case of transfer of the marketing authorization, the failure to submit, within the specified period, by the transferee, the name, surname, address, telephone number, and KEP address of the transferee, together with the updated summary of product characteristics of the advanced therapy medicinal product, the patient information leaflet, a sample of each of the inner and outer packaging, and in transfers made through a notary, the original of the previously issued marketing authorization for the product in question; and in cases where the updated summary of product characteristics and the patient information leaflet cannot be submitted, the complete undertaking prepared by the transferee stating that all necessary changes and updates regarding the summary of product characteristics and the patient information leaflet of the advanced therapy medicinal product will be made in accordance with the relevant guidelines after the completion of the marketing authorization transfer procedures of the advanced therapy medicinal product, and that no sales permit application will be made without obtaining approval, l) The failure of the marketing authorization holder to place on the market, within six months from the date of request, an advanced therapy medicinal product of importance in terms of public health and sustainability of access to medicines, despite the request of the Agency, m) In marketing authorization transfer applications made within the scope of Article 25, the failure of the marketing authorization holder to submit the document demonstrating that manufacturing is carried out in accordance with good manufacturing practice guidelines at the manufacturing site(s) on which the marketing authorization is based, and the Manufacturing Site Permit for active substance manufacturing site(s) operating in Türkiye, upon the determination of non-compliance with at least one of the above circumstances and its substantiation, the marketing authorization of the advanced therapy medicinal product shall be suspended by the Agency in accordance with the result of the evaluation made by the Agency, which shall also include safety, regarding the relevant non-compliance, or upon the request of the marketing authorization holder for the cancellation of

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the product's marketing authorization. (2) The production or importation for placing on the market of an advanced therapy medicinal product whose marketing authorization has been suspended shall be halted. Advanced therapy medicinal products that have already been imported or produced may not be placed on the market unless otherwise decided by the Agency. The decision regarding advanced therapy medicinal products present on the market shall be given by the Agency, taking into account the grounds for the suspension of the marketing authorization. (3) The list of advanced therapy medicinal products whose marketing authorizations have been suspended shall be published on the official website of the Agency. (4) In cases where products whose marketing authorizations have been suspended for the reasons specified in subparagraphs (i) or (j) of the first paragraph are intended to be placed on the market again, an application shall be made to the Agency for the lifting of the suspension, in accordance with the procedures determined by the Agency, together with a commitment to place the product on the market within six months at the latest. If deemed appropriate by the Agency, the marketing authorization of the product shall be lifted from suspension. For products that are not placed on the market within the committed period, proceedings shall be initiated in accordance with Article 22.

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Cancellation of the Marketing Authorization

ARTICLE 22- (1) In the presence of one of the following circumstances, the marketing authorization issued for an advanced therapy medicinal product shall be cancelled: a) In cases where documents proving the contrary of the grounds for suspension are not submitted by the marketing authorization holder within six months at the latest from the date of suspension, or the documents explaining the situation are not deemed appropriate by the Agency, for products whose marketing authorization has been suspended due to one or more of the reasons enumerated in the first paragraph of Article 21. b) Upon the request of the marketing authorization holder and the approval of the Agency, provided that there is no seizure or injunction decision notified to the Agency on the marketing authorization. c) The failure of the marketing authorization holder to place on the market, within six months from the date of request, an advanced therapy medicinal product of importance in terms of public health and public finance, despite the request of the Agency. (2) In cases where applicants request the cancellation of existing marketing authorizations in variation applications made within the scope of the Regulation on Variations to Licensed Human Medicinal Products, the existing marketing authorizations shall be cancelled simultaneously without suspension upon issuance of the marketing authorization for the products for which the variation application was made. (3) The production or importation of an advanced therapy medicinal product whose marketing authorization has been cancelled shall be halted. The decision regarding advanced therapy medicinal products currently present on the market shall be given by the Agency, taking into account the grounds for the cancellation of the marketing authorization. (4) Marketing authorizations suspended upon the cancellation procedure being deemed appropriate in accordance with subparagraph (b) of the first paragraph shall be published on the official website of the Agency for a period of six months. Marketing authorizations announced as suspended on the official website of the Agency within the scope of this paragraph may, upon request, be transferred, provided that the conditions for a marketing authorization transfer application are met, to natural or legal persons who have undertaken to place the product on the market and who fulfill the conditions for applying for a marketing authorization as determined by this Regulation, provided that such persons so request and the marketing authorization holder consents. The cancellation procedures for marketing authorizations for which a transfer application has been made shall not be continued. (5) In cases where products for which cancellation of the marketing authorization is requested in accordance with subparagraph (b) of the first paragraph are advanced therapy medicinal products that are co-marketed and for which the marketing authorization application was made with a complete and full file, the marketing authorization holder shall be obliged to submit to the Agency the list of other advanced therapy medicinal product(s) subject to co-marketing. (6) The suspension period of marketing authorizations of products suspended in accordance with subparagraphs (l) and (m) of the first paragraph of Article 21 may be extended by a further six months if deemed appropriate by the Agency. (7) For advanced therapy medicinal products that are on the list of medicines from abroad or that would pose a public health risk due to inability to be supplied, the Agency may extend the marketing authorization suspension period regarding the matters covered by the fourth and sixth paragraphs. (8) The list of advanced therapy medicinal products whose marketing authorizations have been cancelled by the Agency shall be published on the official website of the Agency. (9) In cases where the Agency decides to cancel a conditional marketing authorization as a result of the annual evaluation for an advanced therapy medicinal product conditionally licensed within the scope of Article 34 of the Regulation on Licensing of Human Medicinal Products, the marketing authorization cancellation procedures for the products in question shall be carried out in accordance with Article 21 without performing a marketing authorization suspension procedure.

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Loss of the Marketing Authorization or the Product File

ARTICLE 23- (1) In the event of the loss of a marketing authorization issued by the Agency, the marketing authorization holder shall make an application to the Agency for the lost marketing authorization together with a newspaper announcement demonstrating the loss of the marketing authorization. In this case, a new marketing authorization certificate shall be issued. (2) In the event of the loss of the marketing authorization file of an advanced therapy medicinal product for which a marketing authorization application has been made, an application for the lost marketing authorization file shall be made to the Agency by the applicant or the marketing authorization holder. For applications deemed justified by the Agency, a copy of the file shall be provided to the applicant.

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Responsibility of the Marketing Authorization Holder

ARTICLE 24- (1) The marketing authorization holder is obliged to notify the Agency at least thirty days in advance that it will be unable to place a product on the market, should such circumstance arise for any reason. (2) The marketing authorization holder is responsible to the Agency for the following matters concerning the advanced therapy medicinal product for which it holds the authorization: a) Manufacture of the advanced therapy medicinal product in accordance with the specifications provided in the application dossier and accepted by the Agency. b) Taking into account scientific and technical progress with regard to manufacturing and control methods, and submitting to the approval of the Agency any and all modifications necessary to ensure that the advanced therapy medicinal product is manufactured and controlled by generally accepted scientific methods. c) Updating the Summary of Product Characteristics and the patient information leaflet, where necessary, to ensure the correct and safe use of the advanced therapy medicinal product. ç) Notifying the Agency of any modification relating to the advanced therapy medicinal product in accordance with the provisions of the relevant guideline, should any such modification occur. d) Providing timely responses to matters requested by the Agency concerning the advanced therapy medicinal product. e) Fulfilling the obligations specified in the Regulation on the Safety of Medicines within the framework of pharmacovigilance activities. f) Taking the necessary measures to prevent infections that may be transmitted through the advanced therapy medicinal product. g) Ensuring the availability of the advanced therapy medicinal product for which it holds the authorization on the market. ğ) Notifying the Agency immediately, with all details, of any and all measures taken in cases where the authorization of the advanced therapy medicinal product is suspended or withdrawn on grounds of efficacy or the protection of public health. h) Notifying the Agency in cases where, for reasons of quality, efficacy, or safety, advanced therapy medicinal products that are imported, exported, or manufactured in our country under license have their authorization suspended, revoked, withdrawn from the market, or recalled in other countries where they are authorized; or in cases where the authorization application is rejected in other countries where an application has been submitted, or the application is withdrawn by the applicant. ı) Payment of the determined fees and charges relating to advanced therapy medicinal products. (3) The marketing authorization holder or applicant is obliged to submit an application in accordance with the principles specified in this Regulation, to fulfill the commitments presented to the Agency, and to confirm the accuracy of the information and documents submitted to the Agency, and accepts any and all legal liability arising from the consequences of such information and documents. (4) The marketing authorization holder or applicant is responsible for retaining the originals of all documents submitted to the Agency concerning the product and for presenting them to the Agency upon request. (5) The authorization of an advanced therapy medicinal product shall not affect the legal and criminal liability of the marketing authorization holder. (6) The Agency may request additional information and documents for products for which an authorization has been issued in accordance with current scientific requirements. The marketing authorization holder is obliged to submit the information and documents requested by the Agency to the Agency within the specified period. (7) Marketing authorization holders are obliged to register products in the Agency's information management system in accordance with the requirements determined by the Agency and to ensure that such data are kept up to date.

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****Transfer of Marketing Authorization****

ARTICLE 25- (1) The marketing authorization of an advanced therapy medicinal product authorized by the Agency may be transferred. The following documents shall be submitted to the Agency for marketing authorization transfer procedures: a) A court decree evidencing the transfer of the authorization by the court, a decision by the enforcement office evidencing the forced sale of the authorization through compulsory execution, or a certificate of registry extract belonging to the parties subject to the transfer agreement, together with a contract executed before a notary public and containing the following matters: 1) The name, authorization date, and authorization number of the advanced therapy medicinal product subject to the transfer procedure. 2) The names and addresses of the natural or legal persons who will transfer and who will receive the authorization. 3) A minutes evidencing that the current advanced therapy medicinal product dossier, which has been approved by the Agency and is complete and updated, has been delivered in full to the transferee. b) Documents demonstrating that the transferee possesses the capacity to fulfill all responsibilities expected of a marketing authorization holder: 1) A diploma original or notarized copy evidencing membership in one of the professions specified in Article 7 for persons eligible to apply for a marketing authorization, or a graduation certificate obtained from the Council of Higher Education. 2) In the case of a legal person, the Turkish Trade Registry Gazette indicating the shareholders of the company and the positions and titles of the responsible persons. 3) Documents relating to the pharmacovigilance officer within the scope of the Regulation on the Safety of Medicines. 4) A document describing the scientific service within the scope of the Regulation on Promotional Activities for Human Medicinal Products, together with the address, telephone number, and KEP (Registered Electronic Mail) address of such service. c) The name, surname, address, telephone number, and KEP address of the transferee, together with the updated Summary of Product Characteristics, patient information leaflet, one sample each of the inner and outer packaging of the advanced therapy medicinal product, and in the case of transfers executed through a notary, the original of the previously issued authorization for the product in question; in cases where the updated Summary of Product Characteristics and patient information leaflet cannot be submitted, a letter of undertaking prepared in full by the transferee stating that all necessary variations and updates relating to the Summary of Product Characteristics and patient information leaflet of the advanced therapy medicinal product will be carried out in accordance with the relevant guidelines after the completion of the marketing authorization transfer procedures of the advanced therapy medicinal product, and that no sales permit application will be made without obtaining approval, a document demonstrating that manufacturing is carried out at the manufacturing site(s) on which the authorization is based in accordance with good manufacturing practice guidelines, and a Manufacturing Site Authorization Certificate for active substance manufacturing site(s) operating in Turkey. ç) In the case of importation of the advanced therapy medicinal product, a document issued by the licensor company evidencing that the natural or legal person importing the product in question is the sole authorized representative for the importation into Turkey, authorization in Turkey, and sale of the product in question, and in the case of co-marketing, a document evidencing that co-marketing authorization has been granted to a natural or legal person other than the sole authorized representative in Turkey, together with the written approvals of the natural or legal persons who will engage in co-marketing regarding the co-marketing arrangement. d) In the case where the advanced therapy medicinal product is manufactured under license, a document issued by the licensor company evidencing that the natural or legal person manufacturing the product is the sole authorized representative for the authorization in Turkey, manufacture, and sale of the product in question, and in the case of co-marketing, a document evidencing that co-marketing authorization has been granted to a natural or legal person other than the sole authorized representative in Turkey, together with the written approvals of the natural or legal persons who will engage in co-marketing regarding the co-marketing arrangement. e) In cases where the applicant for advanced therapy medicinal products to be manufactured in Turkey is not the manufacturer, a

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contract manufacturing agreement concluded with a manufacturer possessing the conditions specified in the Regulation on Human Medicinal Product Manufacturing Facilities and the Regulation on the Quality and Safety of Human Tissues and Cells and Centers Related Thereto published in the Official Gazette No. 27742 dated 27/10/2010, together with the certificate of registry extract belonging to the parties. (2) In the case of transfers executed through a notary public, the following provisions shall apply in addition to the documents enumerated in paragraph one: a) A letter of undertaking prepared by the transferee stating that no modification has been made to the advanced therapy medicinal product during the transfer application shall be submitted. b) Provided that the circumstances deemed necessary by the Agency in accordance with the relevant guideline published by the Agency are excepted, upon complete submission of a letter of undertaking prepared by the transferee stating that all necessary variations and updates relating to the human medicinal product will be carried out following the completion of the transfer procedure, the necessary updates relating to the current product dossier and the procedures for remedying any deficiencies, if any, shall be carried out after the marketing authorization transfer procedures of the human medicinal product have been completed, in accordance with the relevant guidelines, and no application for a sales permit may be made without obtaining approval. However, in circumstances deemed necessary by the Agency, an application for the updates relating to the current product dossier and the procedures for remedying any deficiencies, if any, may be requested. c) Upon request, subject to the written and notarized mutual agreement of the transferor and transferee companies, the manufacture of products bearing old barcodes and their placement on the market solely by the transferee company shall be permitted for a period of six months after the date on which the new authorization is issued. The control procedures relating to the manufacturing notifications of products in this situation shall be carried out through the Pharmaceutical Tracking System. Such products may remain on the market until their expiry dates. For products transferred at the time of importation, the placing on the market by the transferor company shall be discontinued. Products bearing old barcodes may be imported by the transferor company for a period of six months after the date on which the new authorization is issued, subject to the written and notarized mutual agreement of the transferor and transferee companies. However, such products may be placed on the market by the transferor company subject to the condition that a manufacturing notification is submitted to the pharmaceutical tracking system by the transferor company and that the products are transferred to the transferee company through the pharmaceutical tracking system. (3) In cases where the licensor company changes the natural or legal person it has authorized regarding the authorization/sale/manufacture of the product in question in Turkey, in addition to the documents enumerated in paragraph one, the submission of a letter from the current marketing authorization holder notifying that it has returned the original authorization shall be required; where a court decision demonstrating that the current marketing authorization holder no longer holds authorization is submitted, all requirements set forth in this Article shall be fulfilled, together with the current Module 1 dossier of the advanced therapy medicinal product, with the exception of paragraph one subparagraph (a). However, in cases where the product in this situation constitutes the sole diagnostic or sole treatment option for a disease in our country, the Agency may accept and conclude the transfer application relating to the authorization/permit or registration certificate without awaiting the court decision. (4) The Agency shall evaluate the marketing authorization transfer application within thirty days. (5) In cases where the information and documents requested by the Agency, or the necessary explanation regarding the inability to submit such information and documents together with the date information on which they will be submitted, are not submitted to the Agency within thirty days at the latest, the transfer application shall be cancelled.

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****Transfer of Marketing Authorization Application****

ARTICLE 26- (1) The natural or legal person making a marketing authorization application may transfer the rights arising from the application to another natural or legal person by fulfilling the relevant conditions specified in Article 24.

****Obtaining a Sales Permit****

ARTICLE 27- (1) It is mandatory to obtain a sales permit for an advanced therapy medicinal product that will be placed on the market for the first time, having been authorised by the Agency under the provisions of this Regulation. (2) For advanced therapy medicinal products that will be placed on the market for the first time having been authorised by the Agency, the marketing authorisation holder shall submit to the Agency, together with the sales permit application: in cases where the holder carries out, at facilities belonging to its own natural or legal personality, the storage activities for advanced therapy medicinal products for which the sale price application to the warehouse has been approved by the Agency, the document issued by the Agency; and in cases other than this, the document issued by the Agency pertaining to the storage site, the document signed between the parties for the storage of the product, and the registry certificates of the parties. (3) The Agency examines the packaging sample and the instructions for use of the advanced therapy medicinal product for which a sales permit application has been made and the price of which has been approved by the Agency, with respect to the required information. (4) There is no need to obtain a new sales permit for operations that lead to a change in the packaging information or characteristics on the basis of which the marketing authorisation of the advanced therapy medicinal product was granted, and/or in its instructions for use. However, in the event of the transfer of the manufacturing site from abroad to our country or from our country to abroad, changes in packaging size, following marketing authorisation transfer procedures, and for products the suspension of whose marketing authorisation has been lifted pursuant to the fourth paragraph of Article 21, a sales permit shall be obtained by applying to the Agency together with the documents specified in the second paragraph and a sales sample before the products are placed on the market. (5) For advanced therapy medicinal products to be used in emergencies against public health threats recognised by the World Health Organization or the European Union or accepted by the Ministry of Health, and the supply of which is to be carried out solely by the public sector, the Agency may define, in the sales permit, restrictions concerning the public healthcare institutions and organisations through which the products in question may be placed on the market. The restrictions in question shall be specified in the sales permit. Post-authorisation variations

ARTICLE 28- (1) With the exception of Article 25, following the authorisation of an advanced therapy medicinal product, an application shall be made to the Agency by the marketing authorisation holder for all modifications relating to this product, in accordance with the provisions of the relevant regulation and guidelines. (2) Upon application, the Agency may provide scientific advice to the applicant following the authorisation of the advanced therapy medicinal product, provided that it is subject to a fee specified in the fee schedule. Donation, procurement and testing

ARTICLE 29- (1) Where an advanced therapy medicinal product contains human cells or tissues, the donation, procurement and testing of such cells or tissues shall be carried out in accordance with the Regulation on Quality and Safety of Human Tissues and Cells and the Centres Related Thereto. Clinical Trials

ARTICLE 30- (1) The eleventh paragraph of Article 8 of the Regulation on Clinical Trials of Human Medicinal Products, relating to gene therapy and somatic cell therapy medicinal products, shall be applied to tissue engineered products. SECTION FOUR Summary of Product Characteristics, Packaging and Instructions for Use Summary of Product Characteristics

ARTICLE 31- (1) Without prejudice to Article 10 of the Regulation on Licensing of Human Medicinal Products, the information listed in Annex-2 shall be included. Instructions for use

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ARTICLE 32- (1) Without prejudice to Article 8 of the Regulation on Packaging Information, Instructions for Use and Tracking of Human Medicinal Products, the instructions for use of an advanced therapy medicinal product shall be prepared in accordance with the summary of product characteristics and shall contain the information listed in Annex-4. (2) The instructions for use shall be easy to read and clearly comprehensible. Outer packaging

ARTICLE 33- (1) Without prejudice to Articles 5, 6 and 7 of the Regulation on Packaging Information, Instructions for Use and Tracking of Human Medicinal Products, the outer packaging of an advanced therapy medicinal product, or where there is no outer packaging, its immediate packaging, shall bear the information listed in Annex-3. Immediate packaging

ARTICLE 34- (1) In addition to Article 6 of the Regulation on Packaging Information, Instructions for Use and Tracking of Human Medicinal Products, the immediate packaging of an advanced therapy medicinal product shall bear the following information: a) The unique donation identification number and product code specified in the Regulation on Quality and Safety of Human Tissues and Cells and the Centres Related Thereto. b) In cases where autologous use of advanced therapy medicinal products is at issue, the unique patient identifier and the statement "For autologous use only". SECTION FIVE Post-authorisation Requirements Post-authorisation efficacy, adverse reaction monitoring and risk management

ARTICLE 35- (1) In addition to the pharmacovigilance requirements within the scope of the Regulation on Safety of Medicines, the applicant shall specify in detail, in the marketing authorisation application, the measures foreseen to ensure the monitoring of the efficacy of advanced therapy medicinal products and of adverse reactions to these products. (2) In cases of doubt, the Agency shall require, as part of the marketing authorisation, the design of a risk management system aimed at the identification of advanced therapy medicinal products, the determination of their characteristics, and the prevention or minimisation of any risks that may arise in relation to these products. In this case, the marketing authorisation holder shall submit to the Agency information regarding the establishment of the system, the effectiveness assessment of the risk management system or the conduct of specific post-authorisation studies. Where necessary, the Agency may require the submission of additional reports assessing the effectiveness of the risk management system and the results of the studies conducted. (3) The assessment of the effectiveness of the risk management system and of the results of the studies conducted shall be included in the periodic benefit/risk evaluation report specified in the Regulation on Safety of Medicines. (4) In the event that a serious adverse reaction occurs in relation to combined advanced therapy medicinal products, the provisions of the Medical Devices Regulation shall be applied by the Agency. Traceability

ARTICLE 36- (1) The marketing authorisation holder shall establish and operate, in accordance with the Regulation on Quality and Safety of Human Tissues and Cells and the Centres Related Thereto, a system ensuring the traceability of the product, its starting materials and raw materials, including all substances coming into contact with the cells and tissues it may contain, throughout its procurement from the source, manufacture, packaging, storage and transport, and its distribution to the hospital, institutions and organisations, or private treatment centres where the product is used. (2) The hospital, institutions and organisations or private treatment centre where the advanced therapy medicinal product is to be used shall establish and operate a system for patient and product traceability. The said system shall contain sufficient information on the link between each product and the patient using that product, or the link between each patient and the product received. (3) Where the advanced therapy medicinal product contains human cells or tissues, the marketing authorisation holder and the hospital, institutions and organisations or private treatment centre where the product is used shall ensure that the traceability systems established pursuant to the first and second paragraphs comply with, and are complementary to, the requirements specified in the relevant articles of the Regulation on Quality and Safety of Human Tissues and Cells and the Centres Related Thereto concerning human cells and tissues other than blood cells. (4) The marketing authorisation holder shall retain the data specified in the

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first paragraph for at least thirty years after the expiry date of the product. This period may be longer where so required by the Agency under the marketing authorisation. (5) In the event of the bankruptcy or liquidation of the marketing authorisation holder, and in cases of transfer of the marketing authorisation, the information specified in the first paragraph shall be communicated to the Agency. (6) In cases where the marketing authorisation is suspended, revoked or withdrawn, the marketing authorisation holder shall remain subject to the obligations set out in the first, third and fourth paragraphs of this Article. (7) The Personal Data Protection Code No. 6698 dated 24/3/2016 shall be complied with in the traceability system relating to advanced therapy medicinal products. Combined advanced therapy medicinal products

ARTICLE 37- (1) Where a combined advanced therapy medicinal product is at issue, the entire product shall be subject to the assessment of the Agency. (2) In an application for a marketing authorisation for a combined advanced therapy medicinal product, evidence of compliance with the essential requirements of the Medical Devices Regulation shall be submitted. (3) In an application for a marketing authorisation for a combined advanced therapy medicinal product, where applicable, the assessment results of a notified body in compliance with the Medical Devices Regulation shall be submitted for the medical device part. The Agency shall recognise the results of this assessment in the evaluation of the medicinal product in question. The Agency may request the relevant notified body to communicate any and all information relating to the results of its assessment. The notified body shall communicate the information within thirty days. (4) If the marketing authorisation application does not contain assessment results, the Agency shall request an opinion from a notified body identified in liaison with the applicant, unless the Agency decides that the involvement of a notified body is not necessary. (5) The medical device or implantable device forming an integral part of a combined advanced therapy medicinal product shall meet the essential requirements of the Medical Devices Regulation. SECTION SIX Miscellaneous and Final Provisions Reliance

ARTICLE 38- (1) Previous assessments carried out by other medicines authorities with comparable standards, or by regional or international organisations, may be taken into consideration in accordance with the guideline published by the Agency. Fees

ARTICLE 39- (1) The Agency may apply fees for the activities within the scope of this Regulation. Guidelines

ARTICLE 40- (1) Where the Agency deems necessary, it shall publish guidelines or communiqués for the implementation of this Regulation. Confidentiality

ARTICLE 41- (1) Information submitted to the Agency by the applicant in order to obtain a marketing authorisation for an advanced therapy medicinal product is confidential. Such confidentiality shall be protected by the Agency. Recall

ARTICLE 42- (1) For products falling within the scope of this Regulation; the provisions of the Recall Regulation published in the Official Gazette No. 29537 dated 19/11/2015 shall apply to the collection and recall procedures to be carried out for products subject to recall. Compulsory licence

ARTICLE 43- (1) For products deemed appropriate by the President to be manufactured under a compulsory licence within the scope of Article 132 of the Industrial Property Code No. 6769 dated 22/12/2016, a marketing authorisation application may be made to the Agency within the framework of the requirements, the detailed matters of which shall be determined by the Agency. Alignment with the legislation of the European Union

ARTICLE 44- (1) This Regulation has been prepared within the framework of alignment with the European Union legislation, taking into account Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, Commission Regulation (EC) No 507/2006 of 29 March 2006 on conditional marketing authorisations for medicinal products for human use, and Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

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Applicants holding advanced therapy medicinal product applications PROVISIONAL ARTICLE 1- (1) For marketing authorisation applications for advanced therapy medicinal products made to the Agency, prior to the entry into force of this Regulation, in accordance with the Communiqué on the Licensing of Human Tissue and Cell Products and on the Centres Carrying Out the Manufacturing, Importation, Exportation, Storage and Distribution Activities of These Products, dated 4/4/2014 and numbered 28962, the applicants shall submit to the Agency their updated files, in compliance with the provisions of this Regulation, within three months as of the publication date of this Regulation. (2) The necessary assessment shall be carried out within thirty days of the receipt of the application file by the Agency, and the outcome shall be notified to the applicant. In the event that the application is found to be incomplete, the applicant shall complete the deficiencies within thirty days. The second preliminary assessment to be conducted after the deficiencies have been completed and submitted to the Agency shall also be concluded within thirty days. (3) In the cases listed below, the application shall be rejected on procedural grounds and returned to its holder: a) Failure to make a second application within the prescribed time limit upon completion of the deficiencies related to the first preliminary assessment conducted by the Agency under Article 11, or failure to complete the deficiencies related to the first preliminary assessment in the second preliminary assessment application. b) Failure to pay the authorisation fee within sixty days following the date on which the applicant is officially notified that the authorisation process has been completed. c) Failure to submit to the Agency, at the latest within thirty days, the information and documents requested by the Agency outside the preliminary assessment process, or the necessary explanation regarding the inability to submit such information and documents, together with the information on the date on which they are to be submitted. (4) The files of advanced therapy medicinal products for which no file update application has been made pursuant to the first paragraph shall be returned. Entry into Force

ARTICLE 45- (1) This Regulation shall enter into force on the date of its publication. Execution

ARTICLE 46- (1) The President of the Turkish Medicines and Medical Devices Agency (TİTCK) shall execute the provisions of this Regulation.

Click here for the Annexes.

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