EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 October 2016
EMA/CAT/633806/2016
Committee for Advanced Therapies (CAT)

SCIENTIFIC RECOMMENDATION ON CLASSIFICATION OF ADVANCED THERAPY MEDICINAL PRODUCTS Article 17 – Regulation (EC) No 1394/2007

FINAL VERSION

The present scientific recommendation refers exclusively to the case as presented to the Agency without prejudice to future evaluations by the Agency.
It is stressed that the scientific recommendation on advanced therapy classification does not amount to any endorsement of the plausibility of the product, including the mode of action or therapeutic indication(s) claimed by the applicant.

1. CAT OUTCOME SUMMARY

Proposed product invented name or identifier ("the Product")	Bone marrow-derived autologous non-hematopoietic stem cells for treatment of multiple sclerosis.	
Company developing the Product (applicant)	Aztar sp. z o.o., Poland	
Brief description (common name or international non proprietary name where available) of Active substance(s)	Bone marrow-derived autologous non-hematopoietic stem cells.	
Brief description of the finished Product	Suspension of cells for infusion.	
Proposed Indication (as proposed by the applicant)	Treatment of multiple sclerosis.	
Advanced therapy medicinal product classification (as agreed by the CAT)	Not ATMP	
	Gene therapy medicinal product	
	Somatic cell therapy medicinal product	
	Tissue engineered product	X
	Combined ATMP	
CAT Co-ordinator	Dariusz Sladowski	
ITF Co-ordinator	Emil Cochino	

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

2. APPLICANT'S scientific background information and proposed regulatory classification and justification

- According to the information provided by the applicant, the product is composed of human bone (ilium) marrow-derived autologous non-hematopoietic stem cells
- The applicant claims that the manufacturing process involves filtration, washing, depletion of cells using CliniMACS magnetic separation device which the applicant considers as non-substantial manipulation.
- According to the information submitted, the product would be indicated for the treatment of multiple sclerosis.
- The claimed primary mechanism of action of the product is based on the immunomodulatory, immunosuppressive, neurotrophic, and repair-promoting properties of stem cells.
- Applicant's ATMP claimed product classification:

Not ATMP	
Gene therapy medicinal product	
Somatic cell therapy medicinal product	
Tissue engineered product	X
Combined ATMP	

3. EMA/CAT scientific recommendation and conclusion

The product is composed of human bone (ilium) marrow-derived autologous non-hematopoietic stem cells used is non-homologous setting. The cells are only mechanically separated, which is a non-substantial manipulation.
The product is intended for the treatment of multiple sclerosis by immunomodulatory, immunosuppressive, neurotrophic, and repair-promoting properties of stem cells, so the product can be considered as somatic cell therapy and tissue engineering medicinal product.

3.2 Fulfilment of definition of advanced therapy medicinal product

Product **Bone marrow-derived autologous non-hematopoietic stem cells for treatment of multiple sclerosis** is a biological medicinal product as the active substance bone marrow-derived autologous non-hematopoietic stem cells is extracted from a biological source, bone marrow, of human origin. Characterisation and the determination of its quality requires a combination of physico-chemical-biological testing, together with the production process and its control.

Product **Bone marrow-derived autologous non-hematopoietic stem cells for treatment of multiple sclerosis** consists of cells that are not intended to be used for the same essential function in the recipient as in the donor and is administered to human beings with a view to regenerate a human tissue.

Based on the above considerations, EMA/CAT considers that the Product Bone marrow-derived autologous non-hematopoietic stem cells for treatment of multiple sclerosis falls within the definitions of a somatic cell therapy medicinal product and tissue

engineered product and based on that is considered as Tissue Engineered Product as provided in Article 2(4) of Regulation (EC) No 1394/2007.

4. **Summary for Public Release**

**Information to be extracted from the respective sections of the adopted classification report, redacted to delete commercial confidential information.*

Scientific recommendation on classification of advanced therapy medicinal products

Article 17 – Regulation (EC) No 1394/2007

Disclaimer: This document is a summary for public release of a scientific recommendation on classification of advanced therapy medicinal products. The original text adopted by the Committee for Advanced Therapies (CAT) has been redacted to delete commercially confidential information.

The present scientific recommendation refers exclusively to the case as presented to the European Medicines Agency (EMA) without prejudice to future evaluations by the Agency.

It is stressed that the scientific recommendation on advanced therapy classification does not amount to any endorsement of the plausibility of the product, including the mode of action or therapeutic indication(s) claimed by the applicant.

Brief description (or name where available) of the active substance(s)

Bone marrow-derived autologous non-hematopoietic stem cells

Brief description of the finished product

Cell suspension for infusion

Proposed indication

Multiple sclerosis

EMA/CAT conclusion

On the basis that:

a) Consists of engineered cells that are not intended to be used for the same essential function or functions in the recipient as in the donor

b) is administered to human beings with a view to treating a disease through the metabolic/ immunological action of the active substance and repair/regeneration of a human tissue.

the EMA/CAT considers that the product falls within the definition of a somatic cell therapy and tissue engineered medicinal product.

ANNEX(ES)

- **ANNEX A:** Applicable European Regulations (for information purpose)
- **ANNEX B:** Scientific recommendation request form (scientific and regulatory information provided by the applicant)

ANNEX A

Applicable European Regulations (for information purpose)

Article 1(2) of Directive 2001/83/EC – Definition of medicinal product:
"(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis"

Article 2(1) of Directive 2001/83/EC:

"This directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process."

Web link to Directive 2001/83/EC:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20110721:EN:PDF

Annex I, Part I, Module 3, section 3.2.1.1 of Directive 2001/83/EC – Definition of biological medicinal product:
Web link to Directive 2001/83/EEC:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20110721:EN:PDF

"For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.
The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex. "

Regulation (EC) No 1394/2007 – Article 2 – Definitions:

Web link to Regulation (EC) No 1394/2007:
http://eur-lex.europa.eu/LexUriServ/site/en/oj/2007/l_324/l_32420071210en01210137.pdf

"1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:
- a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a tissue engineered product as defined in point (b).

(b) 'Tissue engineered product' means a product that:
- contains or consists of engineered cells or tissues, and

- 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.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

(c) Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

- the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,
- the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

(d) 'Combined advanced therapy medicinal product' means an advanced therapy medicinal product that fulfils the following conditions:

- it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and
- its cellular or tissue part must contain viable cells or tissues, or

its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

2. Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product.

3. An advanced therapy medicinal product containing both autologous (emanating from the patient himself) and allogeneic (coming from another human being) cells or tissues shall be considered to be for allogeneic use.

4. A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product.

5. A product which may fall within the definition of:

- a somatic cell therapy medicinal product or a tissue engineered product, and
- a gene therapy medicinal product,

shall be considered as a gene therapy medicinal product."

Directive 2009/120/EC amending Directive 2001/83/EC Annex I Part IV (extracts):
Web link to Directive 2009/120/EC:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:242:0003:0012:EN:PDF

2.1. GENE THERAPY MEDICINAL PRODUCT

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

2.2. SOMATIC CELL THERAPY MEDICINAL PRODUCT

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological

characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No

1394/2007, in particular, shall not be considered as substantial manipulations.

ANNEX B

Scientific recommendation request form (scientific and regulatory information provided by the applicant)

ITF coordinator to attach the Briefing document from the applicant