16 June 2016
EMA/CAT/423125/2016
Procedure Management and Committees Support Division

Committee for Advanced Therapies (CAT)

Agenda for the meeting on 16-17 June 2016

Chair: Paula Salmikangas - Vice-chair: Martina Schüßler-Lenz

16 June 2016, 09:00 – 18:30, room 03-E
17 June 2016, 09:00 – 12:00, room 03-E

Health and safety information

In accordance with the Agency's health and safety policy, delegates are to be briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in this agenda is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the CAT meeting reports once the procedures are finalised.

Of note, this agenda is a working document primarily designed for CAT members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the agenda cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the CAT plenary session to be held on 16 - 17 June 2016. See June 2016 CAT minutes (to be published post-July 2016 CAT meeting).

1.2. Adoption of agenda

CAT agenda for 16 - 17 June 2016

1.3. Adoption of the minutes

CAT minutes of 18 - 20 May 2016

1.4. Technical information

2. Evaluation of ATMPs

2.1. Opinions

2.1.1. Characterised viable haploidentical herpes simplex virus thymidine kinase (HSV-Tk) and human low affinity nerve growth factor receptor (ΔLNGFR) transfected donor lymphocytes; *Orphan*; EMA/H/C/002801

MolMed SpA; treatment of adjunctive treatment in haploidentical haematopoietic stem cell transplantation of adult patients with high-risk haematological malignancies

Scope: Opinion

Action: for adoption

Documents:
-Draft updated CAT AR
-Draft Opinion
-Draft PI
-Draft SPC
-BWP report

Outstanding questions raised by PRAC and CHMP (at their May 2016 plenaries) adopted by written procedure by CAT/CHMP on 30.05.16. Oral explanation held on 18.05.2016; 3rd List of Outstanding Issues adopted on 23.03.16. Eight-month clock-stop agreed on 17.04.15. 2nd List of Outstanding Issues adopted on 22.01.16. 1st List of Outstanding Issues adopted on 20.03.15. List of Questions adopted on 18.07.14.

2.2. Oral explanations

No items

2.3. Day 180 List of outstanding issues

No items

2.4. Day 120 Lists of questions

No items

2.5. Day 80 assessment reports

Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue; *Orphan*; EMA/H/C/0004258TiGenix S.A.U.; Treatment of complex perianal fistula(s)Scope: Oral report by the Rapporteurs on ongoing assessment report

Action: for information

2.6. Ongoing initial full application

No items

2.7. New applications

2.8. Withdrawal of initial marketing authorisation application

No items

2.9. Re-examination of initial application procedures under Article 9(2) of Regulation no. 726/2004

No items

2.10. GMP and GCP inspections requests

No items

2.11. Type II variations

No items

2.12. Other post-authorisation activities

No items

3. Certification of ATMPs

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

3.1. Opinions

No items

3.2. Day 60 evaluation reports

No items

3.3. Ongoing initial application

No items

3.4. New applications

No items

4. Scientific Recommendation on Classification of ATMPs

4.1. New requests – appointment of CAT Co-ordinators

4.1.1. RET activated human cord blood progenitor cells expanded *ex-vivo*; EMA/H0004545

Intended for the treatment of patients undergoing hematopoietic stem cell transplantion

Scope: appointment of CAT Co-ordinator and adoption of timetable

Action: for nomination of CAT Coordinator

Document:
Request received

4.1.2. Adeno-associated viral vector serotype 8 containing the human glucose-6-phosphatase gene; EMA/H0004544

Intended for the treatment of glycogen storage disease type Ia (GSDIa)

Scope: appointment of CAT Co-ordinator and adoption of timetable

Action: for nomination of CAT Coordinator

Document:
Request received

4.1.3. Recombinant adeno-associated virus 2 human aromatic L-amino acid decarboxylase gene; H0004546

Intended for the treatment of Parkinson's disease (PD)

Scope: appointment of CAT Co-ordinator and adoption of timetable

Action: for nomination of CAT Coordinator

Document:
Request received

4.1.4. Collagenase from *Clostridium histolyticum*; H0004547

Intended to be used for *ex-vivo* dissociation of adipose tissue

Action: for adoption

Document:
Request received
ATMP classification report

4.2. Day 30 Co-ordinators' first reports

4.2.1. Live attenuated *Listeria monocytogenes* transfected with plasmids encoding HPV-16E7 protein fused to a truncated fragment of the *Lm* protein listeriolysin O

Intended for the treatment of cervical cancer

Action: for adoption

Document:
ATMP classification report

4.2.2. Heterologous human adult liver-derived progenitor cells (HHALPC)

Intended for the treatment of liver diseases

Action: for adoption

Document:
ATMP classification report

Note: In May 2011, CAT classified the same product for the indication 'treatment of inborn errors of liver metabolism' as a somatic cell therapy product

4.2.3. Autologous expanded human fibroblasts

Intended for the treatment of scar of different aetiology as post- traumatic, post-surgical or outcomes of acne scars

Action: for adoption

Document:
ATMP classification report

4.2.4. Autologous concentrated bone marrow

Intended for critical limb ischemia without surgical option

Action: for adoption

Document:
ATMP classification report

4.3. Day 60 Co-ordinators' revised reports following List of Questions

4.3.1. Hepatitis B virus DNA vaccine delivered via electroporation

Intended for the treatment of chronic hepatitis B virus infection

Action: for adoption

Document:
Revised ATMP classification report
Applicant's responses to LoQ

4.4. Finalisation of procedures

4.4.1. Adeno-associated viral vector containing the ChrimsonR-td tomato gene

Intended for the treatment of retinitis pigmentosa

Action: for information

Document:
ATMP classification report

The European Commission raised no comments

4.4.2. Autologous regulatory T lymphocytes $CD3^+CD4^+CD25^+CD127^-FoxP3^+$

Intended for the treatment of, and prevention of progression of, recently diagnosed paediatric type I diabetes mellitus

Action: for information

Document:
ATMP classification report

The European Commission raised no comments

4.4.3. Allogeneic Epstein-Barr virus cytotoxic T lymphocytes

Intended for the treatment of Epstein-Barr virus-associated post-transplant lymphoproliferative disorder

Action: for information

Document:
ATMP classification report

The European Commission raised no comments

4.4.4. Bone marrow derived mesenchymal stem cells

Intended for the treatment of children's encephalopathy, children's epilepsy, children's spinal cord injury

Action: for information

Document:
ATMP classification report

The European Commission raised no comments

4.5. Follow-ups and guidance

4.5.1. Precedent cases borderline classification: gene *versus* vaccine

Action: for information

Document:
Presentation

5. Scientific Advice

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

5.1. New requests – appointment of CAT Co-ordinators

5.2. CAT Rapporteurs' reports

5.3. Lists of issues

5.4. Finalisation of Scientific Advice procedures

5.5. Follow-up of Scientific Advice procedures

No items

6. Pre-Authorisation Activities

Disclosure of information related to this section cannot be released at the present time as it is deemed to contain commercially confidential information.

6.1. Paediatric investigation plans

6.2. ITF briefing meetings in the field of ATMPs

6.3. Priority Medicines (PRIME) – Eligibility requests

6.3.1. Month 0 - Start of the procedure

6.3.2. Month 1 – Adoption of eligibility

6.3.3. Month 2 – Recommendation for PRIME eligibility

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the CAT

7.1.1. Strategic Review & Learning meeting

CAT-PDCO-CTFG joint Strategic Review & Learning, Utrecht, Netherlands in early June 2016 under the auspices of the Dutch Presidency of the Council of the European Union

CAT resources: Hans Ovelgönne, Paula Salmikangas;
Scope: feedback from the Strategic Review & Learning meeting of 1-2 June 2016

Action: for information and action

Documents**:**
Presentation of day 2 of the meeting

7.1.2. Strategic Review & Learning meeting

CAT resources: Maura O'Donovan

Action: for information

Note: Ireland, under the auspices of the Slovak Presidency of the Council of the European Union, will organise this meeting in Dublin on 24 – 26 October 2016

7.1.3. Good manufacturing practice (GMP) requirements for ATMPs

CAT drafting group members: Ivana Haunerova, Margarida Menezes-Ferreira, Guido Panté, Ilona Reischl, Paula Salmikangas, Belaid Sekkali, Marcos Timón, Christiane Niederlaender, Jurgen Scherer, Marcel Hoefnagel

Scope: feedback from the drafting group's discussions in the next steps

Action: for information

7.2. Coordination with EMA Scientific Committees

7.2.1. Committee for Medicinal Products for Human Use (CHMP)

Scope: Summary of Outcomes (SoO) for the May 2016 meeting

Action: for information

Documents:
Summary of Outcomes

7.2.2. Fee reductions for scientific advice requests on PRIME products for SMEs and applicants from the academic sector

Scope: Executive Director decision on fee reductions for scientific advice requests on PRIME products for SMEs and applicants from the academic sector

Action: for information

Document:
Executive decision:

Note: adopted by CHMP in May 2016

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

No items

7.4. Co-operation within the EU regulatory network

No items

7.5. Co-operation with international regulators

7.5.1. ATMP cluster teleconference with FDA, Health Canada and PMDA (Japan)

The teleconference will take place during the plenary meeting on Thursday 16th June from 14.00hrs – 15.00hrs

CAT resources: Paula Salmikangas

Action: for adoption

Document table:
Agenda

7.5.2. International Pharmaceutical Regulators Forum (IPRF) Gene therapy group

CAT resource: Paula Salmikangas

Scope: oral feedback from the teleconferences that took place on 14th June 2016

Action: for information

7.6. CAT Work Plan

7.6.1. Guideline on requirements for investigational ATMPs

CAT drafting groups: Tiina Palomäki (Rapporteur), Ilona Reischl (Rapp), Metoda Lipnik-Stangelj, Margarida Menezes Ferreira, Maura O'Donovan, Simona Badoi, Tomas Boráň, Christiane Niederlaender, Paolo Gasparini, Olli Tenhunen, Carla Herberts

Scope: Feedback from the drafting group meeting of 18th May 2016

Action: for information

An outline of the structure of the above guideline was provided. CAT will be kept informed of the progress.

7.6.2. Questions and Answers on minimally manipulated ATMPs

CAT drafting group: Metoda Lipnik-Stangelj, Paula Salmikangas, Tiina Palomäki, Egbert Flory, Margarida Menezes Ferreira, Pieter Doevendans, Mikuláš Hrubiško

Scope: creation of a Q&A document following the discussion that took place at the CAT-CHMP joint Strategic Review & Learning meeting in May 2015

Action: feedback from the break out meeting that will take place on 15.06.16

Note:
The Questions-and-Answers will describe the quality, non-clinical and clinical requirements for the marketing authorisation for a minimally manipulated ATMP (CD34+ cells for cardiac repair). In the answers, a practical explanation will be provided how to use the risk based approach to identify and justify deviations for the standard requirements for cell-based ATMPs as included in Annex I Part IV of Dir. 2001/83/EC.

7.7. Planning and reporting

7.7.1. ATMP Expert meeting, 27 May 2016

Action: for information

Link to the published stakeholders report:
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/06/WC500208080.pdf

Note: EMA will present at the CAT July 2016 meeting both the stakeholders and the regulators reports and the action plan

7.7.2. Planning estimates of forthcoming Advanced Therapies Medicinal Products (ATMP) MAAs

Action: for information

7.8. Others

7.8.1. International Society for Cellular Therapy (ISCT) 2016 annual meeting, Singapore, 25-28 May 2016

CAT resource: Martina Schüßler-Lenz

Scope: Quality and Operations Track 6: presentation given by CAT speaker on *'Evolving regulatory regime for cell-based therapies in the EU faster and early access – PRIME'*

Action: for information

Documents:
Programme
Presentation

7.8.2. Guide to EMA publications on medicines

Action: for information

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000169.jsp&mid

Note: this guide describes the different types of information the Agency currently publishes for both centrally and non-centrally authorised medicines, at the various stages of a medicine's life cycle. For each document, it also provides precise information on the publication times and its location on the EMA's website. The objective is to help stakeholders and partners know what kind of information they can expect on medicines undergoing evaluations and other regulatory procedures. The aim is to keep it continuously up-to-date to ensure it fulfils its objective.

7.8.3. Gene therapy for Wiskott-Aldrich syndrome (WAS0: long term efficacy and safety findings

CAT resource: Martina Schüßler-Lenz

Scope: finding of leukaemia cases in patients treated with retroviral vector containing the gene for WAS protein

Action: for information

7.8.4. 2016 Parenteral Drug Association (PDA) Europe advanced therapy medicinal products conference, Berlin 7-8 June 2016

CAT resource: Margarida Menezes-Ferreira

Scope: sessions on '*Process validation of ATMPs'* and *'Introduction to GMP for ATMPs'*

Action: for information

Agenda

8. Any other business

8.1. Procedure Management Department

Scope: new operational model from 1st June 2016

Action: for information

Documents:
-Regulatory procedural information - improving the way procedure managers support evaluation procedures - PM and PA allocation
-Regulatory info workload optimisation

Note: a presentation on 'New operational model in the Procedure Management Department' was tabled in the CAT MMD April folder (folder 08.)

Date of next CAT meeting:
Wednesday 13th to Friday 15th July 2016

9. Explanatory notes

The Notes give a brief explanation of relevant agenda items and should be read in conjunction with the agenda.

Abbreviations / Acronyms

AR: Assessment Report

ATMP: Advanced Therapy Medicinal Product

BWP: Biologics Working Party

CAT: Committee for Advanced Therapies

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

CTFG: Clinical Trial Facilitation Group

DG: Drafting Group

EC: European Commission

FDA: Food and Drug Administration

FL: Final Letter

GCP: Good Clinical Practice

GLP: Good Laboratory Practice

GMO: Environmental Risk Assessment

GMP: Good Manufacturing Practice

HTA: Health Technology Assessment Bodies

HSPC: Hematopoietic Stem and Progenitor Cells

ITF: Innovative Task Force

JR: Joint Report

LoOI: List of outstanding issues

LoQ: List of questions

MA: Marketing Authorisation

MAA: Marketing Authorisation Applicant

MAH: Marketing Authorisation Holder

MSC: Mesenchymal stem cells

PDCO: Paediatric Committee

PMDA: Pharmaceuticals and Medical Devices Agency (Japan)

PIP: Paediatric Investigation Plan

PL: Package leaflet

PRAC: Pharmacovigilance and Risk Assessment Committee #

PRIME: Priority Medicines

RMP: Risk Management Plan

RP: Reflection paper

RSI: Request for supplementary information

SA: Scientific Advice

SAG-O: Scientific Advisory Group Oncology

SAWP: Scientific Advice Working Party

SR: Summary Report

SWP: Scientific Working Party

SME: Small and medium size enterprises

SmPC: Summary of Products Characteristics

TT: Timetable

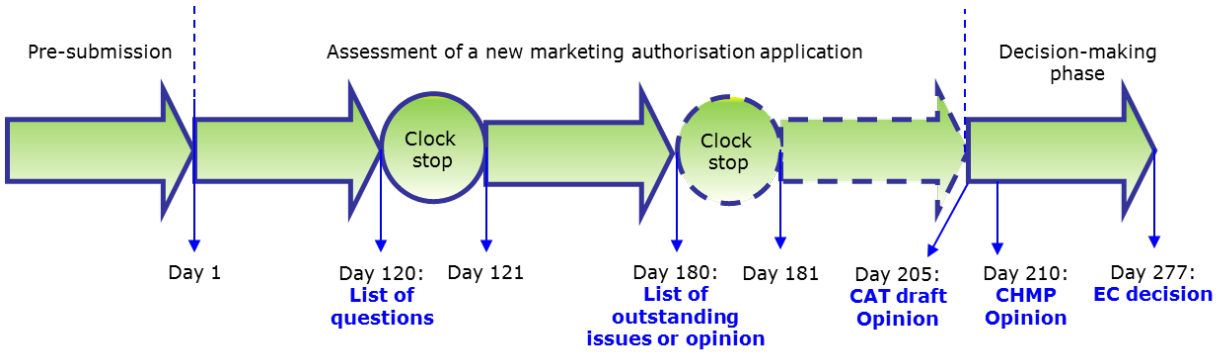
Evaluation of ATMPs (section 2)

This section lists applications for marketing authorisations of new Advanced Therapy Medicinal Products (ATMPs) that are to be discussed by the Committee. It also lists any ATMP related inspection requests (*section 2.9*) and Post-authorisation activities (*section 2.10*).

New applications (sections 2.1. to 2.12.)

Section 2.1 is for ATMPs nearing the end of the evaluation and for which the CAT is expected to adopt a draft **opinion** at this meeting on whether marketing authorisation should be granted. Once adopted, the CAT opinion is transmitted to the CHMP for final adoption. The CHMP opinion will be forwarded to the European Commission for a final legally binding decision valid throughout the EU. More information on the evaluation of ATMPs can be found here.

The other items in the section are listed depending on the stage of the evaluation, which is shown graphically below:



The assessment of an application for a new medicine takes up to 210 'active' days. This active evaluation time is interrupted by at least one 'clock-stop' during which time the applicant prepares the answers to questions from the CAT. The clock stop happens after day 120 and may also happen after day 180, when the CAT has adopted respectively a **Day 120 list of questions** (section 2.3) or a List of outstanding issues to be addressed by the company, which is listed in the agenda under sections 2.7 (**Ongoing evaluation procedures**). Section 2.7 also includes the CAT discussions at any other timepoint of the evaluation procedure of new applications.

Oral explanation (section 2.2.)

Prior to adoption of the CAT opinion, marketing authorisation applicants are normally invited to the CAT plenary meeting to address questions raised by the Committee.

Oral explanations normally relate to ongoing applications, but they can also relate to any other issue for which the CAT would like to discuss with company representatives in person.

Re-examination procedures (new applications) under article 9(2) of regulation no 726/2004 (section 2.6.)

This section lists applications for new marketing authorisation for ATMPs for which the applicant has requested a re-examination of the opinion previously issued by the CHMP. Similar to the initial evaluation of a marketing authorisation of an ATMP, CAT will adopt a draft re-examination opinion, which is transmitted to the CHMP for final adoption.

Withdrawal of applications (section 2.7.)

This section includes information on marketing authorisation applications that are withdrawn by the applicant. Applicants may decide to withdraw applications at any stage during the assessment and a CAT opinion will therefore not be issued. Withdrawals are included in the agenda for information or discussion, as necessary.

New applications (section 2.9.)

In this section, information is included on upcoming marketing authorisation applications for ATMPs, as well as information on appointment of Rapporteurs for new ATMP applications.

GMP and GCP Inspections Issues (section 2.10.)

This section lists inspections that are undertaken for ATMPs. Inspections are carried out by regulatory agencies to ensure that marketing authorisation holders comply with their obligations. Inspection can relate to good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP) or good pharmacovigilance practice (GVP).

Post-authorisation activities (section 2.12.)

This section lists type II variations, extension application according to Annex I of Reg. 1234/2008, re-examination procedures for type II variations (including extension of indication applications) for which the applicant has requested re-examination of the opinion previously issued by the CHMP and other issues concerning authorised medicines that are not covered elsewhere in the agenda such as annual reassessments, 5-year renewals, supply shortages, qualify defects. Issues that have been discussed at the previous meeting of the PRAC, the EMA's committee responsible for evaluating and monitoring safety issues for medicines, will also be included here.

Certification of ATMPs (section 3)

This section includes the scientific evaluation by the CAT of quality and non-clinical data that small and medium-sized enterprises have generated at any stage of the ATMP development process. More information on the ATMP certification procedure can be found here.

Scientific Recommendation on Classification of ATMPs (Section 4)

This section includes the scientific recommendation by the CAT on whether medicines based on genes, cells or tissues meet the scientific criteria that define ATMPs. More information on the ATMP classification procedure, including the outcomes of finalised classifications, can be found here.

Scientific Advice (section 5)

This section includes all scientific advice given to companies during the development of an ATMP. Information related to the number of ATMP related scientific advices discussed by CAT can be found in the CAT Monthly reports. Further information on SAWP can be found here.

Pre-Authorisation (section 6)

Paediatric Investigation Plan (PIP)

This section includes the discussion of an ATMP before a formal application for marketing authorisation is submitted. These cases refer for example to requests for an accelerated assessment for medicines

that are of major interest for public health or can be considered a therapeutic innovation: in case of an accelerated assessment the assessment timetable is reduced from 210 to 150 days.

CAT contributes to the evaluation of a Paediatric Investigation Plan (PIPs) for ATMPs by the Paediatric Committee. These PIPs are included in this section of the Agenda.

ITF Briefing meeting in the field of ATMPs

This section refers to briefing meetings of the Innovation Task Force and International co-operations activities of the CAT

The Innovation Task Force (ITF) is a body set up to encourage early dialogue with applicants developing innovative medicines. Minutes of meetings with applicants developing ATMPs and of other ITF meetings of interest to the CAT are included in this section of the agenda. Further information on the ITF can be found here.

Organisational, regulatory and methodological matters (section 7)

This section includes topics related to regulatory and procedural guidance, CAT workplan, CAT meeting organisation (including CAT membership), planning and reporting, co-ordination with other committees, working parties and scientific advisory groups.

Furthermore, this section refers to the activities of the CAT drafting groups developing scientific guidelines for gene therapy medicinal products and for cell-based medicinal products, cooperation within the EU regulatory network and international regulators as well as direct interaction with interested parties. It also includes topics of scientific interest for the Committee that are not directly related to the work of the CAT drafting groups or CAT associated working parties.

Any other business (section 8)

This section is populated with miscellaneous topics not suitable under the previous headings.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/