

Entwurfvorlage

**Risk Management Plan
(RMP)**

**für
Arzneimittel für neuartige Therapien
(Advanced Therapy Medicinal Products, ATMP)
Genehmigungsverfahren
nach §4b Arzneimittelgesetz (AMG)**

Version: 2.0, 15.08.2023

Product name | RMP

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Risk Management Plan (RMP)

For Advanced Therapy Medicinal Products (ATMP)
(Genehmigungsverfahren nach §4b AMG)

Product:
Active Substance:

MAH:

Date of application in
Germany:

Date of authorisation in
Germany:
Authorisation number: PEI.A.XXXXX.01.1

Data lock point for this RMP:	Version number: #.#
Date of final sign off:	

General considerations and guidance

Text in *green* is meant to provide further advice or examples regarding the topics that should be discussed in the respective sections.

The template is intended to provide guidance for the preparation of an RMP document, which aims to describe the risk management system considered necessary for a medicinal product. The RMP needs to be tailored to the specific product, the available clinical data and the anticipated safety profile. If a section included in the template does not apply to the product, please state 'Not applicable'.

An RMP should be assigned a new RMP version number and a date each time the RMP is updated and submitted for assessment (e.g. versions 0.1, 0.2, etc. for an initial submission of an RMP; versions 1.1, 1.2, etc. and 2.1, 2.2 etc. for RMP updates).

Key elements/sections of an RMP are:

- i) a description of the **safety profile** of the product, and its important identified/potential risks and missing information ('safety specification'), some of which may need to be managed proactively or further studied;
- ii) a plan of **pharmacovigilance** activities to further characterise the products safety profile and clinically relevant risks ('pharmacovigilance plan');
- iii) a plan of **risk minimisation** measures to address key concerns ('risk minimisation plan').

Randomized controlled trials are the gold standard to assess the safety and efficacy of a new medicinal product. The less data is available from (completed) clinical trials, the more important alternative forms of data collection become in order to increase the knowledge base on which the benefit-risk balance of a medicine can be evaluated. All such activities should be specified in the RMP pharmacovigilance plan.

Complex medicinal products, complicated administration procedures or severe adverse reactions may necessitate risk mitigation, for example, by means of specific training material for treating physicians, which should be specified in the RMP section on risk minimisation.

This guidance should be read in conjunction with the most recent EMA GVP module V on risk management systems, because this document is in parts based on EMA GVP module V rev.2 and the accompanying guidance on the format of the RMP (EMA RMP template). An RMP submission in German language is also acceptable.

If a central authorization procedure is planned, this template will not be sufficient for the RMP required for a central application procedure. In such cases please refer to the EMA website for more information. If preferred, the EMA RMP template can also be used for applications according to §4b AMG.

Green texts should be deleted before RMP submission.

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List of Abbreviations

e.g., AE	e.g., Adverse Event

1. Product overview

Information in this section needs to be in line with the SmPC (Fach- und Gebrauchsinformation).

1.1. Product details

Invented name of the medicinal product (product short name)	
Active substance(s) (INN or common name)	
Pharmaco-therapeutic group (ATC Code)	
Medicinal Product Code (From EudraVigilance)	
Authorisation procedure(s) Application date: Authorization Date:	Germany: §4b AMG
Name of Marketing Authorisation Holder or Applicant	
Brief description of product (chemical class, origin, production/modification, mode of action etc.)	
Indication(s) (target population)	
Dosage	
Pharmaceutical form and strength (concentration)	
Route of administration	

2. Safety Specifications

2.1. Epidemiology of indication and target population

Note for clarification: This section should provide a brief and concise overview of the epidemiology of the indication(s) and target population(s) and summarize information that might be relevant for the assessment of safety and risk management, incl. relevant risk factors, expected co-morbidities and co-medications in the target population, standard of care with the view of the expected outcome in the absence of treatment with the medicinal product. In case the product is expected to have several authorised indications, the data for the different indications should be integrated if sensible from a clinical perspective. If there are clinically relevant differences between the indications, separate sections are expected for each indication.

Incidence	
Prevalence	
Natural History incl. Mortality and Morbidity	
Important co-morbidities	
Main Existing Treatment Options (SOC)	

2.2. Non-clinical part of the safety specification

Note for clarification: This section should present a high-level summary of the significant non-clinical safety findings. Please provide a summary of relevant studies and model systems employed. The topics should normally include, but do not need to be limited to, key safety or efficacy issues from non-clinical studies and relevance to human usage, including acute or repeat-dose toxicity, biodistribution and persistence, immunogenicity, reproductive/developmental toxicity, genotoxicity, carcinogenicity.

What constitutes an important non-clinical safety finding will depend upon the medicinal product, the target population and experience with other similar compounds or therapies in the same class. Significant areas of toxicity (by target organ system) and the relevance of the findings to the use in humans should be discussed. Also, quality aspects, if relevant to safety (e.g. genotoxic impurities), should be discussed. If, based on the assessment of the non-clinical or clinical data, additional non-clinical studies are considered warranted, this should be briefly discussed here. Where the non-clinical safety finding could constitute an important (potential) risk to the target population, it should be included as a safety concern later on.

Name/Type of Study	Study details	Key safety /toxicity findings	Relevance to use in Humans

Conclusion from the non-clinical safety assessment

2.3. Clinical part of the safety specification

Note for clarification: In this section, summary information on the clinical trial exposure should be provided in an appropriate format (e.g. tables/graphs), to assess the limitations of the human safety database. The categories are suggestions; tables/graphs should be tailored to the product according to the availability of data and proposed indication. Many ATMP are administered only once, which is why the duration of follow-up may be more relevant than the classical duration of exposure. When providing data by age group, the age group should be relevant to the target population; this should be reflected in the choice of age categories for this table. Please indicate the status of clinical trials (e.g., ongoing, completed).

2.3.1. Clinical trial exposure

Demographics in clinical trials

	Phase 1	Phase 2	Phase 3	Total
Number of subjects				
Age				
Age group				
Gender				
Ethnicity				
Country				
Etc.				

Baseline Characteristics in clinical trials

	Phase 1	Phase 2	Phase 3	Total
Indication/ disease type				
Disease stage				
Dose of exposure				
Duration of follow-up				
Non-responder				
Drop-outs				
Etc.				

Summary of cumulative subject exposure in clinical trials

2.3.2. Additional clinical data sources (outside of clinical trials)

(if applicable)

Note for clarification: If data from clinical trials is very limited, additional information from clinical practice outside of (controlled) trials may be informative for the product's safety profile. Please summarize such data in a concise and appropriate format (e.g. tables/graphs) and clearly state the origin of the data and its limitation (e.g., lack of controls or randomization).

Demographics in study XYZ; title ###; EudraCT ###;

	Number of subjects	Duration of follow-up
Age		
Age group		
Gender		
Ethnicity		
Country		
Etc.		

Baseline Characteristics in study XYZ; title ###; EudraCT ###;

	Number of subjects	Duration of follow-up
Indication/ disease type		
Disease stage		
Dose of exposure		
Duration of follow-up		
Non-responder		
Drop-outs		
Etc.		

Summary of cumulative subject exposure from additional clinical data sources

2.3.3. Population(s) not included in clinical trials

Note for clarification: This section should briefly discuss the limitations of the clinical trial population in relation to predicting the safety of the medicinal product(s) in real life use. Please discuss the populations which have not been studied or have only been studied to a limited degree in the pre-approval phase and the implications of this with respect to predicting the safety of the medicinal product in the marketplace. Important exclusion criteria from the clinical trial development programme should be included as missing information only when they are relevant for the approved and proposed indication.

Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

<Criterion>
Reason for exclusion
Is it to be considered missing information?
Rationale (if not included as missing information)

2.3.4. Limitations of ADR detection in the clinical development programme

Discuss briefly limitations for the detection of ADR and the implication for the products safety specification. E.g.: small study size means that even common ADR might not be detected; limited follow-up data may qualify as missing information.

2.4. Patient exposure based on AMG §4b approval

Note for clarification: When available, data on patients exposed post §4b AMG approval should be provided in an appropriate manner. Details and methods used to calculate person- and person-time exposure should be briefly presented; however, this section is not intended to duplicate the information already available in the PSUR and should only be presented as an overview.

Planned patient exposure per year:

Actual patient exposure (if applicable)

Indication	Gender	Age	Dose
Total			

2.5. Additional requirements for the safety specification

Note for clarification: Because of the nature of ATMP, risks may occur that are not normally a concern with other medicinal products. Such risks need to be taken into consideration when developing the safety specification and additional pharmacovigilance and risk minimisation activities. Providing a high-level flow-chart of the logistics of the therapy may be helpful (e.g., tissue harvest, manufacturing, transport, administration).

Please address, if applicable: Potential for transmission of infectious agents, Potential for misuse for illegal purposes, Potential harm from overdose, Potential for medication errors, Potential for off-label use.

Please address ATMP-associated risks if applicable, such as but not limited to: risks to living donors, risks associated with autologous products, risks in relation to quality characteristics, storage and distribution of the product, risks for close contact persons/HCPs; risks of germ line transformation, transmission of vectors, oncogenesis, unknown long-term effects.

2.6. Identified and potential risks

Note for clarification: The safety profile of the product should be concisely presented, as it is known at the time of the RMP data lock point. Appropriate presentation may depend on the specific product and the available clinical data basis. Relevant information for the identification of important identified and important potential risks and missing information should be discussed.

2.6.1. Pharmacological class effects

Please summarize significant safety information regarding related medicinal products; important identified risks of similar products may need to be considered as risk of a new product (class effect).

2.6.2. Important Risks for Inclusion in the List of Safety Concerns in the RMP

Note for clarification: Important risks to be included in the RMP are those risks which have an impact on the risk-benefit balance of the medicinal product. These risks may warrant further evaluation as part of the pharmacovigilance plan or risk minimisation activities, either routine or additional. Whether a risk is considered identified risk or potential risk would depend on the strength of evidence supporting the causal association with the medicinal product. Risks for adverse reactions may be identified from multiple sources such as non-clinical findings confirmed by clinical data; clinical trials, epidemiological studies, spontaneously reported data and published literature.

Please note: Not all adverse events/reactions reflect separate risks that require detailed consideration. For example, if an ATMP is administered as part of a surgery, several surgery-related complications may be grouped together if sensible from a clinical perspective. Public EU-RMP summaries of similar products may be consulted as an example.

<Important Identified/Potential Risk>:

Potential mechanism:

Frequency in clinical development:

Frequency following §4b AMG approval:

Risk factors and risk groups:

Preventability:

Risk-benefit impact: present the reasons for this classification, consider seriousness and outcome, frequency and severity.

For example, cytokine release syndrome (CRS) is an important identified risk of CD19-directed CAR T cells; a mechanistic link, risk factors and treatment interventions have been described in the literature; risk-benefit impact: XY% of clinical trial participants experienced CRS; CRS can be life threatening if detected/treated late; close monitoring and treatment is required to minimize the risk and to ensure an acceptable risk-benefit balance.

2.6.3. New safety concerns and reclassification with a submission of an updated RMP

(if applicable)

Note for clarification: Changes to the safety concerns (new identified and potential risks; re-classification or removal) together with an evaluation / justification should be provided in this section, with appropriate reference to the safety data.

2.6.4. Summary of safety concerns

A summary of the safety concerns identified in the previous sections.

Summary of safety concerns	
Important identified risks	
Important potential risks	
Missing information	

3. Pharmacovigilance plan

3.1. Routine pharmacovigilance activities

Routine pharmacovigilance is the primary/minimum set of activities required to fulfil the legal requirements for pharmacovigilance.
Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
Specific adverse reaction follow-up questionnaires for <safety concerns> (if applicable)

3.2. Additional pharmacovigilance activities

Note for clarification: The nature of many ATMP necessitates additional pharmacovigilance activities, for example, to ensure long-term follow-up of treated patients. Ongoing clinical trials should be included. Collecting data post §4b AMG approval might be important, for example due to limited safety and/or efficacy information from clinical trials or potentially relevant differences between trial settings and real world use. If a study aims to evaluate the effectiveness of risk minimisation measures, this needs to be highlighted in the study summary of objectives.

<Study short name and title:>
<Rationale and study objectives:>
Indicate the rationale for conducting the study (include also all the safety concerns addressed). Present briefly the study objectives.
<Study design:>
<Study population and size:>
<Milestones:>

Include milestones for reporting to the regulatory authorities (e.g. protocol submission, reporting in PSURs, interim reports, and final report submission) as well as major milestones from study protocol (e.g. registration in the EU PAS register, start/end of data collection, interim progress reports, final study report completion, date of publication).

Justification that proposed pharmacovigilance activities will be sufficient:

3.3. Summary of the Pharmacovigilance Plan

Note for clarification: This section should be a complete overview of all on-going and planned studies included in the pharmacovigilance plan.
Protocols (synopses) for studies in the pharmacovigilance plan should be provided in the annex of the RMP until completion of the study and final study report submission to the competent authority.

Table of on-going and planned additional pharmacovigilance activities and post-authorisation efficacy studies

Study/activity and status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

4. Risk Minimisation Measures

Routine risk minimisation activities are those that apply to every medicinal product and, for example, relate to the summary of product characteristics/package leaflet (Fach- und Gebrauchsinformation); labelling; legal status of the product.

4.1. Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
<Safety concern>	<Routine risk communication in SmPC/PL: >

4.2. Additional Risk Minimisation Measures

Additional risk minimisation measures should only be suggested when essential for the safe and effective use of the medicinal product. Key messages of additional risk minimisation activities should be provided in the annex. Further guidance on additional risk minimisation measures is provided in GVP Module XVI.

For example: criteria for the required expertise in a treatment centre (i.e, controlled distribution programme), HCP information/training material such as a pharmacy/surgical guide or a HCP guide on the specific risks of the ATMP, patient or parent/carer guide, a patient alert card in case of a gene therapeutic product.

<Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.> Or

<Additional risk minimisation 1>

<Objectives: >

Include objectives including a list of risks addressed.

<Rationale for the additional risk minimisation activity: >

<Target audience and planned distribution path: >

Include very brief summary of planned communication plan.

<Plans to evaluate the effectiveness of the interventions and criteria for success: >

Justification that proposed Risk Minimization Measures will be sufficient:

5. Summary of pharmacovigilance and risk minimisation activities

Include all safety concerns identified in the summary of safety concerns

Summary table of pharmacovigilance activities and risk minimisation activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
<Safety concern 1>	<Routine risk minimisation measures> <Additional risk minimisation measures:>	<Additional pharmacovigilance activities:>

6. Summary of the risk management plan for <invented name> (<active substance>)

Note for clarification: This section summarises key elements of the RMP. It needs to be in line with the other parts of the RMP and should not contain any references to other sections of the document as it is meant for publication.

I. The medicine and what it is used for

According to section 1.1 Product details.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

II.A List of important risks and missing information

Important risks of <invented name> are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of <invented name>. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
As stated in RMP section 2.6.4. Summary of safety concerns	
Important identified risks	
Important potential risks	
Missing information	

II.B Summary of risk minimisation measures

<Important <identified> <potential> risk > or <Missing information>	
Risk minimisation measures	<Routine risk minimisation measures:> <Additional risk minimisation measures:> <No risk minimisation measures>

II.C Pharmacovigilance Plan

II.C.1 Studies which are conditions of the approval according to §4b AMG

<The following studies are conditions of the marketing approval:>

C.2 Other additional pharmacovigilance activities

<Study short name>

Purpose of the study/activity: Include text from section 3.2 Additional pharmacovigilance activities 'Rationale and study objectives'.

<There are no studies required for <invented name>.>

7. Stufenplanbeauftragter / QPPV

Name	
Position	
Qualifications	
Contact details	
Signature	

8. ANNEXES

- 8.1. SmPC (summary of medical product characteristics) or CCDS (Company core data sheet) and package leaflet**
- 8.2. Tabulated summary of completed pharmacovigilance study programme**
- 8.3. Protocol synopses for proposed, on-going and completed studies in the pharmacovigilance plan**
- 8.4. Key details of proposed additional risk minimisation activities**
- 8.5. Other supporting data (e.g. Questionnaires, references)**
- 8.6. Summary of changes to the risk management plan over time**

A list of all significant changes to the Risk Management Plan over time, incl. version and approval date.