Individualized Risk Assessment

Linking Substance Specific Data of [insert substance name] With Patient Specific Data

Version number	**Version X.X**
Last update of current version	dd.mm.yyyy

Updates

Last update of EPAR information:	dd.mm.yyyy
Last update of SmPC information:	dd.mm.yyyy
Last update of FDA information:	dd.mm.yyyy
Last update of registered paediatric studies:	dd.mm.yyyy
Last update of VigiAccess™ ADR database:	dd.mm.yyyy
Last update of EMA ADR database (EU):	dd.mm.yyyy
Last update of BfArM / PEI ADR database (DE):	dd.mm.yyyy
Last update of INFORM registry (ADR):	dd.mm.yyyy
Last update of literature:	dd.mm.yyyy

Sources of product information

- European public assessment report (EPAR)
- Summary of Product Characteristics (SmPC)
- FDA product information
- Drug databases: Drugdex, Drugbank (if applicable, add further sources)

Registries

- WHO International Clinical Trials Registry Platform
- NIH Clinical Trials Register “clinicaltrials.gov”
- EU clinical trial register

ADR databases

- VigiAccess™ ADR database (WHO)
- EMA ADR database (EU)
- BfArM / PEI ADR database (DE)

Literature search

- PubMed

Table of Contents

A. Drug-specific information

A.I. Summary of currently published product information

A.I.1. Authorization details

A.I.1.1. Substance

Name of the medicinal product: *insert name of medicinal product*
Active substance: *insert name of active substance*

A.I.1.2. Status of marketing authorization in Europe / current decisions of the EMA

- Date of initial authorization: *dd.mm.yyyy*
- Renewal of the marketing authorization: *if applicable, insert date*
- Approval details: *additional monitoring, conditional approval; yes / no*
- Orphan drug status: *yes / no*
- Dosage forms and strengths: *insert forms and strengths*
- Currently pending decisions: *if applicable, insert type and date of pending decisions (decisions on paediatric use should be described in chapter A.I.1.5).*
- Withdrawn application: *if applicable, insert reason and date*

For Germany only: *status of benefit assessment of (**substance name**) in accordance with the German Social Code, Book Five (SGB V), section 35 a.*

A.I.1.3. Status of marketing authorization in USA

- Initial U.S. Approval: *dd.mm.yyyy*
- FDA application No.: *insert initial application (new drug application (NDA)) number*
- Current version of label information: *insert date and no of supplement*
- Renewal of the marketing authorization: *if applicable, insert date*
- Accelerated approval: *yes / no*
- Orphan drug status: yes / no
- Dosage forms and strengths: *insert forms and strengths*
- Withdrawn application: *if applicable, insert reason and date*

A.I.1.4. Marketing authorization holder (MAH)

Name and localization of MAH

A.I.1.5. Paediatric use: current state of authorization

Insert status of paediatric use. Usually substance is not authorized for paediatric use. If substance is authorized for paediatric use, please refer to chapter A.I.2.2.2 for paediatric indication(s). For paediatric clinical trials please refer to chapter A.II.2.1.

A.I.1.5.1. Paediatric investigation plan (PIP) and decisions of the Paediatric Committee of the EMA (PDCO)

Please consider that decisions of the EMA cannot be commented in detail due to lack of essential documents (PIP and further EMA decisions). Essential documents are not publicly available.

- PIP: *insert EMA no (source of information: search by **substance name** on EMA website[1])*
- Pharmaceutical form(s): *insert formulation details according to EMA information*
- Condition(s)/indication(s): *insert condition(s)/indication(s) according to EMA information*
- Decision(s): *insert decision(s) no (P/xxxx/year) according to EMA information*

1. Waivers: *if applicable, insert details of EMA decision(s) on waiver(s). Describe condition(s) with reference to waiver*

2. Paediatric Investigation Plan: *if applicable insert details of EMA decision(s) on PIP. Describe indication(s), subset(s) of paediatric population(s), pharmaceutical form(s), studies, and date of PIP completion.*

A.I.1.5.2. Decisions of the Paediatric Committee of the FDA

If applicable insert details of FDA decision(s) concerning paediatric use. These details are generally described in the initial approval letter or supplement letter(s), chapter "required pediatric assessments". If drugs are neither approved for children nor for adults free search on the FDA website is recommended to detect the current state of approval process. Depending on individual drugs information packages for meetings of the "Pediatic Oncology Subcommitee of the Oncolgic Drugs Advisory Committee" are provided which focus on paediatric authorization(s).

A.I.2. Indications

A.I.2.1. Pharmaceutical group

Insert information of EPAR if authorized in the EU / EEA. If drug is authorized only in the U.S. please refer to FDA approval documents.

A.I.2.2. Therapeutic indication

A.I.2.2.1. Adults

Insert information of EPAR if authorized in the EU / EEA. If drug is authorized only in the U.S. please refer to FDA approval documents.

A.I.2.2.2. Children

Usually substance is not authorized for paediatric use. If substance is authorized for paediatric use, refer to EPAR or FDA approval documents.

A.I.3. Mechanism of action

Insert figure of the pathway to visualize the mechanism of action and description of mechanism of action according to the SmPC. If SmPC is not available due to lack of marketing authorization in the EU, please refer to FDA documents.

1 http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp&mid=; last request: 25.10.2016

A.I.4. Pharmacological characteristics

Short summary of pharmacological characteristics bases on SmPC or FDA documents. Additionally drug databases (DrugBank and/or DRUGDEX) offer quick overviews which can be used in this chapter.

A.I.4.1. Pharmacodynamic properties

For source of information see chapter A.I.4 above.

A.I.4.2. Pharmacokinetics

- Absorption:
- Distribution:
- Metabolism:
- Excretion:
- Elimination Half Life:
- Effects of age and gender:
- Hepatic and renal impairment:

For source of information see chapter A.I.4 above. Only insert key data to keep the document clearly arranged.

A.I.4.3. Preclinical data

Insert data according to the chapter 5.3 of the SmPC. If SmPC is not available due to lack of marketing authorization in the EU, please refer to FDA documents. Information of the MAH can also be used in this section. If these data are confidential, this part should be marked as confidential and should not be provided to third parties.

Tab. 1: Summary of preclinical safety data according to [insert source of information] of substance name

Toxicity	Animal model	Result
……		
……		
……		
……		

A.I.4.4. Juvenile animal data

A.I.4.4.1. Juvenile animal data according to the SmPC

Check SmPC for juvenile animal data and insert relevant information, if available. If the MAH provides the investigators' brochure also use this document as source of information.

A.I.4.4.2. Juvenile animal data according to FDA prescribing information

Check FDA prescribing information (chapter 8.4 (pediatric use)) and insert relevant information. Also check the pharmacology review(s) of initial or supplemental approval(s) for juvenile animal data which can be relevant for paediatric studies or use.

A.I.5. Interactions

Short summary of interactions bases on SmPC or FDA prescribing information (chapter 7). Additionally drug databases (DrugBank and/or DRUGDEX) offer quick overviews which can be used in this chapter. Indicate as reference which sources are used. Keep in mind that categories may change depending on individual drug.

A.I.5.1. Effect of other medicinal products on substance name

A.I.5.1.1. Active substances that may increase **substance name** plasma concentrations

A.I.5.1.2. Active substances that may decrease **substance name** plasma concentrations

A.I.5.2. Effect of substance name on other medicinal products

A.I.5.3. Effect of food on drug

A.I.6. Safety profile, adverse events and risk management plan

A.I.6.1. Warning letters

Warning letters ("Rote-Hand-Briefe") of the MAH published by BfArM

Although contents of warning letter(s) are already integrated in the SmPC, warning letter(s) are mentioned additionally to emphasize these post approval findings.
Indicate date and contents of warning letter(s).

FDA Warning letters / drug safety communications:

Although contents of warning letter(s) are already integrated in the prescribing information, warning letter(s) are mentioned additionally to emphasize these post approval findings. Indicate date and contents of warning letter(s).

A.I.6.2. Summary of main adverse events / reactions according to the EPAR / SmPC

*Insert EPAR summary "What are the risks associated with **substance name**" as quick overview. Also refer to chapter 4.8 "Undesirable effects" of the SmPC. Add a list of adverse reactions according to the SmPC (chapter 4.8) as annex A.I-1. Indicate as reference which sources are used.*

A.I.6.3. Warnings, precautions and adverse reactions according to the FDA product information

Warnings and precautions

Insert warnings and precautions according to highlights of prescribing information (most actual version). Also refer to chapter 5 of the prescribing information. Indicate as reference which sources are used.

Adverse Reactions

Insert adverse reactions according to highlights of prescribing information (most actual version). Also refer to chapter 6 of the prescribing information. Indicate as reference which sources are used.

A.I.6.4. Summary of risk management plan

This chapter depends on marketing authorization in the EU / EEA. If the drug is authorized in the EU / EEA, the EPAR can contain a summary of the RMP. If the drug is authorized only in the U. S., please refer to initial approval documents (risk assessment and risk mitigation review(s)) of the FDA. Indicate as reference which sources are used.

Tab. 2: Summary of the RMP according to risk categories

Summary of important identified risks according to the risk management plan		
Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
…..		
…..		
Summary of important potential risks according to the risk management plan		
…..	–	
…..	–	
Summary of important potential risks according to the risk management plan		
Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimization activities**
…..		
…..	–	
Summary of important missing information according to the risk management plan		
…..	–	
…..	–	
Summary of other potential concerns according to the risk management plan		
…..	–	
…..	–	

A.II. Safety information of the paediatric population using substance name

A.II.1. Individual case safety reports of spontaneous reporting systems

A.II.1.1. WHO ADR database "VigiAccess™"

Insert graph of age-specific distribution of ADRs.
Additionally insert graph of ADR distribution categorized by system organ classes (SOCs).

A.II.1.2. EMA ADR database

Insert graph of age-specific distribution of individual cases.
Insert table of age-specific ADRs categorized by SOCs and highlight ADRs of paediatric subjects.

Tab. 3: Overview of distribution of ADRs categorized by reaction groups

	Number of suspected adverse reactions								
Reaction Group / Age Group	**Not specified**	**0-1 Month**	**2 Months-2 years**	**3-11 Years**	**12-17 Years**	**18-64 Years**	**65-85 Years**	**More than 85 Years**	**Total**
…									
…									

A.II.1.3. BfArM or PEI ADR database

Insert graph of suspected adverse drug reactions categorized by SOC.
Additionally, insert a table of age-specific distribution of ADRs according to the SOCs (annex A.II-1, available in German only).
For results of PEI ADR database search: insert table of age-specific ADRs since categorization of ADRs by SOCs is not provided by PEI.
If paediatric cases have been reported request narratives from BfArM or PEI and insert these information as table (annex A.II-2, available in German only).

A.II.2. Safety reports of organized data collection systems

A.II.2.1. Paediatric clinical trials

A.II.2.1.1. Information of the marketing authorization holder (MAH)

Information exchange depends on individual collaboration with the MAH (negotiation on how to use confidential information). Source of information are:

- *Paediatric investigation plan (PIP)*
- *Investigator's brochure (IB) for paediatric studies, if applicable*
- *Development safety update report (DSUR) on paediatric studies, if applicable*
- *Periodic safety update report (PSUR)*

Insert a summary of safety information of paediatric clinical trials of these documents, if provided by the MAH. Information of these documents should be marked as confidential and should not be provided to third parties.

A.II.2.1.2. Information of the EMA on paediatric clinical trials

Insert summary of assessment reports of selected paediatric clinical trials published in the EPAR, if available. These reports are published according to article 46 of the Regulation (EC) No 1901/2006. Download(s) of these documents are provided in the section "assessment history" of the EPAR. Indicate as reference which sources are used.

Provide a separate subsection for each paediatric clinical trial and focus on safety assessment, paediatric formulation, and pharmacokinetics depending on individual assessment reports.

A.II.2.1.3. Information of investigator initiated paediatric clinical trials

Currently not applicable, for future use only.

Prerequisite: patient accepts data transfer and agreement with principial investigator to use safety data for individualized risk assessment. Information of these sources should be marked as confidential and should not be provided to third parties.

A.II.2.2. Registries, observational studies and other systematic data collection projects

A.II.2.2.1. INFORM registry

Insert safety information of INFORM registry if drug is used in the INFORM registry. Individual cases to be summarized as annex A.II-3.

The INFORM registry also includes pharmacogenomics analyses. Insert these results too, if provided by the collaborating partner M. Schwab (Institute of Clinical Pharmacology (IKP) Stuttgart).

Information of the INFORM registry should be marked as confidential and should not be provided to third parties.

A.II.2.2.2. Other GPOH projects (e. g. registries)

Currently, no further registries, observational studies or other systematic data collection projects using targeted drugs are performed by the Society of Paediatric Oncology & Haematology. Only for future use.

Information of these projects should be marked as confidential and should not be provided to third parties.

A.II.3. Registered paediatric clinical trials and observational studies

Insert overview of paediatric studies registered at the WHO register, the NIH register "clinicaltrials.gov" and / or at the EU Clinical Trials Register. Use selection criteria "currently recruiting studies" if more than 30 paediatric studies are registered.

Tab. 4: Overview of paediatric studies, results of different registries

Protocol title	Sponsor	Trial status	Reference
…	…	-Number of patients: -Age min: -Age max: -Phase: -Conditions: -Countries:	Link to website

…	…	-Number of patients: -Age min: -Age max: -Phase: -Conditions: -Countries	Link to website

A.II.4. Actual literature concerning safety aspects in children

Insert results of paediatric projects concerning safety aspects of PubMed Search. Use the general search strategy as shown in table 5 below and insert this table in the risk assessement. Insert search results of search #4. Depending on number of publications insert results of search #2 and #3 (optional). Only insert relevant publications to keep the document clearly arranged.

Table 5: Overview of literature research strategy

Search	Keyword # 1*	Keyword # 2**	Keyword # 3***	No of publications	No of duplicates	Used for individualized risk assessment
# 1	Term 1	--	--	n_1	--	--
# 2	Term 1	Term 2	--	n_2	d_1	optional
# 3	Term 1	--	Term 3	n_3	d_2	optional
# 4	Term 1	Term 2	Term 3	n_4	d_3	X

* Term 1: Substance name or Trade name or Product code (different spelling)

** Term 2: Drug reaction or Adverse event or Adverse Reaction or Toxicity or Safety

*** Term 3: Children or Child or Pediatric or Paediatric or Newborn or Infant or Adolescent

Insert list of references according to research strategy, results of search #4 (#2 and #3 optionally)

A.III. Annexes

Annex A.I-1

Insert Annex A.I-1: List of side effects according to the SmPC (see chapter A.I.6.2) if drug is approved in the EU.

System organ class	Frequency	Adverse reaction
…	…	…
…	…	…

Annex A.II-1

Insert Annex A.II-1: Age-specific distribution of suspected adverse drug reactions (available in German only) according to the German ADR database (see chapter A.II.1.3).

Organsystem:							
Nebenwirkung	**0 bis 3**	**> 3 bis 12**	**> 12 bis 18**	**> 18 bis 65**	**> 65**	**k.A.**	**Summe**
ADR	No	No	No	No	No	No	Subtotal
ADR	No	No	No	No	No	No	Subtotal
Zwischensumme der Nebenwirkungen pro Organsystem							**No / SOC**
Organsystem:							
ADR	No	No	No	No	No	No	Subtotal
…	…	…	…	…	…	…	Subtotal
Zwischensumme der Nebenwirkungen pro Organsystem							**No / SOC**
							TOTAL

Annex A.II-2

Insert Annex A.II-2: Detailed safety information (narratives) of paediatric individual case reports, if available (see chapter A.II.1.3).

Depending on individual cases table should include the following items:

- *Basic data*
  - ✓ *age*
  - ✓ *sex*
- *Reporting data*
  - ✓ *primary source*
  - ✓ *reported via*
  - ✓ *report type*
- *Indication and medication*
  - ✓ *indication*
  - ✓ *drug*
  - ✓ *concomitant medication*
  - ✓ *resistance*
- *Efficacy*
- *Characterisation of reported events*
  - ✓ *events/reactions,*
  - ✓ *outcome,*
  - ✓ *seriousness/toxicity,*
  - ✓ *onset,*
  - ✓ *therapy stop/interruption*
  - ✓ *serious*
- *Assessment of seriousness*
  - ✓ *death,*
  - ✓ *life-threatening,*
  - ✓ *hospitalization,*
  - ✓ *disabling,*
  - ✓ *congenital,*
  - ✓ *other,*
  - ✓ *medical confirmed*
- *Detailed information on death (cause)*
- *Causality assessment*

Annex A.II-3: Detailed safety information of the INFORM registry

If applicable, insert summary of drug use of the INFORM registry (see chapter A.II.2.2.1). Information of the INFORM registry should be marked as confidential and should not be provided to third parties.

Depending on individual cases table should include the following items:

- *Administrative and baseline data*
  - ✓ *registry ID,*
  - ✓ *tumor diagnosis,*
  - ✓ *gender,*
  - ✓ *date of primary malignant disease,*
  - ✓ *date of INFORM registration)*
- *Targeted therapies (for each therapy use separate columns):*
  - ✓ *drug name,*
  - ✓ *substance name,*
  - ✓ *start date,*
  - ✓ *stop date,*
  - ✓ *premature stop,*
  - ✓ *toxicity*
- *Death*
  - ✓ *date*
  - ✓ *cause of death*
- *Separate toxicity report*
  - ✓ *toxicity*
  - ✓ *grading*
  - ✓ *start date*
  - ✓ *outcome*
  - ✓ *reason of toxicity*

B. Patient-specific information

B.I. Individual patient-specific data

*The safety information of the short profile of **substance name** (chapter A) is used as backbone for the patient-specific individualized risk assessement. This risk assessment consists of two columns of information. Column I encompasses substance-specific information as descripted in chapter A. Patient-specific data is the second source of information and represents column II. These information are collected for the individual patient according to chapter B of the short profile. As patient-specific information differs by patient, this short profile contains a universal questionnaire to evaluate the current status of the patient focused on safety information.*

B.I.1. Personal data

- Age
- Sex
- Height
- Weight
- Developmental stage (percentiles)
- Ethnical background

B.I.2. Classification of the oncological disease / medical history

- Tumor
- Localisation of the tumor
- Stage
- Onset
- Disease progress (relapse / progression)
- Date of onset of relapse / progression
- Number of relapses
- Metastases
- Localisation of metastases
- Molecular characterization of the tumor / metastases
- Date of molecular characterization
- Sort of therapy: drug / radiotherapy / surgery or combination(s)
- Quality of life parameters
- Method(s) to verify disease / disease progress

B.I.3. Drug history (previous chemotherapy)

Information of the previous chemotherapy should be provided to get a complete overview of the medical history.

- Name of applied drug(s) or chemotherapy protocol
- Dosing scheme of applied drug(s)
- Start of drug therapy
- End of drug therapy
- Observed organ toxicities (for details see toxicities and adverse reactions)
- Toxicity associated dose adaption(s)

- Start of drug dose adaption(s)
- End of drug dosis adaption(s)
- Current state

B.I.4. Toxicities and adverse events

A detailed description of toxicities which are emerged during tumor therapy is a substantial part of the individualized risk assessment. All emerged toxicities should be descripted in-depth giving an impression of the toxicity profil of an individual patient.

- Description of adverse event using the MedDRA nomenclature, if applicable
- System organ class
- Grading
- Onset of adverse event
- End of adverse event
- Development of adverse event
- Outcome
- Renal function (laboratory parameters)
- Liver function (laboratory parameters)
- EKG
- Suspected reason for adverse event (causality)
- Assessment of causality according to regulatory definitions
- Permanent damage
- In case of suspected causality: has the adverse event been reported to competent authorities or to the Drug Commission of the German Medical Association (AkdÄ)?
- How does the adverse event or its development influence the quality of life of the patient in a long-term perspective?

B.I.5. Previous treatment with targeted therapie(s)

Has the patient been previously treated with drug? If yes, drug name history and safety information should be provided.

B.I.6. Concomitant medication for planned targeted therapy

Information for each concomitant medication should be provided to determine potential drug-drug interactions.

- Name of concomitant medication(s)
- Indication(s)
- Dosing scheme of concomitant medication(s)
- Formulation(s)
- Known interactions

B.I.7. Pharmacogenomic characterization

- ADME genes (according to pharmacovigilance manual)

C. Main features of individualized risk assessment

Information of chapter A and B will be merged to provide an individual risk assessment. The individualized risk assessment focuses on the following questions:

- Which therapy options exist focusing on toxicity and adverse reactions?
- Is a targeted therapy recommended due to the medical history and patient-specific information?
- Which targeted therapy is recommended according to the target pathway and the safety profile of the drug name?
- Has the patient an increased risk of performing adverse events using a selected targeted therapy?
- Which system organ class(es) should be extensively monitored?
- Which special clinical monitoring actions should be applied?
- Which combinations of targeted therapies should be avoided?
- Which concomitant therapies should be avoided?
- Which dosing scheme is preferred?