Annex 14
to Pharmacovigilance Procedure
(item 6 of chapter 4 of part V)

STRUCTURE
of risk management plan

Part I. Overview

Part II. Safety specification

Module SI. Epidemiology of the indication(s) and target population(s)

Module SII. Non-clinical part of the safety specification

Module SIII. Clinical trial patient exposure

Module SIV. Populations not studied in clinical trials

Module SV. Post-registration experience

Module SVI. Additional Ukraine's, EU requirements for the safety specification

Module SVII. Identified and potential risks

Module SVIII. Summary of the safety concerns

Part III. Pharmacovigilance plan

Part IV. Plans for post-registration efficacy studies

Part V. Risk minimisation measures

Part VI. Summary of the risk management plan

Part VII. Annexes

REQUIREMENTS
for information submitted in risk management plan

Type of new application	Part I	Part II - Module SI	Part II - Module SII	Part II - Module SIII	Part II - Module SIV	Part II - Module SV	Part II - Module SVI	Part II - Module SVII	Part II - Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Biosimilar medicinal product	√	*	√	√	√	√	√	√	√	√	√	√	√	√
Informed consent	√	√	√	√	√	√	√	√	√	**	**	√	**	√

Generic medicinal product	√	*	*	*	*	*	*	*	√	**	**	√	**	√
Hybrid medicinal product	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Fixed-combinations	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Well-established medicinal use **	√	√	**	**	**	√	√	√	√	√	√	√	√	√
Same active substance**	√	√	**	**	**	√	√	√	√	√	√	√	√	√

For hybrid medicinal products or fixed combinations only the data on the fixed combination or data relating to the differences compared with the reference medicinal product need be supplied for modules SII (Non-clinical part) and SIII (Clinical trial patient exposure).

_____

* Not required.

** Modified requirements.

RISK MANAGEMENT PLAN

(title page)

Name of active pharmaceutical ingredient by International Nonproprietary Name	
Pharmacotherapeutic group ATC code	
Name of registration certificate holder/applicant	
Medicinal product(s), vaccine(s), tuberculin to which risk management plan refers.	1. 2. 3. ...
Trade name(s) of medicinal product(s), vaccine(s), tuberculin	

Data lock point for this risk management plan _____ (dd/mm/yy) Version number _____

Date of final sign off _____ (dd/mm/yy)

OVERVIEW OF MEDICINAL PRODUCT(S), VACCINE(S), TUBERCULIN* TO WHICH RISK MANAGEMENT PLAN REFERS

Title of part of the risk management plan	Title of module/annex of the risk management plan	Date when the risk management plan was last updated	Version number of the last update of the risk management plan**
1	2	3	4
PART I. Overview	Administrative data		
PART II. Safety specification	Module SI. Epidemiology of the indication(s) and target population(s)		
	Module SII. Non-clinical part of the safety specification		
	Module SIII. Clinical trial patient exposure		
	Module SIV. Populations not studied in clinical trials		
	Module SV. Post-registration experience		
	Module SVI. Additional Ukraine's, EU requirements for the safety specification		
	Module SVII. Identified and potential risks		
	Module SVIII. Summary of the safety concerns		
PART III. Pharmacovigilance plan (including post-registration safety studies)			
PART IV. Plans for post-registration efficacy studies			
PART V. Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)			
PART VI. Summary of the risk management plan			
PART VII. Annexes***	Annex 1.		

	Main information in the risk management plan in a structured electronic format		
	Annex 2. Approved (current) or proposed (if medicinal product is not registered) summary of product characteristics, instructions for medical use, package leaflet.		
	Annex 3. Worldwide registration status of medicinal product		
	Annex 4. Synopsis of on-going or completed clinical trial protocol		
	Annex 5. Synopsis of on-going and completed pharmacoepidemiological study protocol		
	Annex 6. Protocols for on-going and proposed studies indicated in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in part III of the risk management plan.		
	Annex 7. Specific adverse reaction follow-up forms		
	Annex 8. Protocols for on-going and proposed studies indicated in part IV of the risk management plan		
	Annex 9. Synopsis of study reports for parts III, IV of the risk management plan.		
	Annex 10. Details of additional risk minimisation activities (if applicable).		
	Annex 11. Mock up examples of the material provided to healthcare professionals and patients		
	Annex 12. Other supporting data		

* Hereinafter – medicinal product.

** A new risk management plan version number shall be assigned each time such risk management plan is updated. When no information is provided in some modules/parts of the risk management plan, "Date when the risk management plan was last updated" field shall be left blank, and "Not applicable" shall be written in "Version number of the last update of the risk management plan" field.

*** Annexes 1 - 3, 10, 11 shall be provided for each medicinal product within the risk management plan.

PART I. OVERVIEW

ADMINISTRATIVE DATA

Full name of qualified person responsible for pharmacovigilance (QPPV)	
QPPV signature	
Contact person for the risk management plan related issues	
E-mail address or telephone number of contact person	

OVERVIEW OF VERSIONS

Version number of last agreed risk management plan:	
Version number	
Agreed within	(indicate procedure)

CURRENT VERSION OF RISK MANAGEMENT PLAN UNDER EVALUATION

Risk management plan version number	Date of submission	Procedure for submission

Trade name	
Registration procedure	
Brief description of the medicinal product:	
Anatomical Therapeutic Chemical (ATC) Classification	
Summary of mode of action	

Important information about composition of the medicinal product (information about composition of the medicinal shall be provided: active pharmaceutical ingredient and its origin (e.g. biological or other), relevant adjuvants or residues for vaccines)	
Indication(s) for use: **Approved (current) (if applicable);** **Proposed for approval (if applicable)**	
Posology and route of administration: **Approved (curren)t (if applicable);** **Proposed for approval (if applicable)**	
Pharmaceutical form(s) and strengths	
Country and date of first registration of the medicinal product	
Country and date of first launch of the medicinal product	
Country and date of first authorisation of the medicinal product in the EU	

IS THIS MEDICINAL PRODUCT SUBJECT TO ADDITIONAL MONITORING

YES ☐	**NO** ☐

PART II. SAFETY SPECIFICATION

MODULE SI. EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

(this shall be completed for each indication)

Indication for use	
Trade name of medicinal product	

If a medicinal product has an indication for both prevention or treatment of the same disease (e.g. malaria) but used in combination with different other therapies (e.g. antineoplastics), it may be appropriate to include the “linked” indications together.

If the indication targets a subpopulation of patients with the disease, the information for the target population as well as the disease as a whole (e.g. patients with metastatic breast cancer who have failed one or more prior treatment shall be provided).

If a disease can target both sexes, despite being predominately in one, information should be provided for both (e.g. breast cancer), unless it is a medicinal product contraindicated in one sex.

SI.1. Epidemiology of the disease

Indication for use	
Incidence	
Prevalence	
Demographics of the target population	
Important co-morbidities in the target population (If applicable, information shall be provided on the important co-morbidities in the target population shall be provided (e.g. if a medicinal product is intended for treating prostate cancer, the target population is men over the age of 50 years. But this population is also at increased risk of myocardial infarction. To identify whether a medicinal product might be increasing the risk of myocardial infarction, it is important to know how many cases of myocardial infarction would be expected in the target population (ideally) or men in the same age group, not taking the medicinal product. Estimation of the risk in the target population, as compared with the same age group may be particularly important if the disease itself increases the risk of a particular adverse event.))	
Differences in the epidemiology in the different regions (countries of the world) but the emphasis shall be on epidemiology in Ukraine of the indications for use (if there are differences in the different countries their analogue shall be provided, if possible, the data shall be presented by age, sex, and racial and/or ethnic origin)	
Risk factors for the disease (specify the risk factors that may lead to a disease, if possible (e.g. sex, age, weight, bad health habits, physical or emotional burden, excessive exercise activities, physical inactivity, co-morbidities, use of any medicinal product, malnutrition, history of allergies, gene polymorphism, etc.))	
Main treatment options (specify treatments, which are usually used to treat this disease)	
Mortality and morbidity (natural history) (specify mortality rates for this disease if possible))	

SI.2. Concomitant medication(s) in the target population

Specified shall be other medications that are frequently used with the medicinal product to which the risk management plan refers, either to treat the disease or complications of it (e.g. antihypertensives will frequently be used alongside hypoglycaemic medication in the treatment of diabetes, etc.).

SI.3. Important co-morbidities in the target population

Co-morbidities found in the target population shall be specified. If possible, incidence, prevalence and mortality from the co-morbidities in the target population shall be provided. If the incidence of

a comorbid disease commonly found in the target population is increased compared with the incidence in the general population of the same age/sex as a result of this pathology, this should be specifically discussed (e.g. for a medicinal product to treat rheumatoid arthritis, the incidence of coronary heart disease is increased in people with rheumatoid arthritis compared with that seen in patients without rheumatoid arthritis of the same age and sex)

MODULE SII. NON-CLINICAL PART OF THE SAFETY SPECIFICATION

This module shall present a summary of the important non-clinical safety study findings for the medicinal product. Negative findings and their potential relevance to the target population (e.g. negative reproductive toxicity) shall be mentioned. This module should normally present (but should not be limited to) the following data:

Key safety findings (from non- clinical studies)	Relevance to human usage
Toxicity including: single and repeat-dose toxicity; reproductive toxicty (must be discussed if medicinal product might be used in women of child-bearing potential); developmental toxicity; nephrotoxicity; hepatotoxicity; genotoxicity; carcinogenicity	
General safety pharmacology: cardiovascular (including potential for QT interval prolongation); nervous system; etc.	
Mechanisms for drug interactions	
Other toxicity-related information or data	

It shall be specified whether there is a need for additional non-clinical study data if the medicinal product(s) is/are to be used in special populations**.**

SII.1. Conclusions on non-clinical study data

Specified shall be safety concerns from non-clinical data that have:

been confirmed by clinical data;

have not been adequately refuted by clinical data;

where further research needed;

which are of unknown significance.

Safety concerns	List
Important identified risks (confirmed by clinical data)	
Important potential risks (not refuted by clinical data or which are of unknown significance)	
Missing information	

These safety concerns should be carried forward to Part II Module SVIII.

MODULE SIII. CLINICAL TRIAL PATIENT EXPOSURE

SIII.1 Brief overview of lifecycle for the medicinal product

Details shall be provided of how the approved (current) indications and target populations have changed during the lifecycle for the medicinal product(s). This shall include:

original indication /trade name(s) of the medicinal product(s);

new populations (e.g. extensions of indications/ new medicinal product(s);

any other significant changes (e.g. change in route of administration).

SIII.2 Clinical trial patient exposure

Information in the following tables shall be be provided for each indication with a summary table showing total exposure. Each table shall be provided, where available, based on exposed (to medicinal product of interest) patients in:

randomised, blinded trial population only;

all clinical trial populations (including open extension clinical trials of medicinal products).

Data presented in tables shall be pooled and not shown per trial unless there are justified reasons (to be provided) why some data should not be amalgamated. When the reason for providing an updated risk management plan is a new population (either extension of indication or a new medicinal product with the same active pharmaceutical ingredient) or a new strength or formulation, the new data should be presented separately first, as well as being included in the cumulative tables.

Data should be provided either in a table or graphically. The categories below are suggestions and tables/graphs should be tailored to the medicinal product. When patients have been enrolled in more than one trial (e.g. open label extension study) they should only be included once in the tables completed by age, sex, ethnic origin. Where differences in the total numbers of patients arise between tables, the tables should be annotated to reflect the reasons for the discrepancy.

If the medicinal product has only one indication, tables 2, 4, 7, 9 and 11 shall not be provided. Table 6 need not be provided if only one product in the risk management plan.

Table 1: Duration of patient exposure (by indication)		
Indication 1 (patient time shall only be provided for final duration category and total)		
Duration of patient exposure (at least)	Number of patients	Patient time
1 month		
3 months		
6 months		
12 months etc.		
Total patient time		

Indication 2 (patient time shall only be provided for final duration category and total)		
Duration of patient exposure (at least)	Number of patiens	Patient time
1 month		
3 months		
6 months		
12 months etc.		
Total patient time		

Table 2: Duration of patient exposure (totals)		
Total exposed population (patient time shall only be provided for final duration category and total)		
Duration of patient exposure (at least)	Number of patients	Patient time
1 month		
3 months		
6 months		
12 months etc.		
Total patient time		

Table 3: Patient distribution by dose (by indication)		
Indication 1		
Dose of exposure	Number of patients	Patient time
Dose 1		

Dose 2 etc.		
Total		
Indication 2		
Dose of exposure	Number of patients	Patient time
Dose 1		
Dose 2 etc.		
Total		

Table 4. Patient distribution by dose (totals)		
Total population		
Dose of exposure	Number of patients	Patient time
Dose 1		
Dose 2 etc.		
Total		

When providing data by age group, the age group shall be relevant to the target population. Artificial categories such as <65, >65 should be avoided. Paediatric data shall be divided by categories (e.g. in accordance with ICH HARMONISED TRIPARTITE GUIDELINE. CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION). Similarly, the data on elderly patients shall be stratified into categories such as 65 – 69 years; 70 – 74 years; 75 - 79 years. For teratogenic medicinal products, stratification into age categories related to childbearing potential might be appropriate for the female population. If the risk management plan is prepared for more than one medicinal product, the total population table shall be provided for each medicinal product as well as a combined table.

Table 5. Patient distribution by age group and gender (by indication)				
Indication 1				
Age group	**Number of patients**		**Patient time**	
	M	**F**	**M**	**F**
Age group 1				
Age group 2 etc.				
Total				
Indication 2				
Age group	**Number of patients**		**Patient time**	

	M	F	M	F
Age group 1				
Age group 2 etc.				
Total				

Table 6: Patient distribution by age group and gender (by medicinal product)				
Total population by medicinal product 1				
Age group	**Number of patients**		**Patient time**	
	M	**F**	**M**	**F**
Age group 1				
Age group 2 etc.				
Total				
Total population by medicinal product 2				
Age group	**Number of patients**		**Patient time**	
	M	**F**	**M**	**F**
Age group 1				
Age group 2 etc.				
Total				

Table 7: Patient distribution by age group and gender (totals)				
Total population				
Age group	**Number of patients**		**Patient time**	
	M	**F**	**M**	**F**
Age group 1				
Age group 2 etc.				
Total				

Table 8: Distribution by ethnic or racial origin (by indication)		
Indication 1		
Ethnic/racial origin	**Number of patients**	**Patient time**

Ethnic origin 1		
Ethnic origin 2 etc.		
Total		
Indication 2		
Ethnic/racial origin	**Number of patients**	**Patient time**
Ethnic origin 1		
Ethnic origin 2 etc.		
Total		

Table 9: Distribution by ethnic or racial origin (totals)		
Total population		
Ethnic/racial origin	**Number of patients**	**Patient time**
Ethnic origin 1		
Ethnic origin 2 etc.		
Total		

Table 10: Distribution by special populations (by indication)		
Indication 1	**Number of patients**	**Patient time**
Pregnant women		
Lactating women		
Patients with renal impairment (specify or categorise)		
Patients with hepatic impairment (specify or categorise)		
Patients with cardiac impairment (specify or categorise)		
Sub-populations with genetic polymorphism (specify)		
Immuno-compromised patients		
Indication 2	**Number of patients**	**Patient time**
Pregnant women		
Lactating women		
Patients with renal impairment (specify or categorise)		
Patients with hepatic impairment (specify or categorise)		

Patients with cardiac impairment (specify or categorise)		
Sub-populations with genetic polymorphism (specify)		
Immuno-compromised patients		

Table 11: Distribution by special populations (totals)		
Total population	**Number of patients**	**Patient time**
Pregnant women		
Lactating women		
Patients with renal impairment (specify or categorise)		
Patients with hepatic impairment (specify or categorise)		
Patients with cardiac impairment (specify or categorise)		
Sub populations with genetic polymorphism (specify)		
Immuno-compromised patients		

MODULE SIV. POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Data on the limitations of the clinical trial population in relation to predicting the safety of the medicinal product(s) in the pharmaceutical market place shall be provided. Suggestions and the discussion in Module SIV.3 shall be tailored to the medicinal product and its intended use and so may include other categories where there has been limited or no research. Limitations may also arise due to use in a different setting.

SIV.1 Limitations of adverse reaction detection common to clinical trial development programmes

Clinical trial development programmes are unlikely to detect the following types of adverse reactions due to well-known inherent limitations. Based on the number of patients exposed in clinical trials, the duration of patient exposure, total dose of medicinal product, action of medicinal product etc., it shall be discussed what adverse reactions could have been detected.

Ability to detect adverse reactions	**Limitation of clinical trial programme**	**Implications for target population**
Rare adverse reactions (it may be appropriate to choose other adverse reaction frequencies)	(e.g. 12,600 patients were exposed to the medicinal product over the whole clinical trial programme)	(E.g. adverse reactions with a frequency greater than 1 in 4,200 could be detected if there were no background incidence)

Adverse reactions due to prolonged exposure	(e.g. 3000 women were exposed to mecicinal product X for more than 4 years during which time there were no cases of endometrial carcinoma. In 42 women who used the product X endometrial hyperplasia was observed compared with 35 women in the nonexposed group (2000))	(E.g. according to the data obtained the product X has no impact on endometrial proliferation during the first 4 years of treatment. X is thought to …… (specify))
Adverse reactions due to cumulative effects	(e.g. specific organ toxicity)	
Adverse reaction which have a long latency		

SIV.2 EFFECT OF EXCLUSION CRITERIA IN THE CLINICAL TRIAL DEVELOPMENT PROGRAMME

Exclusion criteria across the clinical trial development programme shall be presented. Information on exclusion criteria shall demonstrate their effect on the clinical trial programme and the implications for treatment of the target population.

Exclusion criteria which are contraindications for use	
Criteria	**Implications for target population**
1	
2 etc	

Exclusion criteria which are not contraindications for use		
Criteria	**Reason for being an exclusion criterion**	**Justification for not being a contraindication for use**
1		
2 etc		

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

The categories listed below are under-represented in the clinical trial programme. Their relevance will depend upon the medicinal product, the indication and the clinical trial programme. There may be other relevant categories, which are applicable.

1. Children

Special consideration should be given to the experience of use in different paediatric age groups (e.g. in accordance with the classification provided in ICH HARMONISED TRIPARTITE GUIDELINE. CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION), since these relate to different physiological and anatomical development stages. If paediatric experience of use has been limited to certain age categories then the implications for other paediatric age groups shall also be discussed:

pre-term newborns;

neonate (birth to 27 days);

infants and toddlers (28 days to 23 months);

children (2 years to e.g. 11 years);

adolescents (e.g. 12 years to 18 years).

2. Elderly patients

Implications on the use in patients of 65 and older shall be discussed with appropriate consideration to the top ranges of the age spectrum. The effect of individual impairment should be discussed in the sections below but the effects of multiple (minor) co-existing impairments and also adverse reactions of particular concern in the elderly should be discussed.

Use of the medicinal product in different age groups (e.g. 65-69, 70-74, 75-79 years).

Need for laboratory screening prior to use of the medicinal product(s).

Effect of multiple co-existing impairments.

Adverse reactions of special concern in the elderly patients (e.g. dizziness, CNS effects).

Effect of multiple medications.

3. Pregnant and/or breast feeding women

If the target population includes women of child-bearing age, the implications for pregnancy and/or breast feeding shall be discussed. If contraception was a inclusion criterion for participation in the clinical trial this item shall also include the following:

Number of pregnancies and outcomes;

Analysis of why contraceptive measures failed (i.e. consideration of whether human error or an interaction between medicinal product and, e.g. oral contraceptives);

Implications for use under less controlled conditions (i.e. if contraception products which are effective under the relatively strict conditions of a clinical trial, have the same effectiveness in real life) and, if necessary, suggestions for improvement).

4. Patients with hepatic impairment.

5. Patients with renal impairment.

6. Patients with other co-morbidity e.g.:

Cardiovascular;

Immuno-compromised including transplant patients.

7. Patients with a disease severity different from the inclusion criteria in the clinical trial population.

8. Sub-populations carrying known and relevant polymorphisms

The extent of pharmacogenetic effects and the implications of genetic biomarker use in the target population shall be discussed, where relevant. The implications for patients with/without a specific genetic marker/specific mutation or with unknown status shall be stated, in particular, where the indication for use requires genetic testing.

9. Patients of different racial and/or ethnic origin

The implications for use of the medicinal product in patients with different racial and/or ethnic origins shall be discussed. In particular, differences in the frequency or types of gene variants for medicinal produtc metabolising enzymes may give rise to important differences in pharmacokinetics and/or frequency of adverse reactions. These variations in frequencies of particular alleles may have implications for medicinal product use or for pre-treatment testing in patients of particular populations (e.g. HLA-B*1502 allele is associated with severe cutaneous adverse reactions to carbamazepine and is found in approximately 10% in some Asian populations but rarely in Caucasian populations).

SIV.4 Conclusions on the populations not-studied and other limitations of the clinical trial development programme

Missing information

Where the missing information according to the clinical trial protocol could constitute an important risk to the target population it should be considered to be a safety concern and shall be stated here. If the missing information has been adequately investigated outside of the clinical trial programme this should be noted (with cross reference to the appropriate section of the risk management plan) in the comment section. Only safety concerns which are still outstanding should be carried through to Module SVIII of Part II of the risk management plan.

Safety concerns due to limitations of the clinical trial programme		**Is a safety concern still outstanding?**
Safety concern	**Comment**	**Yes/No**
1		
2		
...		

MODULE SV. POST-REGISTRATION EXPERIENCE

The purpose of this module is to provide information on the number of patients exposed to the medicinal product in the post-registration period; data on use of the medicinal product in clinical practice (use according to approved indications and off-label use including use in the special populations mentioned in Module SIV of the risk management plan). It should also include brief

information on the number of patients included in on-going or completed clinical studies conducted either to elucidate a safety issue or for drug utilisation purposes. In some cases detailed data may not be available. The tables given below provide guidance on how the data might be provided when available. Details of significant actions taken to update information on the safety of the medicinal product shall also be provided in this module.

SV.1 Action taken by regulatory authorities and/or registration certificate holders for safety reasons

Any significant regulatory action (including those initiated by the registration certificate holder) in any country in relation to a safety concern shall be listed. Significant regulatory action would include (but not limited to) a restriction to the registered indication, a new contra-indication, a new or strengthened warning in section "Peculiarities of use" and/or "Special warnings and precautions" of the instructions for medical use/summary of product characteristics for the medicinal product or any action to suspend or revoke a marketing authorization/registration certificate.

This list shall be cumulative but newly taken action (since last update to the module) shall be presented separately first, as well as being in the cumulative list. Roll-out in multiple countries of a new safety statement initiated by the registration certificate holder/applicant can be presented as one action (but all countries and range of dates (e.g. March-September, 2017) shall be listed). Comments may be added if this regulatory action is not applicable to certain medicinal products/formulations.

Table 1. Detailed description of actions taken by regulatory authorities and/or registration certificate holders for safety reasons since last update to this module

Safety concern	
Background	
Evidence source	
Action taken	
Countries where actions are taken	
Date(s) of actions	

Table 2. Cumulative list of actions taken by regulatory authorities and/or registration certificate holders for safety reasons

Safety concern 1			
Country(ies)	**Action taken**	**Comment**	**Date(s)**
Safety concern 2 etc.			
Country(ies)	**Action taken**	**Comment**	**Date(s)**

SV.2 Non-study post-registration exposure

Where possible, data on patients exposed to medicinal product in post-registration period shall be provided based on market research in the tables below. When the number of persons is calculated on the basis of sales data, details and justification shall be provided of the measure used to calculate exposure. Tables shall be provided for each indication and route of administration where possible.

SV.2.1 Method used to calculate exposure

If different methods have been used to calculate exposure for some tables, this section shall be repeated before the relevant table(s).

SV.2.2 Exposure

Distribution by age group and gender				
Indication				
Age group	**Number of patients**		**Exposure (e.g. packs or patient years)**	
	M	**F**	**M**	**F**
Age group 1				
Age group 1				
...				

Distribution by indication		
Indication	**Number of patients**	**Exposure (e.g. packs or patient years)**
Indication 1		
Indication 2		
...		

Distribution by route of administration		
Route of administration	**Number of patients**	**Exposure (e.g. packs or patient years)**
Oral		
Intravenous		

...		

Distribution by dose		
Indication		
Doses	**Number of patients**	**Exposure (e.g. packs or patient years)**
Dose 1		
Dose 2		
...		

Distribution by country		
Indication		
Countries	**Number of patients**	**Exposure (e.g. packs or patient years)**
Ukraine		
EU countries		
Other countries		
...		

If possible, the data on use in EU countries and non-EU countries shall be presented by country or administrative territorial unit of medicinal product sales. The categories provided are suggestions only and other relevant variables can be used (e.g. duration of treatment etc.).

SV.3 Post-registration use in populations not studied in clinical trials

Data on post-registration use of medicinal product(s) in the special populations identified in module SIV of the risk management plan as having no or limited exposure to medicinal product in clinical trials shall be provided (if available). Estimation of the numbers exposed and the method of calculation shall be provided whether or not the medicinal product(s) is used in these groups in compliance with the approved indications or off-label. Any differences in benefit or risk of medicinal product (s) seen between the special population and the target population as a whole shall be commented on.

Table 1

Paediatric use		
Use (estimated)	**Number of patients**	**Comment on any variation in benefit or risk (from overall target population)**

Pre-term new-borns; Neonates (birth to 27 days); Infants and toddlers (28 days to 23 months); Children (2 years to e.g. 11 years); Adolescents (e.g. 12 years to 18 years)		
Data source		
Method of calculation		

Table 2

Elderly patient use		
Use (estimated)	**Number of patients**	**Comment on any variation in benefit or risk (from overall target population)**
65 - 69 years 70 - 74 years 75 - 79 years		
Data source		
Method of calculation		

Table 3

Pregnant or breast feeding women		
Use (estimated)	**Number of patients**	**Comment on any variation in benefit or risk (from overall target population)**
Pregnant Breast feeding		
Data source		
Method of calculation		

Table 4

Use in patients with hepatic impairment		
Use (estimated)	**Number of patients**	**Comment on any variation in benefit or risk (from overall target population)**
Mild Moderate Severe		
Data source		
Method of calculation		

Table 5

Use in patients with renal impairment		
Use (estimated)	**Number of patients**	**Comment on any variation in benefit or risk (from overall target population)**
Mild Moderate Severe		
Data source		
Method of calculation		

Table 6

Other use		
Use (estimated)	**Number of patients**	**Comment on any variation in benefit or risk (from overall target population)**
Category Category Category		
Data source		
Method of calculation		

CV.4. Post-registartion off-label use

Information on off-label use of a medicinal product; i.e. the intentional use, for a medical purpose, which is not in accordance with the instructions for medical use of a medicinal product. Off-label use includes use of a medicinal product in paediatric age categories in which it (they) is (are) not indicated according to the approved instructions for medical use.

SV.4 Off-label use			
Category of use	**Country**	**Source of information**	**Comment**
(non-registered indication, in which the medicinal product was prescribed)		(source of information on use of the medicinal product for non-registered indication (off-label use))	

SV.5 Epidemiological study patient exposure

Registration certificate holders/applicants shall provide a listing of epidemiological studies, which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilisation or measure

effectiveness of risk minimisation measures. This listing shall include studies undertaken by the registration certificate holder/applicant and/or where the registration certificate holder/applicant is their sponsor. Studies undertaken by a marketing partner of the registration certificate holder/applicant, or studies, the results of which were obtained by the registration certificate holder/applicant from a third party, shall also be included in the list.

Study title and study type (e.g. cohort or case/control)	**Objectives**	**Population studied** (data source and country)	**Duration** (study period)	**Number of persons (in each group or of cases and controls) and person time (if appropriate)**	**Comment**
Study 1					
Study 2					
...					

MODULE SVI. ADDITIONAL UKRAINE'S, EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for harm from overdose

The potential for harm from overdose either intentional or accidental shall be discussed. Special attention shall be given to medicinal products where there is increased risk of overdose or where there is a narrow therapeutic margin or potential for major dose-related toxicity, and/or where there is a high risk of intentional overdose in the target population. Cases of overdose occurred during clinical trials shall be described. Where appropriate, overdose shall be included as a safety concern in Module SVIII of the risk management plan.

SVI.2 Potential for transmission of infectious agents

The potential for the transmission of an infectious agent shall be described. This may be because of the nature of the manufacturing process or the materials involved. For vaccines, any potential for the transmission of live virus shall be discussed. For advanced therapy medicinal products, a cross reference to module SVII of the risk management plan may be made.

SVI.3 Potential for misuse for illegal purposes

The potential for use as a narcotic substance or facilitating assault etc. If appropriate, risk minimization measures shall be presented.

SVI.4 Potential for medication errors

If necessary, this section may be completed separately for each medicinal product.

SVI.4.1 Description of medication errors identified during the clinical trial

Trade name of medicinal product(s)				
Description of	**Number of**	**Analysis of cause**	**Actions taken to**	**Comment**

error	occurrences		prevent medication errors	

SVI.4.2 Measures taken for prevention of medication errors for the final product(s) being marketed

It shall be discussed how the errors have been prevented in the design of the medicinal product, packaging, labelling etc, namely:

Prevention of error due to wrong medication;

Prevention of error due to wrong dose (strength, form, concentration);

Prevention of error due to wrong route of administration.

SVI.4.3 Effect of administration device failure

Information shall be given for medicinal products, which are administered using a specific device.

SVI.4.4 Reports of medication errors

Trade name of medicinal product(s)				
Description of error	**Number of occurrences**	**Analysis of cause**	**Actions taken to prevent medication errors**	**Comment**

For medicinal products of one group with multiple strengths, posologies or concentration, different compositions consideration shall be given to identifying “medication error” and including it as a safety concern.

SVI.5 Potential for off-label use

The potential for off-label use of a medicinal product shall be discussed. This is particularly relevant where a medicinal product has an indication restricted to a subset of the population within a disease area or there are situations where the medicinal product must not be given for safety reasons. The potential for use in other disease areas shall also be considered where this is likely.

SVI.6 Specific paediatric issues

SVI.6.1 Issues identified in paediatric investigation plans

Any issues identified in paediatric investigation plans shall be detailed and the relevance to the indications covered by the risk management plan discussed. Provided shall be details of how

paediatric investigation plan recommendations have been considered. Cross reference may be made to other modules of the risk management plan.

Trade name of medicinal product(s)		
Issue (safety or long term efficacy)	**Background**	**Relevance of issue to data provided in risk management plan and how, if appropriate, it will be addressed.**

SVI.6.2 Potential for paediatric off-label use

If the disease or disorder which is being treated by the medicinal product is found in the paediatric population, and the product is not registered in all paediatric age groups, the potential for off-label paediatric use in the non-registered age groups shall be discussed. If there are limited treatment options doctors are not likely to adhere to the registered indications for use so it is important that potential paediatric issues are discussed and consideration given for their inclusion as a safety concern. Any actual use shall be discussed and cross reference to other relevant risk management plan sections provided.

SVI.7 Conclusions

Safety concerns from this module (to be carried through to Part II Module SVIII)	
Safety concern	**Comment**

MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

More detailed information on the important identified and potential risks shall be provided. This module shall be concise (without a data dump of tables or lists of adverse reactions from clinical trials, without duplication of actual contents of section “Adverse reactions” of the instruction for medical use and/or summary of product characteristics. It shall include only the important identified and potential adverse reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

When determining which of risks is imporatant several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health shall be considered. Any risk which is clinically important and which is/is likely to be included in the “Contraindications”, or “Peculiarities of use” section of the instruction for medical use and/or summary of product characteristics shall be included in this module. In addition, risks, which whilst not serious enough to require specific warnings or precautions, but which occur in a significant proportion of the patients, affect the quality of their life, and which could lead to serious consequences if untreated, shall also be considered for inclusion (e.g. severe nausea and vomiting with chemotherapy).

For some medicinal products, disposal of the used product may constitute a safety concern (e.g. transdermal patches where there may be significant amounts of active pharmaceutical ingredient remaining in the patch when it is discarded). Specified may be occasions where there is an environmental concern over product disposal because of known harmful effects on the environment (e.g. substances which are particularly hazardous to aquatic flora and fauna which should not be disposed of in landfill sites).

Because there are different additional categories of risks to be considered only with advanced therapy medicinal products, for these medicinal product a different version of the template shall be submitted for this module. Only one version of the template of module SVII of the risk management plan shall be used.

SVII.1 Newly identified safety concerns (since last version of this module)

Safety concern	
Details	
Source	
New studies proposed in pharmacovigilance plan?	Yes/No
New risk minimisation actions proposed?	Yes/No

SVII.2 Recent study reports with implications for safety concerns

Study reports (either interim or final, from whichever type of study), which contain results, which have a significant impact on an existing safety concern should be discussed. Such reports shall be processed since the last version of the risk management plan. The conclusions shall be incorporated into the other sections and modules of the safety specification as appropriate with detailed information on the risk provided in module SVII.3. Information of the above safety concerns may also be provided in other modules.

SVII.3 Details of important identified and potential risks from pre-registration and post-registration experience (including newly identified)

Information on the important identified and important potential risks shall be provided. This section should be concise (without a data dump of tables or lists of adverse reactions from clinical trials, without duplication of proposed or actual content of section "Adverse reactions" of the instructions for medical use and/or summary of product characteristics. For risk management plans involving single medicinal products, risks which relate specifically to an indication or formulation can usually be handled as individual safety concerns (accidental intravenous administration could be a safety concern in a single medicinal product with both oral and subcutaneous forms). It may be appropriate to include risks associated with a significant change to a manufacturing process (particularly for biological medicinal products) and risks associated with medication error.

For risk management plans covering multiple medicinal products where there are significant differences in the identified and potential risks for different medicinal products, it may be appropriate to categorise the risks to make it clearer which risks relate to which medicinal product. Division of identified and potential risks using the headings below shall **only** be considered **when** the risks clearly do not apply to some medicnal products covered by the risk management plan and lack of separation could cause confusion. Categories which could be considered include:

Risks relating to the active pharmaceutical ingredient

This category would include important identified or potential risks which are common to all formulations, routes of administration and target populations. It is likely that most risks will fall into this category for the majority of medicinal products.

Risks related to a specific formulation, indication or route of administration.

Examples might include a risk management plan with two medicinal products with completely different indications for use (e.g. sildenafil with an indication in one medicinal product for erectile dysfunction and in a second medicinal product for pulmonary arterial hypertension.

Risks relating to a specific target population.

The paediatric population is an example of a target population where there may be additional risks relating to physical, mental and sexual development which would not be relevant to a medicinal product intended solely for adult patients.

Risks associated with switch of medicinal product to non-prescription status.

For each important identified and important potential risk the following information shall be provided (if available) (this information can be provided outside of the table format. In this case, the sections and items shall be used in the text structure).

Identified/potential risk (specify identified or potential risk)	
Frequency with 95 % CI	It shall be stated clearly which frequency parameter is being used (e.g. incidence rate or incidence risk and the data source, e.g. blinded clinical trial population, epidemiological study). For identified risks incidence shall be presented for the whole population and relevant subpopulations. Where there are clear differences in rates between populations, this shall be specified.
Seriousness/outcomes	The distribution of outcomes shall be provided (e.g. % fatal, % recovered/with/without treatment/sequelae, % not recovered, % hospitalised etc.)
Severity and nature of risk	Information on grades of severity where available shall be provided.
Background incidence/prevalence	Background incidence/prevalence of the risk in the unexposed target population(s)
Risk groups or risk factors	Description shall be provided for groups, patient factors, dose, time or other factors where available including additive or synergistic factors
Potential mechanism	Description of potential mechanism shall be provided
Preventability	Data on predictability or preventability of adverse reactions, effect of known risk factors, mitigation through early detection shall be provided
Impact on patient	Data on effect on quality of life shall be provided
Potential public health impact of safety concern	If possible, description and information shall be provided, using e.g. Numbers Needed to Harm and/or expected number of patients affected, hospitalisations, fatalities given the predicted

	population use.
Evidence source	Brief description and cross references to supporting data in CTD or annex shall be provided
MedDRA terms	Terms used in appropriate annex of the risk management plan for post marketing surveillance

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

The main routes of metabolism and elimination and the potential for interactions due to effects on CYP enzymes, drug transporters etc. shall be discussed.

SVII.4.2 Important identified and potential interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions shall be be discussed in relation to both the medicinal products used to treat a specific disease, and those commonly used in the target population. Important interactions with herbal medicinal products or with food shall also be discussed.

Interacting substance(s)	
Effect of interaction	
Evidence source	
Possible mechanisms	
Potential health risk	
Conclusion	

Including interactions as a safety concern in Module SVIII of Part II shall be considered.

SVII.5 Pharmacological class effects of medicinal product covered by risk management plan

Risks which are believed to be common to the pharmacological class shall be specified.

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

For risks which have been included above in “Details of important identified and potential risks from pre-registration and post-registration experience (including newly identified)”, the following details below shall be provided:

Risk	**Frequency in clinical trials of medicinal product**	**Frequency seen with other medicinal products in same pharmacological class** (source of data/reference)	**Comment**

Risk 1		E.g. Medicinal product A Medicinal product B Medicinal product C Review of adverse reactions BMJ 2008: 5; 214-217	
Risk 2			
...			

SVII.5.2 Important pharmacological class effects not discussed above

Information in the table below shall be provided for each important risk which has not been included in module SVII "Details of important identified and potential risks from pre-registration and post-registration experience (including newly identified)" but which is believed to be common to the pharmacological class. If an important potential risk, associated with other medicinal products of the pharmacological class, is not thought to be a safety concern with the medicinal product this shall be justified and relevant evidence provided.

Potential risk	
Seriousness/outcomes	
Severity and nature of risk	E.g. data by grade of severity where available shall be tabulated
Frequency with medicinal products of the same or similar pharmacological class with 95 % CI	
Risk groups or risk factors	Use, dose, time and susceptibility data or other factors where available shall be provided
Potential mechanism	Information of potential mechanism shall be provided
Comment	

MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

A summary of the safety concerns identified in Modules SII, SIV, SVI, SVII of Part II of the risk management plan shall be prepared. A safety concern may be an:

important identified risk;

important potential risk;

missing information.

For a risk management plan covering multiple medicinal products where there may be significant differences in the important identified and important potential risks for different products, similar to the presentation of risks in module SVII, it may be appropriate to subdivide the summary of safety

concerns under specific headings with the relevant identified and potential risks under each heading. Headings which could be considered include:

safety concerns relating to the active pharmaceutical ingredient;

safety concerns related to a specific formulation or route of administration;

safety concerns relating to the target population;

risks associated with switch of the medicinal product to non-prescription status.

Division of safety concerns by headings shall only be considered when the risks clearly do not apply to some medicinal products and their inclusion as a single list could cause confusion.

SUMMARY TABLE OF SAFETY CONCERNS

Summary of safety concerns	
Important identified risks	(list)
Important potential risks	(list)
Missing information	(list)

PART III: PHARMACOVIGILANCE PLAN

The pharmacovigilance plan shall contain details of pharmacovigilance activities/studies, which are intended to identify and/or characterise safety and efficacy concerns related to use of medicinal product in the target population, and where the medicinal product is in its life-cycle. A pharmacovigilance plan may also include details of studies to measure the effectiveness of risk minimisation measures for important risks where a formal study is required.

If some safety concerns are well characterised routine pharmacovigilance will be sufficient. Depending upon the safety concern, and areas to be investigated, a pharmacovigilance plan may include epidemiological (non-interventional) studies (such as cohort, case control, extract from registries, drug utilisation etc.) but may also include interventional studies or more rarely pre-clinical studies (e.g., clinical trials, *in vivo* or *in vitro* studies).

Each safety concern and areas, which need investigation, shall be considered in Section III.1 of the pharmacovigilance plan. Section III.2 provides details of any actions taken to measure the effectiveness of risk minimisation activities. The results of any studies should be briefly summarised in section III.3. If the study results concern the effectiveness of risk minimisation activities, brief results shall be provided in section III.3. If the results suggest that the risk minimisation measure is uneffective, analysis of this situation, and proposal for rectification of mistakes shall be provided in Part V of the risk management plan. Details of the individual studies and milestones shall be given in Section III.4. Section III.5 summarises the data provided in the pharmacovigilance plan concerning completed, on-going and planned activities.

III.1 SAFETY CONCERNS AND OVERVIEW OF PLANNED PHARMACOVIGILANCE ACTIONS

For each safety concern specified in module SVIII of Part II, details of specific areas that still need confirmation or further investigation (e.g. confirmation of incidence, investigation of risk factors). If a safety concern is well characterised the proposed action will be limited to routine

pharmacovigilance. Some areas may need more than one activity to characterise a safety concern with different activities having different objectives. If a specific questionnaire is planned for collecting structured data on a safety concern of special interest this is still considered to be routine but should be mentioned and provided in annex 7 of the risk management plan. A requirement to report on specific adverse reactions to the medicinal product at defined intervals resulting from a previous evaluation (e.g. periodic safety update report/periodic benefit/risk evaluation report) shall be considered as routine pharmacovigilance but shall be detailed in the table against the specific safety concern. Outstanding additional pharmacovigilance activities shall be described in section III.4.

Safety concern 1		
Areas requiring confirmation or further investigation	Proposed routine and additional pharmacovigilance activities	Objectives
1		
2		
...		

Safety concern 2 etc.		
Areas requiring confirmation or further investigation	Proposed routine and additional pharmacovigilance activities	Objectives
1		
2		
...		

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES TO ASSESS EFFECTIVENESS OF RISK MINIMISATION MEASURES

Information on risk minimisation measures, which require the use of non-routine pharmacovigilance activities to measure the effectiveness, shall be provided.

Risk minimisation measure		
Component which is measured and needs further activity(ies)	**Activity(ies)**	**Rationale**
Component 1		
Component 2		
...		

III.3 STUDIES AND OTHER ACTIVITIES COMPLETED SINCE LAST UPDATE OF PHARMACOVIGILANCE PLAN

A summary of completed studies and/or activities since the last update of the pharmacovigilance plan. The concise study report shall be provided in respective annex of the risk management plan.

Study/activity title	
Safety concern(s)/risk minimisation measure investigated	
Brief summary of results	
Implications	

III.4 DETAILS OF OUTSTANDING ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The registration certificate holder/applicant shall propose categories for new additional pharmacovigilance studies/activities in the pharmacovigilance plan, which will be confirmed or recategorised during the evaluation of the risk management plan. The updated risk management plan shall reflect the information on new additional pharmacovigilance studies/activities in the pharmacovigilance plan as agreed by regulatory authority (authorized expert institution) (along with any proposed new studies).

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit-risk)

Imposed activities considered key to the benefit-risk of the medicinal product

№	**Description of activity** (or study title if known)	**Milestone(s)**	**Date(s)**
1		1. (e.g. protocol submission for approval)	
		2. (e.g. study start)	
		3. (e.g. study finish)	
		4. (e.g. final report)	
2		1. (e.g. protocol submission for approval)	
		2. (e.g. study start)	
		3. (e.g. study finish)	
		4. (e.g. final report)	

III.4.2 Mandatory additional pharmacovigilance activity (specific obligations)

№	**Description of activity** (or study title if known)	**Milestone(s)**	**Date(s)**
1		1. (e.g. protocol submission for approval)	

		2. (e.g. study start)	
		3. (e.g. study finish)	
		4. (e.g. final report)	
2		1. (e.g. protocol submission for approval)	
		2. (e.g. study start)	
		3. (e.g. study finish)	
		4. (e.g. final report)	

Non-interventional studies included in categories 1 and 2 are subject to the supervision exercised under Chapter 5 of Section V of the Pharmacovigilance Procedure concerning non-interventional studies.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

Information shall be provided concerning category of activities that are conducted or financed by the registration certificate holder/applicant to address particular safety concerns but do not include studies which are imposed or which are specific obligations (i.e. categories 1 or 2 above). These activities may include trials or studies which may be on-going (e.g. from clinical trials where the activity would be to provide a report) or be planned (where the activity is to conduct the study). This would include studies or activities relating to safety concerns requested by another regulatory authority. Studies which have been specifically requested by the regulatory authority (which are not conditions for issuing the registration cetrtificate) or which may be suggested by the registration certificate holder/applicant to investigate a safety concern shall also be included in this section. Studies to measure the effectiveness of risk minimisation measures would normally fall into this category.

Required additional pharmacovigilance activities

№	**Description of activity** (or study title if known)	**Milestone(s)**	**Date(s)**
1		1. (e.g. protocol submission for approval)	
		2. (e.g. study start)	
		3. (e.g. study finish)	
		4. (e.g. final report)	
2		1. (e.g. protocol submission for approval)	
		2. (e.g. study start)	
		3. (e.g. study finish)	
		4. (e.g. final report)	

III.4.4 Stated additional pharmacovigilance activities

Information on activities, which may provide additional supporting evidence but are not primarily intended to investigate a specific safety concern, shall be provided. These activities would include drug utilisation studies of the medicinal product being conducted as a condition for reimbursement, studies requested by other regulatory authorities for reasons not related to a specific safety concern or safety studies carried out by a third party which the registration certificate holder/applicant is aware of, but is not providing funding.

Additional pharmacovigilance activities.

№	**Description of activity** (or study title if known)	**Expected date of report**
1		

III.5 SUMMARY OF THE PHARMACOVIGILANCE PLAN

III.5.1 On-going and planned additional pharmacovigilance studies (activities according to the pharmacovigilance plan)

A complete overview of all on-going and planned studies in categories 1-3 shall be provided.

Study/activity type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
(e.g. CRUCIAL Cancer Registry at University College IdAho Liver unit (noninterventional cohort, 3))	(e.g. to investigate long term survival, time to progression, safety profile and quality of life in patients with primary liver cancer or solid tumour metastases)	(e.g. bradycardia, thrombosis, leukopenia, use in patients with renal impairment)	(e.g. protocol submitted to Pharmacovigilance Risk Assessment Committee (PRAC))	(e.g. interim reports planned – June, 2018, 2019, final study report - December, 2020)
(e.g. validation of antibody test (non-clinical, 3))	(e.g. comparison of Supertest kit with current gold standard)	(e.g. development of antibodies)	(e.g. planned start March, 2017)	(e.g. final study report – December, 2018)

III.5.2 Table of completed studies/activities from the pharmacovigilance plan

Information on all completed studies in categories 1-3 shall be provided.

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (Completed)	Date of submission of final study report
(e.g. ABC-124 (randomised controlled trial, 3))	(e.g. comparison of time to disease progression with 3 different doses, comparison of safety profile of different doses)	(e.g. bradycardia, development of antibodies, use in patients with renal impairment)	(e.g. completed, final study report submitted)	(e.g. final study report submitted on March 31, 2012)

PART IV: PLANS FOR POST-REGISTRATION EFFICACY STUDIES

IV.1. APPLICABILITY OF EFFICACY DATA TO ALL PATIENTS IN THE TARGET POPULATION

A brief discussion whether there are any gaps in knowledge about efficacy of the medicinal product in the target population and whether there is a need for further efficacy studies in the post-registration period shall be presented. Information on efficacy studies aimed at extending the indication shall not be provided. The above information shall be provided by the registration certificate holder/applicant based on the data from Modules SIII, SIV and SV of Part II of the risk management plan.

Factors, which might be relevant, include:

applicability of the efficacy data on the medicinal product to all patients in the target population (e.g. if 98% of patients in trials were Caucasians it is necessary to discuss whether efficacy is likely to be same in other races in target population);

factors, which might affect the efficacy of the medicinal product in everyday medical practice (e.g. use in general practice rather than the clinical trial in hospital unit);

long term efficacy;

any evidence that there might be variability in efficacy of treatment for subpopulations.

IV.2 DATA ON POST-REGISTRATION EFFICACY STUDIES

The registration certificate holder/applicant shall provide a list of any post-registration efficacy studies which are proposed by him and also include a list of those studies which have been imposed by the regulatory authority or which are specific obligations. A synopsis of the protocols shall be provided in respective annex of the risk management plan.

Efficacy studies which are specific obligations and/or conditions for issuing a registration certificate:

Description of study (including	**Milestone(s)**	**Date(s)**

objectives and study number)		
	1. (e.g. protocol submission for approval)	
	2. (e.g. study start)	
	3. (e.g. study finish)	
	4. (e.g. final report)	

Other efficacy/effectiveness studies

Description of study (including objectives and study number)	**Milestone(s)**	**Date(s)**
	1. (e.g. protocol submission for approval)	
	2. (e.g. study start)	
	3. (e.g. study finish)	
	4. (e.g. final report)	

IV.3 SUMMARY OF POST-REGISTRATION EFFICACY STUDY PLAN

A complete overview of all studies (on-going, planned)

Study (type and study number)	**Objectives**	**Efficacy uncertainties addressed**	**Status** (planned, started)	**Date for submission of interim or final reports**

IV.4. SUMMARY OF COMPLETED POST-REGISTRATION EFFICACY STUDIES

Study (type and study number)	**Objectives**	**Efficacy uncertainties addressed**	**Status** (Completed, Study report submitted)	**Date of submission of final study report**

PART V. RISK MINIMISATION MEASURES

Information on each safety concern identified in module SVIII "Summary of the safety concerns" measures shall be provided in the context of the need of risk minimization measures. If no risk minimisation measures are proposed, then "none proposed" shall be entered against the objective.

If several components make up one risk minimisation measure (e.g. a pregnancy prevention plan may have educational material for doctors and patients, algorithms for deciding on child-bearing potential, patient reminder cards etc.) these shall be grouped together.

For each safety concern, details of what criteria will be used to judge whether risk minimisation measures are a success (e.g. fewer than 2 pregnancy reports in period X, no cases of liver failure reported, drug utilisation study showing <5% off-label use etc) shall be provided.

V.1 RISK MINIMISATION MEASURES BY SAFETY CONCERN

Safety concern	
Objective(s) of the risk minimisation measures	
Routine risk minimisation measures	(Proposed) text for the instructions for medical use/summary of product characteristics for the medicinal product (e.g. dose reduction in "Posology and method of administration" section; warning in "Peculiarities of use" section; adding information to "Adverse reactions" section, etc.)
	Comment (e.g. on any differences between instructions for medical use/summaries of product characteristics for the medicinal product)
	Other routine risk minimisation measures (e.g. prescription only medicinal product; use restricted to doctors experienced in the treatment, etc.)
Additional risk minimisation measure(s) (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	If a study is planned, this shall also be included in Part III.2 "Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures" of this annex
Criteria for judging the success of the proposed risk minimisation measures	
Planned dates for assessment	
Results of effectiveness measurement	Latest assessment at each update of the risk management plan shall be provided. For risk minimisation measures where studies are planned,

	any results shall be mentioned in Part III.2 with the implications and any remedial actions for the safety concern specified in section……, module….
Impact of risk minimisation	
Comment	

V.2. Risk minimisation measure failure (if applicable)

A list of the safety concerns and risk minimisation measures which are judged to have failed shall be provided.

Safety concern	Risk minimisation measure

V.2.1. Analysis of risk minimisation measure(s) failure

When risk minimisation measures for a safety concern are thought to be inadequate, a root cause analysis of where it is failing shall be undertaken.

Safety concern	
Risk minimisation measure(s)	
Component 1 (analysis)	
Component 2 (analysis)	
...	
Conclusions	

V.2.2. Revised proposal for risk minimisation

Information on new proposed (or revised) risk minimisation measures for the safety concern. Such data should be based on the analysis of why the risk minimisation activities were inadequate.

Safety concern	
Objective(s) of the risk minimisation activities	
Routine risk minimisation activities	(Proposed) text for the instructions for medical use/summary of product characteristics for the medicinal product

	Comment (e.g. on any differences between instructions for medical use/summaries of product characteristics for the medicinal product)
	Other routine risk minimisation activities
Additional risk minimisation measure(s) (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale
Comment on how revised proposals will address failings	
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	If a study is planned, this shall also be included in Part III.2: "Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures" of this annex
Criteria for judging the success of the proposed risk minimisation measures	

V.3. SUMMARY TABLE OF RISK MINIMISATION MEASURES

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(Proposed) text for the instructions for medical use/summary of product characteristics for the medicinal product and other routine risk minimisation measure	List from V.1 shall be provided
	(e.g. stating a dose reduction in "Posology and method of administration" section; warning in "Peculiarities of use" section; adding information to "Adverse reactions" section, etc.). Other routine risk minimisation measures (e.g. prescription only medicinal product; use restricted to doctors experienced in the treatment, etc.)	

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

A separate Part VI of the risk management plan shall be provided for each medicinal product in the risk management plan.

VI.1 ELEMENTS FOR SUMMARY TABLES

VI.1.1. Summary table of safety concerns

Information shall be copied from Module SVIII of Part II.

Summary of safety concerns	
Important identified risks	(list)
Important potential risks	(list)
Missing information	(list)

VI.1.2. On-going and planned studies in the post-registration pharmacovigilance plan

Information shall be copied from part III.5.1.

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports** (planned or actual)
(e.g. CRUCIAL Cancer Registry at University College IdAho Liver unit (noninterventional cohort, 3))	(e.g. to investigate long term survival, time to progression, safety profile and quality of life in patients with primary liver cancer or solid tumour metastases)	(e.g. bradycardia, thrombosis, leukopenia, use in patients with renal impairment)	(e.g. protocol submitted to Pharmacovigilance Risk Assessment Committee (PRAC))	(e.g. interim reports planned – June, 2018, 2019, final study report - December, 2020)

VI.1.3. SUMMARY TABLE OF POST-REGISTRATION EFFICACY STUDY PLANS

Information shall be copied from Table IV.3 of Part IV.

Study (type and number)	**Objectives**	**Efficacy uncertainties addressed**	**Status** (planned, started)	**Date for submission of interim or final reports**

VI.1.4. Summary table of risk minimisation measures

Information shall be copied from Table V.3 of Part V.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures

VI.2. ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1. Overview of disease epidemiology

Maximum 150 words per indication.

Abbreviated version of Module SI of Part II of the risk management plan shall be stated in lay language understandable for the target population.

VI.2.2. Summary of treatment results

The summary of treatment benefits of the medicinal product shall be in lay/understandable language and nonpromotional, shall not exceed a maximum of 200 words (up to 300 if the medicinal product has multiple indications). The following shall be considered for inclusion in the summary:

Brief description of each pivotal study, including total participant numbers (randomised figure where applicable) (the primary endpoint shall be explained in lay language);

If there are multiple indications, bullet points shall be used to separate the studies per indication. In some cases several studies for one indication with a similar design may be described together;

For each study, the primary endpoint results shall be described directly after the description of the study (either in the same paragraph, or a separate paragraph if needed). When using percentages, absolute value shall be specified in brackets (e.g. the average survival time for patients in the main study treated with 475 mg of drug X in addition to drugs Y and Z increased by 19.5 months to 55.5 months compared with treatment 2 (36 months) and 17 months (57.5 months) compared with treatment 3 (40.5) months

VI.2.3. Unknowns relating to treatment efficacy

One short paragraph per indication of 50 words maximum.

A short summary of the applicability of efficacy to all patients in the target population, and version of Part IV, IV.1 of the risk management plan shall be provided in language understandable for the lay reader. It shall describe any relevant parts of the target population, where experience with the medicinal product is limited, and expected differences in efficacy in this population, e.g. by factors such as age, sex, race, and organ impairment. If there is evidence that efficacy is either enhanced or reduced (e.g. ACE inhibitors and the Afro-Caribbean population) this shall be stated (e.g. in the main and supporting studies nearly all patients were white Caucasians aged between 52 and 86 with most patients aged over 65. There is no evidence to suggest that results would be any different in patients of other race, etc.)

VI.2.4. Summary of safety concerns

IMPORTANT IDENTIFIED RISKS

Risk	What is known	Preventability
Safety concern in lay language (medical term)	Brief summary in lay language	Ways to minimise or mitigate the risk (if possible)
(e.g. damage to the nerves in hands and feet (peripheral neuropathy))	(e.g. aproximately one in two people treated with X will experience some form of nerve damage which may increase to three out of four people after 12 months of treatment. The nerve damage varies from mild tingling and altered sensation to irreversible disabling damage in the most severe cases. Early symptoms usually resolve or improve upon dose adjustment or discontinuation of therapy)	(e.g. by monitoring for early symptoms)
(e.g. blood clots (thromboembolic events))	(e.g. the medicinal product may affect the arteries or veins. In the veins this may lead to a painful swelling of the legs (deep vein thrombosis) and very occasionally life threatening or fatal clots in the lungs. Clots in the arteries may lead to a heart attack or stroke – particularly in patients who already have problems with their arteries. Patients with cancer who are being treated with oestrogen are already at higher risk of blood clots so it is difficult to assess what extra risk is caused by X)	(e.g. use of preventative anti-thrombotic medicines)

IMPORTANT POTENTIAL RISKS

Risk	What is known (including reason why it is considered a potential risk)
(e.g. secondary neoplasms)	(e.g. patients treated with X may be at an increased risk of developing new cancers. There is theoretical probability that more patients treated with X developed new cancers than those not treated with X)

MISSING INFORMATION

Risk	What is known
(e.g. limited information on use in patients with kidney impairment)	(e.g. product X itself is not eliminated to any significant extent by the kidney so it is unlikely that kidney impairment will lead to problems. Some of its metabolites are eliminated by the kidney so it is recommended that patients with severe renal impairment are monitored carefully.)

VI.2.5. Summary of risk minimisation measures by safety concern

All medicinal products have instructions for medical with details on how to use the medicinal product, the risks and recommendations for minimising them. The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

Additional risk minimisation measures are presented below.

SAFETY CONCERN IN LAY TERMS (MEDICAL TERM)

Risk minimisation measure(s)
Objective and rationale
Summary description of main additional risk minimisation measures Key points
E.g. damage to the nerves in hands and feet (peripheral neuropathy) Healthcare professional and patient education Objective and rationale Patients and health care professionals to understand the risk of peripheral neuropathy and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. Proposed action: educational materials to be provided to doctors and pharmacists including advice on: Use of electromyogram prior to and during treatment; Importance of adherence to dosing recommendations; Management of neuropathy including dose reduction and treatment discontinuation; Direct health care professional communication prior to launch (information letter); Patient booklet with information on symptoms of nerve damage are and the importance of informing their doctor if any occur

VI.2.6. Post-registration development plan (planned activities in post-registration period))

Information from summary tables in Part III and Part IV shall be provided.

LIST OF STUDIES IN POST-REGISTRATION DEVELOPMENT PLAN

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Date for submission of interim and final reports

STUDIES WHICH ARE A CONDITION FOR OBTAINING THE REGISTRATION CERTIFICATE

None of the above studies are conditions for obtaining the registration certificate

Study(ies) is (are) a conditions(s) for obtaining the registration certificate

A list of all studies (including specific obligations) which are conditions for obtaing the registration certificate shall be provided.

VI.2.7. Summary table of changes to the risk management plan

Major changes to the risk management plan over time.

Version	Date	Safety concern	Comment
	At time of authorisation dd/mm/yyyy	Identified risks Potential risks Missing information	
(e.g. 7.0)	(e.g. 17/08/2012)	(e.g. allergic conditions added as an identified risk; hypersensitivity removed as an identified risk; severe infection added as an identified risk; convulsions added as a potential risk)	(e.g. the previous term “hypersensitivity” was updated to allergic conditions to include angioedema and urticaria)

Part VII: ANNEXES

Annex 1. Main information in the risk management plan in a structured electronic format (if applicable).

Annex 2. Approved (current) or proposed (if medicinal product is not registered) summary of product characteristics, instructions for medical use, package leaflet.

Annex 3. Information on worldwide registration status of the medicinal product(s) to which the risk management plan refers

3.1. Information on registration in Ukraine.

3.2. Information on registration in EU.

3.3. Information on registration in other countries.

Annex 4. Synopsis of on-going or completed clinical trial protocol.

Annex 5. Synopsis of on-going and completed pharmacoepidemiological study protocol.

Annex 6. Protocols for on-going and proposed studies indicated in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in part III of the risk management plan.

Annex 7. Specific adverse reaction case follow-up forms.

Annex 8. Protocols for on-going and proposed studies indicated in part IV of the risk management plan.

Annex 9. Synopsis of study reports for parts III, IV of the risk management plan.

Annex 10. Details of additional risk minimisation activities (if applicable).

Annex 11. Mock up examples of the material provided to healthcare professionals and patients

Annex 12. Other supporting data

Annex 1. Main information in the risk management plan in a structured electronic format (if applicable).

Available in electronic format only.

Annex 2. Approved (current) or proposed (if medicinal product is not registered) summary of product characteristics, instructions for medical use, package leaflet

Approved (current) (or proposed if medicinal product is not registered) instructions for medical use/summary of product characteristics and package leaflet(s) for each medicinal product in the risk management plan.

If multiple versions of the above documents are included, they shall show in which country(s) they are applicable. In addition, if available, a core instructions for medical use/summary of product characteristics shall be provided with an overview of the changes applicable to it in each country where the medicinal product is registered (application for registration is submitted).

Annex 3. Information on worldwide registration status of the medicinal product(s) to which the risk management plan refers

For each medicinal product in the risk management plan.

3.1. Information on registration in Ukraine

Country	Current registration status	Date of registration status	Date first marketed in country	Trade name	Comments

		action*			
	One of the following options shall be chosen: registered; refused a registration; under review; suspended; expired; withdrawn				

* The date of the most recent change to the registration status (e.g. date of approval or date of suspension of the registration certificate).

3.2. Information on registration in EU

Country	**Current registration status**	**Date of registration status action***	**Date first marketed in country**	**Trade name**	**Comments**
	One of the following option shall be chosen: registered; refused a registration; under review; suspended; expired; withdrawn				

* The date of the most recent change to the registration status (e.g. date of approval or date of suspension of the registration certificate).

3.3. Information on registration in other countries

Country	**Current registration status**	**Date of registration status action***	**Date first marketed in country**	**Trade name**	**Comments**
	One of the following option shall be chosen: registered; refused a registration; under review; suspended; expired; withdrawn				

Annex 4. Synopsis of on-going or completed clinical trial protocol

Study	Description (phase, short description of study (1 – 2 sentences including comparator name(s)/placebo)	Countries	Study design (type)	Planned/actual number of patients	Duration of follow up	Estimated/ actual completion date
Main or pivotal studies						
(e.g. study ABC)	(e.g. study versus ibuprofen in adults with mild postoperative pain Phase III)	(e.g. Germany, USA, Chile)	(e.g. Randomised double blind)	(e.g. 4075)	(e.g. 14 days)	(e.g. Jan 2018)
Further safety/efficacy studies						
Studies in special populations (e.g. paediatric, elderly)						

Annex 5. Synopsis of on-going and completed pharmacoepidemiological study protocol

Study	Research question	Study design (type)	Population & study size	Duration of follow up	Milestones & dates	Status
						One of the following options shall be chosen: Planned; Protocol under development; Protocol agreed; Data collection started; Data collection ended; Study

						completed

Annex 6. Protocols for on-going and proposed studies indicated in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in part III of the risk management plan

Overview of included protocols.

Study title	Protocol status *	Version of protocol	Date of protocol version
	One of the following options shall be chosen: Draft; Approved; Final version		

* Draft - not approved/final;

Approved - agreed by regulatory authority;

Final version – regulatory authority's agreement not required.

Annex 7. Specific adverse reaction case follow-up forms

Forms provided.

Annex 8. Protocols for on-going and proposed studies indicated in part IV of the risk management plan

Study title	Protocol status *	Version of protocol	Date of protocol version
	One of the following options shall be chosen: Draft; Approved; Final version		

* Draft - not approved/final;

Approved - agreed by regulatory authority;

Annex 9. Synopsis of study reports for parts III, IV of the risk management plan

The study abstract shall be included. For non-interventional studies the abstract format for post-registration safety studies shall be used.

Annex 10. Details of additional risk minimisation activities (if applicable).

Annex 11. Mock up examples of the material provided to healthcare professionals and patients

Mock up examples of the material provided to healthcare professionals and patients should be attached.

Annex 12. Other supporting data

Index of included material.