EU Risk Management Plan for erlotinib

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 19.07.2019

Date of final sign off: 19.07.2019

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission.

Summary of significant changes in this RMP:

- Update of Summary of safety concerns to be in line with latest RMP version of reference medicinal product. All safety concerns were deleted.

QPPV name: Irena Orel MD, MSc

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's/applicant's QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	erlotinib
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic and immunomodulating agents, Antineoplastic agents, Other antineoplastic agents (L01XE03)
Marketing Authorisation Holder or Applicant	KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia and Krka's subsidiaries
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	erlotinib
Marketing authorisation procedure	decentralised
Brief description of the product	Chemical class: Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor.
	Summary of mode of action: Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death. EGFR mutations may lead to constitutive activation of anti-apoptotic and proliferation signaling pathways. The potent effectiveness of erlotinib in blocking EGFR-mediated signalling in these EGFR mutation positive tumours is attributed to the tight binding of erlotinib to the ATP-binding site in the mutated kinase domain of the EGFR. Due to the blocking of downstream-signaling, the proliferation of cells is stopped, and cell death is induced

	through the intrinsic apoptotic pathway.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Please refer to module 1.3.1 of dossier
Indication(s) in the EEA	Current (if applicable)*: <u>Non-Small Cell Lung Cancer (NSCLC):</u> – Erlotinib is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations. – Erlotinib is also indicated for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first-line chemotherapy. – Erlotinib is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. In patients with tumours without EGFR activating mutations, erlotinib is indicated when other treatment options are not considered suitable. <u>Pancreatic cancer:</u> – Erlotinib in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer. * indications may differ from country to country, and each national product information document should always be kept in line with the marketing authorisation granted by the local regulatory authority.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current (if applicable)*: <u>Patients with Non-Small Cell Lung Cancer:</u> The recommended daily dose of erlotinib is 150 mg taken at least one hour before or two hours after the ingestion of food. <u>Patients with pancreatic cancer:</u> The recommended daily dose of erlotinib is 100 mg taken at least one hour before or two hours after the ingestion of food, in

	combination with gemcitabine (see the summary of product characteristics of gemcitabine for the pancreatic cancer indication). In patients who do not develop rash within the first 4 – 8 weeks of treatment, further erlotinib treatment should be re-assessed (see section 5.1). When dose adjustment is necessary, the dose should be reduced in 50 mg steps (see section 4.4). Erlotinib is available in strengths of 25 mg, 100 mg and 150 mg. *Please note that posology may differ from country to country due to possible differencies in indications, and each national product information document should always be kept in line with the marketing authorisation granted by the local regulatory authority
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): 25 mg film-coated tablets 100 mg film-coated tablets 150 mg film-coated tablets
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable.

Part II: Module SIII - Clinical trial exposure

Not applicable.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable.

Part II: Module SVII - Identified and potential risks

Not applicable. The list of safety concerns was obtained from originator's Risk Management Plan (Tarceva, Roche Registration Limited, version 7.1, published on EMA website on 24.04.2019)

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection is considered necessary.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are proposed.

III.3 Summary Table of additional Pharmacovigilance activities

No additional pharmacovigilance activities are proposed.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for erlotinib by Krka (erlotinib)

This is a summary of the risk management plan (RMP) for erlotinib by Krka. The RMP details important risks of erlotinib by Krka, how these risks can be minimised, and how more information will be obtained about erlotinib by Krka's risks and uncertainties (missing information).

Erlotinib by Krka's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how erlotinib by Krka should be used.

Important new concerns or changes to the current ones will be included in updates of erlotinib by Krka's RMP.

I. The medicine and what it is used for

Erlotinib by Krka is authorised for treatment of non-small cell lung cancer (NSCLC) and pancreatic cancer (see SmPC for the full indication). It contains erlotinib as the active substance and it is given orally.

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

Important risks of erlotinib by Krka, together with measures to minimise such risks and the proposed studies for learning more about erlotinib by Krka's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of erlotinib by Krka is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of erlotinib by Krka are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of erlotinib by Krka. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of erlotinib by Krka.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for erlotinib by Krka.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Not applicable.

Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
0.1	CZ/H/0842/001-003/DC (sign off date: 15.1.2019)	/
0.2	CZ/H/0842/001-003/DC (sign off date: 19.07.2019)	Update of Summary of safety concerns to be in line with latest RMP version of reference medicinal product. All safety concerns were deleted.
1.0	CZ/H/0842/001-003/DC (sign off date: 19.07.2019)	Change of version number on request of RMS. No change in content or formatting compared to version 0.2