

Regulatory Affairs

Ranibizumab

RFB002

Summary of the *EU* Safety Risk Management Plan

Active substance(s) (INN or common name):	<i>Ranibizumab</i>
Product(s) concerned (brand name(s)):	<i>Lucentis®</i>
Document status:	<i>Final</i>
Version number of the RMP Public Summary:	<i>22.0</i>
Date of final sign off of the RMP Public Summary:	<i>12-Oct-2022</i>

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of "Lucentis" is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Lucentis" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of "Lucentis" in Switzerland is the "Lucentis" (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Lucentis".

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Summary of the risk management plan for Mekinist and Spexotras (trametinib)

This is a summary of the risk management plan (RMP) for ranibizumab. The RMP details important risks of ranibizumab (how these risks can be minimized), and how more information will be obtained where information is still insufficient (missing information).

The summary of product characteristics (SmPC) and package leaflet for ranibizumab give essential information to healthcare professionals and patients on how ranibizumab should be used.

This summary of the RMP for ranibizumab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR). Important new concerns or changes to the current ones will be included in updates of ranibizumab RMP.

I. The medicine and what it is used for

Ranibizumab is authorised in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to choroidal neovascularisation (CNV), visual impairment due to diabetic macular oedema (DME), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), and proliferative diabetic retinopathy (PDR). Ranibizumab is indicated in preterm infants for the treatment of retinopathy of prematurity (ROP) with Zone I (stage 1+, 2+, 3 or 3+), Zone II, (stage 3+) or aggressive posterior ROP (AP-ROP) disease. Ranibizumab is a solution for injection and must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Further information about the evaluation of ranibizumab's benefits can be found in ranibizumab EPAR, including in its plain-language summary, available on the EMA website, under the medicine's Webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000715/human_med_000890.jsp&mid=WC0b01ac058001d124

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of ranibizumab together with measures to minimize such risks and the proposed studies for learning more about ranibizumab's risks, are outlined below.

Measures to minimize 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 packaging of the medicine;

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- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
 - The legal status of the medicine— the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures. In the case of ranibizumab, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition, 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 ranibizumab is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of ranibizumab are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ranibizumab. 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).

Table II-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Infectious endophthalmitis Intraocular inflammation Retinal detachment and retinal tear Intraocular pressure increase
Important potential risks	Neurodevelopmental impairment (ROP)
Missing information	None

II B: Summary of important risks

Important identified risks for trametinib

Table II-2 Important identified risk – Infectious endophthalmitis

Evidence for linking the risk to the medicine	Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis. Infectious endophthalmitis can possibly lead to a loss of vision and in sometimes even to the loss of the eye itself.
Risk factors and risk groups	To minimize the occurrence of endophthalmitis guidance is provided in SmPC on how to administer an IVT injection and to inform and educate physicians and patients on prevention and management of this event.

Risk minimization measures	Routine risk minimization: SmPC Sections 4.2, 4.3, 4.4, 4.8, 6.6. SmPC Section with specific clinical measure: 6.6 PL Sections 2, 3, 4 Additional Risk Minimization Measures (for indications of AMD, CNV, DME, RVO and PDR): Educational plan for adult patients
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Table II-3 Important identified risk: Intraocular inflammation

Evidence for linking the risk to the medicine	Intravitreal injections, including those with ranibizumab, have been associated with intraocular inflammation. Intraocular inflammation can possibly lead to a loss of vision and in sometimes even to the loss of the eye itself.
Risk factors and risk groups	Proper aseptic injection techniques must always be used when administering ranibizumab.
Risk minimization measures	Routine risk minimization: SmPC Sections 4.3, 4.4. PL Sections 2, 4 Additional routine risk minimization measures (for indications of AMD, CNV, DME, RVO and PDR): Educational plan for adult patients

Table II-4 Important identified risk: Retinal detachment and retinal tear

Evidence for linking the risk to the medicine	Rhegmatogenous retinal detachment occurs when the liquefied vitreous enters between the choroid and the pigmented epithelium detaching the retinal layer from the underlying choroid. Traction retinal detachment occurs when scar tissue or other abnormal tissue grows on the surface of the
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	retina, pulling the retina away from the layer beneath it. This does not necessarily cause a specific tear or break in the retina. In patients with advanced stages of ROP, retinal detachment develops when neovascularisation progresses and proliferous fibrous and vascular tissue lead to traction over the ridge. Exudative retinal detachment occurs when blood or fluid from the choroid flows into the space under the retina and separates the retina from the layer beneath it. The detachment does not involve tears in the retina or traction from the vitreous. Exudative retinal detachment is most often a complication of other diseases including macular degeneration, eye tumors, inflammation in the choroid or the retina, or severe high blood pressure. Retinal detachment leads to visual distortion, and untreated retinal detachment leads to retinal cell death and loss of vision.
Risk factors and risk groups	The following conditions might increase the risk for retinal detachment: previous retinal detachment or retinal tear, eye tumors, inflammation in the choroid or the retina, eye injury, high myopia or severe high blood pressure.
Risk minimization measures	Routine risk minimization: SmPC Section 4.4, 4.8 PL Sections 2, 4 Additional Risk Minimization Measures (for indications of AMD, CNV, DME, RVO and PDR): Educational plan for adult patients.

Table II-5 Important identified risk: Intraocular pressure increase (IOP)

Evidence for linking the risk to the medicine	Following an intravitreal injection of ranibizumab, a transient increase in IOP may be anticipated.
Risk factors and risk groups	Pre-existing high IOP
Risk minimization measures	Routine risk minimization: Ranibizumab should not be administered in the event of an intraocular pressure of ≥ 30 mmHg. SmPC Sections 4.4, 4.8, 4.9. SmPC Section with specific clinical measure: SmPC Section 4.4 - Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. PL Section 2, 4 Additional risk minimization measures (for indications of AMD, CNV, DME, RVO and PDR): Educational plan for adult patients

Table II-5 Important potential risk: Neurodevelopmental impairment (ROP)

Evidence for linking the risk to the medicine	Based on non-clinical studies, the VEGF pathway has been implicated in neurodevelopment and neurodegeneration; systemic suppression of VEGF may be a contributing factor affecting neurodevelopmental outcomes. Higher incidence of mental and psychomotor impairment was reported in ROP patients treated off-label with intravitreal anti-VEGF bevacizumab as compared to laser. Neurodevelopmental impairment as a potential long term effect associated
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	with use of ranibizumab has not been studied in preterm infants with ROP.
Risk factors and risk groups	Presence of other concurrent neurological conditions; neurodevelopmental impairment is an important long-term disability in extremely and very preterm populations, and association of severe ROP was observed for both cognitive and motor impairments in assessments performed at patient ages ranging from 18 months to 18 years.
Risk minimization measures	Routine risk minimization: SmPC Section: This risk is not mentioned in SmPC. PL Sections: This risk is not mentioned in PL Additional risk minimization measures: None

II C: Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation for ranibizumab.

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

There are no other studies required for ranibizumab.