

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Zirabev (bevacizumab)

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

Zirabev's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Zirabev should be used.

This summary of the RMP for Zirabev 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 Zirabev's RMP.

I. The Medicine and What It Is Used For

Zirabev has been developed as a biosimilar to Avastin (bevacizumab), and is proposed to be authorised for the treatment of metastatic colorectal cancer, metastatic breast cancer, advanced, metastatic or recurrent non-small cell lung cancer, advanced and/or metastatic renal cell cancer, and cervical cancer (see SmPC for the full indication). It contains bevacizumab as the active substance and it is administered intravenously.

Further information about the evaluation of Zirabev's benefits can be found in Zirabev's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

<https://www.ema.europa.eu/en/medicines/human/EPAR/zirabev>.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Zirabev, together with measures to minimise such 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 public (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 events 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 Zirabev is not yet available, it is listed under ‘missing information’ below.

II.A. List of Important Risks and Missing Information

Important risks of Zirabev are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PF-06439535. 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 1. List of important risks and missing information

Important identified risks	Bleeding/haemorrhage Pulmonary haemorrhage Proteinuria Arterial thromboembolic events (ATE) Hypertension Congestive heart failure Wound-healing complications Gastrointestinal perforations Posterior reversible encephalopathy syndrome (PRES) Neutropenia Venous thromboembolic events (VTE) Fistula (other than gastrointestinal) Thrombotic microangiopathy Pulmonary hypertension Ovarian failure Hypersensitivity reactions/infusion reactions Gallbladder perforation Peripheral sensory neuropathy Cardiac disorders (excluding CHF and ATE) Osteonecrosis of the jaw Necrotizing fasciitis Adverse events following off-label intravitreal use Embryo-foetal development disturbance Osteonecrosis in children
Important potential risks	None
Missing information	Safety profile of the different treatment combinations in patients with non-squamous NSCLC Long-term effects of bevacizumab when used in the paediatric population Safety and efficacy in patients with renal impairment Safety and efficacy in patients with hepatic impairment Use in lactating women

II.B. Summary of Important Risks and Missing Information

Table 2. Important Identified Risk: Bleeding/Haemorrhage

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Age > 75 years • Uncontrolled hypertension • Chronic liver disease e.g. cirrhosis • Gastric/duodenal ulcer disease • Non-steroidal anti-inflammatory drugs, e.g. aspirin • Anticoagulants, e.g. warfarin • Drug-induced thrombocytopenia, e.g. chemotherapy • Radiation-induced thrombocytopenia • Coagulation defects, e.g. factor VII deficiency • Severe co-morbidity, e.g. sepsis or multi-organ failure associated with disseminated intravascular coagulation
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 3. Important Identified Risk: Pulmonary Haemorrhage

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	Lung cancer with squamous cell histology.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 4. Important Identified Risk: Proteinuria

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increased age • Hypertension • Diabetes mellitus • Chronic kidney disease • Renal cancer
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.</p> <p>Recommendation for monitoring of proteinuria by dipstick urinalysis prior to starting and during therapy in SmPC Section 4.4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 5. Important Identified Risk: Arterial Thromboembolic Events

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increased age • Tobacco smoke • Diabetes mellitus • Hypertension • Hypercholesterolaemia • Personal or family history of arterial thromboembolic events
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 6. Important Identified Risk: Hypertension

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increased age • Tobacco smoke • Family history of hypertension • Obesity • Excess dietary sodium • Chronic kidney disease • Medications e.g. corticosteroids, non-steroidal anti-inflammatory drugs
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.</p> <p>Monitoring of blood pressure is generally recommended during therapy as per SmPC Section 4.4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 7. Important Identified Risk: Congestive Heart Failure

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increased age • Personal history of cardiac disease e.g. myocardial infarction, valve disease • Tobacco smoke • Diabetes mellitus • Hypertension • Hypercholesterolaemia • Medications e.g. anthracyclines • Personal history of chronic respiratory disease e.g. pulmonary fibrosis • Connective tissue disorders e.g. systemic lupus erythematosus, sarcoidosis
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 8. Important Identified Risk: Wound Healing Complications

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin non-clinical data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increased age • Diabetes mellitus • Corticosteroids • Concurrent wound infection • Advanced cancer • Tobacco smoke
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 9. Important Identified Risk: Gastrointestinal Perforation

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Gastrointestinal disorders e.g. colorectal cancer, ulcerative colitis, Crohn's disease, diverticulitis, peptic ulcer disease • Medications e.g. non-steroidal anti-inflammatory drugs, corticosteroids • Abdominal surgery or procedure e.g. laparoscopy
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 10. Important Identified Risk: Posterior Reversible Encephalopathy Syndrome

Evidence for linking the risk to the medicine	Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Hypertension • Pre-eclampsia • Autoimmune disease e.g. systemic lupus erythematosus • Medications e.g. cisplatin
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 11. Important Identified Risk: Neutropenia

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
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Table 11. Important Identified Risk: Neutropenia

Risk factors and risk groups	<ul style="list-style-type: none"> • Increased age • Chemotherapy • Advanced cancer and bone marrow infiltration • Poor nutritional status (Hypoalbuminaemia) and poor performance status • Infection
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 12. Important Identified Risk: Venous Thromboembolic Events

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increased age • Tobacco smoke • Coagulation defects e.g. anti-thrombin, protein C and protein S deficiencies • Gene mutations e.g. Factor V Leiden and prothrombin gene mutations • Anti-phospholipid antibody syndrome (lupus anticoagulant, anti-cardiolipin and anti-β2-glycoprotein I antibodies) • Personal history of previous venous thromboembolic events • Major and minor trauma • Immobilization • Surgery • Cancer • Pregnancy
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 13. Important Identified Risk: Fistula (other than Gastrointestinal)

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<p>Broncho-pleural or broncho-oesophageal fistula:</p> <ul style="list-style-type: none"> • Lung cancer • Pneumothorax • Tuberculosis • Chest radiotherapy • Mechanical ventilation • Lung resection <p>Biliary fistula:</p> <ul style="list-style-type: none"> • Gallstones • Cholecystectomy • Penetrating injury • Biliary cancer

Table 13. Important Identified Risk: Fistula (other than Gastrointestinal)

Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4. <u>Additional risk minimisation measures:</u> None
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Table 14. Important Identified Risk: Thrombotic Microangiopathy

Evidence for linking the risk to the medicine	Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Renal thrombotic microangiopathy • Renal cancer • Chronic kidney disease
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.8; PL Section 4. <u>Additional risk minimisation measures:</u> None

Table 15. Important Identified Risk: Pulmonary Hypertension

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Obstructive sleep apnoea • Female gender • Pregnancy • Congenital heart disease • Systemic lupus erythematosus • Sickle cell disease • Gene mutations e.g. bone morphogenetic protein type 2 receptor (BMP2) gene mutation • Medications e.g. fenfluramine derivatives
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.8; PL Section 4. <u>Additional risk minimisation measures:</u> None

Table 16. Important Identified Risk: Ovarian Failure

Evidence for linking the risk to the medicine	Avastin non-clinical data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increasing age • Ovarian cancer • Hysterectomy and/or oophorectomy • Autoimmune disease e.g. rheumatoid arthritis • Chromosome defects e.g. Turner's syndrome • Radiotherapy • Chemotherapy

Table 16. Important Identified Risk: Ovarian Failure

Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.4, 4.6, and 4.8; PL Section 4. <u>Additional risk minimisation measures:</u> None
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Table 17. Important Identified Risk: Hypersensitivity Reactions/Infusion Reactions

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	Previous history of hypersensitivity or infusion reactions.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.3, 4.4 and 4.8; PL Sections 2 and 4. <u>Additional risk minimisation measures:</u> None

Table 18. Important Identified Risk: Gallbladder Perforation

Evidence for linking the risk to the medicine	Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Cholecystectomy • Biliary cancer • Gallstones • Penetrating injury
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Section 4. <u>Additional risk minimisation measures:</u> None

Table 19. Important Identified Risk: Peripheral Sensory Neuropathy

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Diabetes mellitus • Vitamin B12 and/or folate deficiency • Excess alcohol use • Chronic kidney disease • Infections e.g. Varicella zoster, HIV • Connective tissue disease e.g. systemic lupus erythematosus • Medications e.g. paclitaxel, oxaliplatin
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.8; PL Section 4. <u>Additional risk minimisation measures:</u> None

Table 20. Important Identified Risk: Cardiac Disorders (excluding CHF and ATE)

Evidence for linking the risk to the medicine	PF-06439535 and Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Cardiac disease e.g. valve disease, atherosclerosis, cardiomyopathy • Congenital cardiac disease • Hypertension • Diabetes mellitus • Hypothyroidism and hyperthyroidism • Electrolyte imbalance • Excess alcohol use • Excess caffeine use • Medications e.g. salbutamol, amitriptyline
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.8; PL Section 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 21. Important Identified Risk: Osteonecrosis of the Jaw

Evidence for linking the risk to the medicine	Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Dental procedures or surgery • Poor oral health • Medications e.g. bisphosphonates, corticosteroids • Diabetes mellitus • Excess alcohol use • Sickle cell anaemia
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 22. Important Identified Risk: Necrotizing Fasciitis

Evidence for linking the risk to the medicine	Avastin clinical trial data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increased age • Advanced cancer • Malnutrition • Diabetes mellitus • Congestive heart failure • Renal failure • Trauma e.g. laceration, surgery, open fracture • Medications e.g. chemotherapy, corticosteroids, immunosuppressants
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8; PL Sections 2, 3, and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>

Table 23. Important Identified Risk: Adverse Events Following Off-Label Intravitreal Use of Bevacizumab

Evidence for linking the risk to the medicine	Avastin RMP and Avastin product label.
Risk factors and risk groups	No specific adverse events following off-label intravitreal use have been assessed as identified risks.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.4; PL Section 4. <u>Additional risk minimisation measures:</u> None

Table 24. Important Identified Risk: Embryo-Foetal Development Disturbance

Evidence for linking the risk to the medicine	Avastin non-clinical data, Avastin RMP and Avastin product label.
Risk factors and risk groups	<ul style="list-style-type: none"> • Increased maternal age • Consanguinity • Concomitant teratogenic medications • Maternal infection e.g. syphilis, rubella • Maternal exposure to excess alcohol or radiation during pregnancy • Folate deficiency (neural tube defects)
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.3, 4.6, 4.8, and 5.3; PL Section 2. <u>Additional risk minimisation measures:</u> None

Table 25. Important Identified Risk: Osteonecrosis in Children

Evidence for linking the risk to the medicine	Avastin non-clinical data, Avastin RMP and Avastin product label.
Risk factors and risk groups	Major risk factors for the development of osteonecrosis in children include cancer, use of corticosteroids, major trauma leading to bone fractures and osteomyelitis.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.8; PL Section 2. <u>Additional risk minimisation measures:</u> None

Table 26. Missing Information: Safety Profile of the Different Treatment Combinations in Patients with Non-Squamous NSCLC

Risk minimisation measures	<u>Routine risk minimisation measures:</u> None <u>Additional risk minimisation measures:</u> None
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Table 27. Missing Information: Long-Term Effects of Bevacizumab When Used in the Paediatric Population

Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.2, 4.8, and 5.1; PL Section 2. <u>Additional risk minimisation measures:</u> None
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Table 28. Missing Information: Safety and Efficacy in Patients with Renal Impairment

Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.2 and 5.2. <u>Additional risk minimisation measures:</u> None
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Table 29. Missing Information: Safety and Efficacy in Patients with Hepatic Impairment

Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.2 and 5.2. <u>Additional risk minimisation measures:</u> None
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Table 30. Missing Information: Use in Lactating Women

Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.3 and 4.6; PL Section 2. <u>Additional risk minimisation measures:</u> None
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II.C. Post-Authorisation Development Plan

There are no studies which are conditions of the marketing authorisation or specific obligation of Zirabev.