SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR FLIXABI

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

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

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

I. The medicine and what it is used for

Flixabi is authorised for rheumatoid arthritis, adult Crohn’s disease (CD), paediatric Crohn’s disease, ulcerative colitis (UC), paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis (PsA), and psoriasis (see SmPC for the full indication). It contains infliximab as the active substance and it is given by 100 mg powder for concentrate for solution for infusion.

Further information about the evaluation of Flixabi’s benefits can be found in Flixabi’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/flixabi

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

Important risks of Flixabi, together with measures to minimise such risks and the proposed studies for learning more about Flixabi'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 the case of Flixabi, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below

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 Flixabi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Flixabi 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 Flixabi. 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	Serious infection/sepsis Demyelinating disorders Bacillus Calmette-Guérin (BCG) breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi Malignancy
Important potential risks	Colon carcinoma/dysplasia (in paediatric ulcerative colitis [UC]) Immunogenicity
Missing information	None

II.B Summary of important risks

II.B.1 Important identified risk

Serious infection/sepsis	
Evidence for linking the risk to the medicine	Study SB2-G31-RA; SmPCs for Flixabi and Remicade®, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	*Serious infection/sepsis* Combined use of immunosuppressants is associated with an increased risk of serious infections.[6] The risk factors include age > 65 years, concomitant use of abatacept, and MTX.[3,4] *Hepatitis B virus reactivation*

Serious infection/sepsis	
	Immune suppression, including in patients receiving chemotherapy and immunosuppressive therapy, is seen as a high risk factor in hepatitis B surface antigen (HBsAg)-positive patients.[9] Prophylaxis with entecavir or tenofovir for 6 to 12 months after the end of immunosuppressive therapy is deemed mandatory in these patients. Additionally, screening and vaccination is recommended in serologically negative cases for patients with IBD to prevent HBV reactivation.[10] In a recent study, HBsAg together with detectable HBV DNA, rituximab administration or treatment with steroids were shown to be independent risk factors leading to HBV reactivation.[11] HBV reactivation risk in HBsAg negative patients was assessed at the level of 3-10% in a study of 244 lymphoma patients by Hui et al. Mainly this was attributed to the concomitant administration of rituximab and steroid drugs.[12] *Opportunistic infections* The risk factors include age > 65 years and concomitant use of abatacept, and MTX. Patients suffering from chronic infections or who have a history of recurrent infections, or patients who have travelled or lived in endemic areas for histoplasmosis, blastomycosis, etc., might constitute a risk group for opportunistic infections. *Tuberculosis* Particular immune compromised groups, such as HIV patients and patients receiving immunosuppressive therapy, are at higher risk for TB infection, as well as TB reactivation.[15] The risk factors include age > 65 years, concomitant use of abatacept, and MTX.[3]
Risk minimisation measures	<Routine risk minimisation measures> SmPC Sections 4.3, 4.4, and 4.8, and PL section 2 and 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> SB2-G31-RA Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER, CEDUR, CREDIT See section II.C of this summary for an overview of the post-authorisation development plan.

Demyelinating disorders	
Evidence for linking the risk to the medicine	Study SB2-G31-RA; Flixabi SmPC, Section 4.8 ‘Undesirable effects’ and Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Patients with pre-existing MS or Guillain-Barré syndrome belong to the high-risk group. Additionally, first-degree relatives of

Demyelinating disorders	
	patients with MS have an increased propensity for developing MS, with a sibling relative risk ranging between 18 and 36, evidence strongly suggesting that TNF inhibitors should not be used in first-degree relatives of patients with MS.[17]
Risk minimisation measures	<Routine risk minimisation measures> SmPC Sections 4.4, and 4.8 and PL section 4 Prescription-only medication
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> SB2-G31-RA Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER, CEDUR, CREDIT See section II.C of this summary for an overview of the post-authorisation development plan.

BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi	
Evidence for linking the risk to the medicine	SmPCs for Flixabi and Remicade® Section 4.4 'Special warnings and precautions for use' and Section 4.6 "Fertility, pregnancy and lactation"; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Infliximab crosses the placenta and has been detected in the serum of infants up to 6 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for at least 6 months after birth. Cases of agranulocytosis have also been reported (see section 4.8).[3,4]
Risk minimisation measures	<Routine risk minimisation measures> SmPC Section 4.4, 4.6, and 4.8 and PL section 4 Prescription-only medication <Additional risk minimisation measures> Patient Reminder Card
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER, CEDUR, CREDIT See section II.C of this summary for an overview of the post-authorisation development plan.

Malignancy	
Evidence for linking the risk to the medicine	Study SB2-G31-RA; SmPCs for Flixabi and Remicade®, Section 4.8 'Undesirable effects' and Section 4.4 'Special warnings and precautions for use'; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	*Malignancy*

Malignancy	
	Patients with a history of malignancies. Patients with increased risk of malignancies due to heavy smoking. When considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.[3,4] *Lymphoma* There is an increased background risk for lymphoma and leukaemia in RA patients with long standing, highly active, inflammatory disease.[3,4] Studies by Askling et al.[22] and Baecklund et al.[23] have shown that patients with RA have an approximately 2-fold increased risk of lymphoma and leukaemia. The increase in lymphoma risk is limited to those RA patients who have long standing and very severe disease. In a prospective study designed to determine the rate of lymphoma among patients with RA, those who developed lymphoma (irrespective of treatment) were significantly older, had more comorbidities, were more likely to be male, had more education, and were more likely to be non-Hispanic whites compared with those that did not develop lymphoma.[24] *HSTCL* The vast majority of HSTCL cases with infliximab use have occurred in patients with CD or UC and most were reported in adolescents or young adult males. Almost all patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) concomitantly with or immediately prior to infliximab. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered, as the risk for development of HSTCL among such patients cannot be excluded.[3,4] *Paediatric malignancy* According to the Remicade® and Flixabi SmPCs, children and adolescents exposed to infliximab are the risk groups.[3,4] Underlying autoimmune disease and concomitant use of immunosuppressants could increase the risk of malignancies among patients on infliximab; however, a clear causal relationship could not be established.[25] *Leukaemia* According to the Remicade® and Flixabi SmPCs, patients with long-standing, highly active, inflammatory disease, and those with a history of malignancy are at an increased risk of developing leukaemia after infliximab treatment. Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. Caution should be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking or chronic obstructive pulmonary disease. A risk for the development of malignancies in children and adolescents treated

Malignancy	
	with TNF-blockers cannot be excluded.[3,4] *Melanoma* Patients with risk factors for skin cancer. Among patients considered for TNF-therapy, patients with a history of malignancy, or patients who develop a malignancy during treatment and considering continuation of the treatment. Patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.[3,4] *Merkel cell carcinoma* Factors such as advanced age, immunosuppression (such as organ transplants and HIV), other cancers, and UV light exposure may increase the risk of developing Merkel cell carcinoma.[26] *Cervical cancer* A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age.[3,4]
Risk minimisation measures	<Routine risk minimisation measures> SmPC Sections 4.4 and 4.8, and PL sections 2 and 4 Prescription-only medication
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> SB2-G31-RA Registry: BSRBR-RA, ARTIS, RABBIT, BIOBADASER, CEDUR, CREDIT See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.2 Important potential risk

Colon carcinoma/dysplasia (in paediatric ulcerative colitis)	
Evidence for linking the risk to the medicine	SmPCs for Flixabi and Remicade®, Section 4.8 ‘Undesirable effects’ and Section 4.4 ‘Special warnings and precautions for use’; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Patients with a history of malignancies, with long-standing UC or PSC, with a family history of colorectal cancer.
Risk minimisation measures	<Routine risk minimisation measures> SmPC Section 4.4 Prescription-only medication
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Registry: CEDUR, CREDIT See section II.C of this summary for an overview of the post-authorisation development plan.

Immunogenicity	
Evidence for linking the risk to the medicine	SmPCs for Flixabi and Remicade®; referenced scientific publications. Strength of evidence is not applicable as the information is aligned with the safety profile of the reference product following the regulatory requirements for biosimilar products.
Risk factors and risk groups	Relevant information will be collected further during the post-authorisation period
Risk minimisation measures	<Routine risk minimisation measures> SmPC Section 4.8 Prescription-only medication
Additional pharmacovigilance activities	<Additional pharmacovigilance activities> Monitor the related adverse events (refer to the routine PV activity) in the already proposed registry of the RMP for Flixabi: BSRBR-RA, ARTIS, RABBIT, BIOBADASER, CREDIT See section II.C of this summary for an overview of the post-authorisation development plan.

II.B.3 Missing information

None

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 Flixabi.

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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
BSRBR-RA - The British Society for Rheumatology Biologics Register-rheumatoid arthritis Ongoing	An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.	Serious infection/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, malignancy, immunogenicity	Protocol submission	2015 3Q (No update in the previously submitted protocol; hence, a new version was not submitted and protocol submission is considered as completed)
			Study start	2017 1Q (completed)
			Study finish	2026 (planned)
			Final report	2027 (planned) Annual data reports will be submitted during the study period and until submission of the final report.
ARTIS - Anti-rheumatic Therapies In Sweden Planned	A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other rheumatic disease patients treated with infliximab.	Serious infection/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, malignancy, immunogenicity	Protocol submission	2015 3Q (final protocol submitted)
			Study start	2019 4Q (completed)
			Study finish	2028 (planned)
			Final report	2029 (planned) Annual data reports will be submitted during the study period.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
				The final study report will be submitted within a year of study completion.
RABBIT-RA - Rheumatoid Arthritis Observation of Biologic Therapy Ongoing	A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs	Serious infection/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, malignancy, immunogenicity	Protocol submission	2015 4Q (no update in the previously submitted protocol; hence, a new version was not submitted and protocol submission is considered to be completed)
			Study start	2017 1Q (completed)
			Study finish	2026 (planned)
			Final report	2027 (planned) Annual data reports will be submitted during the study period and until submission of the final report
BIOBADASER - Spanish Registry of Adverse Events of Biological Therapies Ongoing	1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence 2. To identify unexpected adverse events 3. To identify relevant adverse events that occur following the suspension of the treatment 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments	Serious infection/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to Flixabi, malignancy, immunogenicity	Protocol submission	2016 3Q (completed)
			Study start	2016 4Q (completed)
			Study finish	2025 (planned)
			Final report	2026 (planned) Annual reports will be submitted during the study period and until submission of the final report.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	5. To identify risk factors for suffering adverse reactions with these treatments 6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment			
CEDUR – a nationwide German IBD registry Ongoing	To describe the long-term effectiveness of treatment with IBD therapies such as drug survival, effectiveness, side effects of treatment combination, and disease activity achieved	Serious infections/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with in utero exposure to Flixabi, malignancy, colon carcinoma (in paediatric UC),	Regular updates	Data will be reviewed on an ongoing basis as a part of signal detection and reported within PSURs, when available
			Final report	To be determined Biennial interim reports will be submitted during the study period if the final report is expected later than 2022
CREDIT - Czech Register of IBD Patients on Biological Therapy Ongoing	To monitor effectiveness of total population of IBD patients on biological medication in the Czech Republic and regular analytical evaluation of the effectiveness	Serious infections/sepsis, demyelinating disorders, BCG breakthrough infection and agranulocytosis in infants with in utero exposure to Flixabi, malignancy, colon carcinoma/dysplasia (in paediatric UC), immunogenicity	Regular updates	Data will be reviewed on an ongoing basis as a part of signal detection and reported within PSURs, when available
			Final report	To be determined Biennial interim reports will be submitted during the study period if the final report is expected later than 2022

<SB2-G31-RA summary (completed)>

Study short name and title: SB2-G31-RA; A Randomised, Double-blind, Parallel Group, Multicentre Clinical Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Immunogenicity of SB2 Compared to Remicade® in Subjects with Moderate to Severe Rheumatoid Arthritis despite Methotrexate Therapy

Rationale and study objectives: To evaluate safety of Flixabi compared to that of Remicade®

Study design: Randomised, double-blind, parallel group, multicentre (Week 0 to 54); Transition-extension period (Week 54 to 78)

Study population: Patients with moderate to severe RA despite MTX therapy

Milestones:

- Week 30 CSR: Feb 2015
- Week 54 CSR: Jul 2015
- Week 78 CSR: 2016 3Q

<BSRBR-RA summary>

Study short name and title: BSRBR-RA - British Society for Rheumatology Biologics Register – Rheumatoid Arthritis

Rationale and study objectives: An established nationwide register for patients with rheumatological disorders treated with biologic agents. The register is designed as a national prospective study whose primary purpose is to assess long-term toxicity from the use of these agents in routine practice.

Study design: National prospective study

Study population: Patients in the UK with rheumatological disorders treated with biologics and other new advanced targeted therapies

Milestones:

- Protocol submission: 2015 3Q (completed)
- Study start: 2017 1Q (completed)
- Study end: 2026 (planned)
- Final report: 2027 (planned)

<ARTIS summary>

Study short name and title: ARTIS - Anti-rheumatic Therapies In Sweden

Rationale and study objectives: A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected AEs in RA, JIA, and other rheumatic disease patients treated with infliximab.

Study design: National prospective, observational, uncontrolled cohort study

Study population: Patients in the Sweden with rheumatological disorders treated with biologics

Milestones:

- Protocol submission: 2015 3Q (completed)
- Study start: 2019 4Q (completed)
- Study end: 2028 (planned)
- Final report: 2029 (planned)

<RABBIT-RA summary>

Study short name and title: RABBIT-RA - Rheumatoid Arthritis Observation of Biologic Therapy – Rheumatoid Arthritis

Rationale and study objectives: A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs

Study design: Prospective, observational cohort study

Study population: Adult patients in Germany with RA

Milestones:

- Protocol submission: 2015 4Q (completed)
- Study start: 2017 1Q (completed)
- Study end: 2026 (planned)
- Final report: 2027 (planned)

<BIOBADASER summary>

Study short name and title: BIOBADASER - Spanish Registry of Adverse Events of Biological Therapies

Rationale and study objectives: 1. To identify relevant adverse events occurring during treatment of rheumatic diseases with biological therapies, and to estimate the frequency of their occurrence; 2. To identify unexpected adverse events; 3. To identify relevant adverse events that occur following the suspension of the treatment; 4. To estimate the relative risk of occurrence of adverse events with biological therapies in patients with RA compared to those not exposed to these treatments; 5. To identify risk factors for suffering adverse reactions with these treatments; 6. To evaluate, under non-experimental conditions, the treatment duration before the biological medications had been suspended in patients with rheumatic diseases, as well as the reasons for the interruption of the treatment

Study design: National observational study

Study population: Spanish patients with rheumatic diseases who are treated with biologics

Milestones:

- Protocol submission: 2016 3Q (completed)
- Study start: 2016 4Q (completed)
- Study end: 2025 (planned)
- Final report: 2026 (planned)

<CEDUR summary>

Study short name and title: CEDUR – a nationwide German IBD registry

Rationale and study objectives: Head-to-head comparison of different IBD treatments (comparative effectiveness research [CER]) The primary end point is to describe the long-term effectiveness of treatment with IBD therapies such as drug survival, effectiveness, side effects of treatment combination, and disease activity achieved. Additional endpoints include the interplay between disease activity, comorbid conditions and safety outcomes to explore the role of treatment in these interactions.

Study design: long-term descriptive multicentre observational registry

Study population: Patients in Germany with IBD

Milestones:

- Regular updates: Data will be reviewed on an ongoing basis as a part of signal detection and reported within PSURs, when available
- Final report: To be determined

<CREDIT summary>

Study short name and title: CREDIT - Czech Register of IBD Patients on Biological Therapy

Rationale and study objectives: To monitor effectiveness of total population of IBD patients on biological medication in the Czech Republic and regular analytical evaluation of the effectiveness

Study design: Non-interventional multicentric retrospectively-prospective longitudinal follow-up study

Study population: Patients in Czech treated with biological medication for idiopathic bowel inflammations

Milestones:

- Regular updates: Data will be reviewed on an ongoing basis as a part of signal detection and reported within PSURs, when available
- Final report: To be determined