SANDOZ A Novartis Division

Regulatory Affairs Sandoz Biopharmaceuticals

GP2015 (INN: etanercept)
25 mg/0.5 mL and 50 mg/1 mL
Solution for Injection

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Risk Management Plan Summary

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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 Erelzi®/Erelzi SensoReady® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in

Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Erelzi®/Erelzi SensoReady® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Sandoz Pharmaceuticals AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Erelzi®/Erelzi SensoReady®.

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1.1 Part VI.2 Elements for a Public Summary

1.1.1 Part VI.2.1 Overview of disease epidemiology

Erelzi is used for treatment of the following diseases:

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease in which the body's immune system – which normally protects its health by attacking foreign substances like bacteria and viruses – mistakenly attacks the joints leading to pain and irreversible deformation and destruction of the joints if not treated adequately. About 1.5 million people in the United States (US) have RA. (Arthritis Foundation, RA 2015). In European countries between 20 and 50 cases per 100 000 inhabitants are newly diagnosed each year. Worldwide, about 0.5 to 1% of the adult population have RA. In general, more women than men are affected by the disease. The ratio has been reported to be 2:1 or higher. According to the World Health Organization, the highest number of patients can be found in Europe and North America and the lowest in the African, Eastern Mediterranean and Southeast Asian Regions (Koko V, 2015).

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common type of arthritis in children. The term idiopathic means "of unknown origin." About 10 percent of children with JIA have the systemic form, which affects the whole body. Nearly 300,000 children – from infants to teenagers – in the US have some form of arthritis (Arthritis Foundation, JIA 2015). Death rate for patients with JIA is less than 1% in Europe and less than 0.5% in North America. Most patients are affected at a very young age (1-4 years), or at age 6-12 years. More girls are affected by JIA than boys (Sherry DD, 2016).

Psoriatic Arthritis

Psoriatic arthritis (PsA) is an autoimmune disease, meaning it occurs when the body's immune system mistakenly attacks healthy tissue, in this case the joints and skin. The faulty immune response causes inflammation that triggers joint pain, stiffness and swelling. The inflammation can affect the entire body and may lead to permanent joint and tissue damage if it is not treated early and aggressively. The disease usually appears between the ages of 30 and 55 in people who have psoriasis, but it can be diagnosed during childhood (Arthritis Foundation, PsA 2015). PsA occurs in 0.02%–0.42% of the poeple in Europe and America (Liu JT, 2014). Men are affected at the same rate as women. PsA characteristically develops in persons aged 35-55 years, but it can occur at almost any age. In the juvenile (that occurs in children) form, the age of onset is 9-11 years (Hammadi AA, 2016).

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a type of inflammatory arthritis that primarily affects the spine or back. The joints and ligaments along the spine become inflamed. Nearly half a million people in the United States are affected by AS. The disease is more common in men than in women. Ankylosing spondylitis may develop in childhood, and boys are more likely to have it than girls. This disease occurs more often in Caucasians, Asian and Hispanic populations (Arthritis Foundation, AS 2015). Out of 10,000 people approximetaly 23.8 people in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America and 7.4 in Africa are affected by the disease. The disease commonly presents in the second decade of life (BMJ, 2016).

Plaque Psoriasis

Plaque psoriasis is the most common form of the disease and appears as raised, red patches covered with a silvery white buildup of dead skin cells or scale. These patches or plaques most often appear on the scalp, knees, elbows and lower back. Men and women develop psoriasis at equal rates. Psoriasis also occurs in all racial groups, but at varying rates. About 1.3 percent of African-Americans have psoriasis, compared to 2.5 percent of Caucasians. Psoriasis often develops between the ages of 15 and 35, but it can develop at any age. About 10 to 15 percent of those with psoriasis get it before age 10. Some infants have psoriasis, although this is considered rare (National Psoriasis Foundation, 2015). Studies have shown that 1.5 – 3% of people among western European populations are affected by the disease (Lui H, 2016). The disease occurs in two peak age periods: the first between 16 and 22 and the second between 57 and 60 years of age (WHO, 2016).

1.1.2 Part VI.2.2 Summary of treatment benefits

Erelzi (company code GP2015) contains the active substance etanercept and is similar to the medicine Enbrel® which is already available in Europe. The studies with Erelzi were designed to show that Erelzi is similar to Enbrel® which has already been proven to provide benefit to patients with the chronic inflammatory disorders discussed above.

The global GP2015 clinical development program conducted 4 pharmacokinetic (study of how the body absorbs, distributes and gets rid off the medicine) studies involving a total of 216 healthy volunteers. In addition, data is available from a study in 531 patients with moderate to severe, chronic (long-term), plaque PsO (raised, red patches covered with a silvery white buildup of dead skin cells or scale mostly on the scalp, knees, elbows and lower back). It was observed that safety profiles (how often side effects occur and which side effects occur) of GP2015 and Enbrel® were similar across all studies.

A multicenter (study conducted at more than one clinic), randomized (a study design that randomly assigns participants to different groups), double-blind (study in which neither the participants nor the experimenters know the particular treatment being received), confirmatory, safety and efficacy study was conducted to show equivalence of efficacy and similarity in safety and immunogenicity (ability of a particular substance to provoke an immune response in the body) of GP2015 and Enbrel® in patients with moderate to severe, chronic, plaque PsO. It was confirmed that GP2015 and Enbrel in patients with moderate to

severe chronic psoriasis are comparable. The study established that there are no clinically meaningful differences between GP2015 and Enbrel®.

1.1.3 Part VI.2.3 Unknowns relating to treatment benefits

As described in Part VI.2.2 the studies of GP2015 have been designed to show that the human body deals with GP2015 in a similar way as with Enbrel® and that both medications were comparable with regards to safety and efficacy in a psoriasis clinical trial. Enbrel is used in other diseases such as rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis.

Clinical experience with Enbrel® is limited in patients with liver and/or kidney function impairment. Increased concentrations of etanercept have not been observed in such patients, therefore, no dose adjustment is required.

There is no data suggesting that the treatment benefits of GP2015 would be different from Enbrel® in these above mentioned diseases or in special populations like patients with hepatic and renal impairment or of different ethnic/racial origins.

1.1.4 Part VI.2.4 Summary of safety concerns

Table 1-1 Important identified risks - all indications

Risk	What is known	Preventability
Development of cancers (including cancer of the lymphatic system [a network of vessels and organs that help rid the body of toxins, waste and other unwanted materials] and cancer of blood and bone marrow [soft blood-forming part of bone]) [Malignancy (including lymphoma and leukemia)]	Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher than average risk of developing lymphoma. Children and adults taking Erelzi may have an increased risk of developing lymphoma or another cancer. Some children and teenage patients who have received Etanercept or other medicines that work the same way as Erelzi have developed cancers, including unusual types, which sometimes resulted in death. Some patients receiving Etanercept have developed skin cancers. Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin.	Patients should tell their doctor if they have or have ever had lymphoma or any other cancer before they are given Erelzi. Patients should tell their doctor if they develop any change in the appearance of the skin or growths on the skin or if they experience any of the other symptoms explained in column “What is known”.

Risk	What is known	Preventability
	Skin cancer (excluding melanoma) is an uncommon side effect (may affect up to 1 in 100 people) of etanercept. Lymphoma, and melanoma (a type of skin cancer) are rare side effects (may affect up to 1 in 1,000 people) of etanercept. Leukemia (cancer affecting the blood and bone marrow), and merkel cell carcinoma (a type of skin cancer) are cancers of unknown frequencies observed with etanercept.	
Serious infections including those which only occur in cases of damaged “good” bacteria or damaged immune system (including tuberculosis, Legionella, Listeria, or parasite infections) [Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection)]	Infections (including colds, inflammation of the air-filled spaces around the nose [sinusitis], inflammation of the airways leading into the lungs [bronchitis], urinary tract infections and skin infections) may occur in more than 1 out of 10 patients treated with Etanercept (very common side effect). Serious infections (including inflammation of the lung [pneumonia], deep skin infections, joint infections, blood infection, and infections at various sites) may occur in up to 1 out of 100 patients treated with Etanercept (uncommon side effects). Cases of tuberculosis have been reported in patients treated with Etanercept.	Patients should not use Erelzi if they have an infection of any kind or are at risk of developing a serious blood infection called sepsis. If the patient is not sure, they should contact their doctors. Before taking Erelzi, patients should inform the doctor about the following: • if they developed a new infection, or are about to have any major surgery. Doctor may wish to monitor the treatment with Erelzi; • if they have a history of recurrent infections or suffer from diabetes or other conditions that increase the risk of infection; • if they have recently travelled outside the European region. Doctor should be notified if the patients develop symptoms of an infection such as fever, chills or cough. Doctor may decide to continue to monitor the patient for the presence of infections even after stopping the treatment with Erelzi. • If they have or have had hepatitis B. Doctor should

Risk	What is known	Preventability
		test for the presence of hepatitis B infection before beginning the treatment with Erelzi. Patient should stop using Erelzi if reactivation of hepatitis B occurs. • If they have or have had hepatitis C. Doctor might wish to monitor the treatment with Erelzi in case the infection worsens Patients' doctor will check for signs and symptoms of tuberculosis before starting Erelzi. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Alert Card. It is very important that patients tell their doctor if they have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, patients should tell their doctor immediately.
Symptoms which resemble Lupus – a disease where white blood cells attack healthy parts of the body (Lupus-like reactions)	Lupus or lupus- like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness) may occur in up to 1 out of 1,000 patients (rare side effect) treated with Etanercept.	If patients notice signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue, they should seek urgent medical attention.
A granulomatous disorder that can affect multiple organs and/or granulomas (Sarcoidosis and/or granulomas)	Sarcoidosis may occur in up to 1 out of 1,000 patients (rare side effect) treated with Etanercept. Erelzi is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease which leads to multiple granulomas and inflammation of vessels.	If patients experience symptoms such as skin rash, skin nodes, lung problems or enlarged lymph nodes, they should talk to their doctor or pharmacist. If patients have Wegener's granulomatosis, they should talk to their doctor.
Injection site reactions	Injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling) may affect more than 1 out of 10 patients	If patients notice any symptoms of bleeding, bruising, redness, itching, pain, and swelling at the injection site or former injection

Risk	What is known	Preventability
	treated with Etanercept (very common side effect). Reactions at the injection site do not occur as often after the first month of treatment. Some patients have developed a reaction at an injection site that was used before.	sites, they should talk to their doctor or pharmacist.
Allergic reactions	Signs and symptoms of an allergic reaction include: - Trouble swallowing or breathing - Swelling of the face, throat, hands, or feet - Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling - Severe rash, itching, or hives (elevated patches of red or pale skin that often itch) Allergic reactions and itching are common side effects (may affect up to 1 in 10 patients) of etanercept. Angioedema (localized swelling of the skin), hives (elevated patches of red or pale skin that often itch), and rash are uncommon side effects (may affect up to 1 in 100 people) of etanercept. Serious allergic reactions (including severe localised swelling of the skin and wheezing), skin rash, which may lead to severe blistering and peeling of the skin are rare side effects (may affect up to 1 in 1,000 patients) of etanercept. Toxic epidermal necrolysis (a rare condition that causes large portions of the skin's outermost layer to detach from the layers of skin below) is a very rare side effect (may affect up to 1 in 10,000 patients) of etanercept.- Severe rash, itching, or hives (elevated patches of red or pale skin that	Patients are advised not to use Erelzi, if allergic to etanercept or any of the other ingredients of Erelzi. Patients should immediatey contact their doctors if they experience allergic reactions such as chest tightness, wheezing, dizziness or rash or any other of the symptoms described in column “What is known”.

Risk	What is known	Preventability
	often itch)	
Severe skin reactions (including potentially life-threatening conditions affecting large parts of the skin in which cell death causes the outer layer of the skin to separate from the middle layer) [Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)]	Severe skin reactions may occur after etanercept injection rarely (may affect up to 1 in 1,000 users). Cutaneous vasculitis (inflamed blood vessels in the skin), skin rash, which may lead to severe blistering and peeling of the skin is rare side effect (may affect up to 1 in 1,000 patients) of etanercept . TEN is a very rare side effect (may affect up to 1 in 10,000 people) of etanercept.	If any skin reactions happen, patients should not inject more Erelzi. They should tell their doctor immediately, or go to the casualty department at their nearest hospital.
Inflammation of the blood vessels [Systemic vasculitis (including ANCA positive vasculitis)]	Inflammation of the blood vessels is an uncommon side effect (may affect up to 1 in 100 patients), but may be a serious condition.	If pain, fever, redness or warmth of the skin, or itching occurs, patients should tell their doctor immediately, or visit the casualty department at their nearest hospital.
Excessive activation of white blood cells associated with inflammation and disorders of several organs (Macrophage activation syndrome)	Excessive activation of white blood cells associated with inflammation and disorders of several organs, so called Macrophage activation syndrome may occur in patients using etanercept (frequency cannot be estimated from the available data).	Caution should be exercised in patients being treated with Erelzi who have a previous history of blood disorders. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood disorders or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Erelzi, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood disorders are confirmed, Erelzi should be discontinued.
Disorders of the nerves inside the brain and spinal cord (Central demyelinating disorders)	Nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis (a disease in which the immune system eats away at the protective covering of nerves) or inflammation of the nerves of the eyes or spinal cord) are rare side effects (may affect up to 1 in 1,000 users) of Erelzi.	Patients should tell their doctor if they have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Their doctor will determine if Erelzi is an appropriate treatment. If patients experience signs of nerve disorders such as numbness, tingling, changes in vision, eye pain, or onset of weakness in an arm or leg, they should consult with their doctor.

Risk	What is known	Preventability
Damages to the nerves outside of the brain and spinal cord [Peripheral demyelinating events (CIDP and GBS)]	There have been very rare reports of damages to the nerves outside of the brain and spinal cord, so called peripheral demyelinating events (may affect up to 1 in 10,000 users).	A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Erelzi to patients with pre-existing or recent onset of peripheral demyelinating disease, or to those who are considered to have an increased risk of developing peripheral demyelinating disease. If patients experience signs of nerve disorders such as numbness, tingling, changes in vision, eye pain, or onset of weakness in an arm or leg, they should consult with their doctor.
Failure of the bone marrow to produce crucial blood cells and combined low platelet, red, and white blood cell count (Aplastic anemia and pancytopenia)	Failure of the bone marrow to produce blood cells, so called aplastic anemia, may affect up to 1 in 10,000 patients (very rare side effect) treated with etanercept, and combined low platelet, red, and white blood cell count, so called pancytopenia, may affect up to 1 in 1,000 patients (rare side effect).	Caution should be exercised in patients being treated with Erelzi who have a previous history of blood disorders. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood disorders or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on Erelzi, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood disorders are confirmed, Erelzi should be discontinued.
Lung diseases affecting the tissue and space around the air sacs of the lungs like scarring of the lungs or inflammation of the lung tissue (Interstitial lung disease (including pulmonary fibrosis and pneumonitis))	Inflammation or scarring of the lungs is an uncommon side effect and may affect up to 1 in 100 patients treated with etanercept.	If symptoms such as shortness of breath and difficulty breathing occur, the patient should seek medical attention with his/her doctor as this could indicate lung problems.
Inflammation of the liver caused by the body's own immune system (Autoimmune hepatitis)	Inflammation of the liver caused by the body's own immune system, so called autoimmune hepatitis may affect up to 1 in 1,000 patients treated with etanercept (rare side effect).	Blood tests can detect how well the liver is able to work. If there are any symptoms of liver damage such as yellow skin and/or eyes or bleeding, then patients should see their doctor immediately.
Liver events in patients with	Recurrence frequency of hepatitis	Patients should be tested for

Risk	What is known	Preventability
liver inflammation due to a virus including this due to a reactivation of a virus which caused the liver inflammation before (Liver events in patients with viral hepatitis (including hepatitis B virus reactivation))	B (a liver infection) in patients treated with etanercept cannot be estimated from the available data. There have been reports of worsening of hepatitis C in patients receiving etanercept.	HBV infection before initiating treatment with Erelzi. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering Erelzi in patients previously infected with HBV or HCV. Patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy.

Table 1-2 Important identified risks – specific indications

Risk	What is known	Preventability
Change in morphology (features) and/or severity of psoriasis in adult and pediatric populations	Although etanercept is effective in the treatment of psoriasis, there have been reports describing new psoriasis eruptions, a worsening of pre-existing psoriasis, or changes in psoriasis features associated with use of etanercept and other tumor necrosis factor (TNF) inhibitors (drug class to which Erelzi belongs). These events occurred in patients who received TNF inhibitors for treatment of psoriasis, as well as in patients treated for diseases other than psoriasis. The mechanism for change in features and/or severity of psoriasis associated with etanercept is not known. Psoriasis (new or worsening) is an uncommon side effect (may affect up to 1 in 100 people) of Erelzi.	Patients should inform their doctor if they have psoriasis and symptoms seem to worsen.
Worsening heart failure in adult patients (Worsening of congestive heart failure in adult subjects)	Worsening heart failure, so called congestive heart failure, may affect up to 1 in 1,000 patients (rare side effect) treated with etanercept.	Patients should tell their doctor if they have a history of congestive heart failure, because Erelzi needs to be used with caution under these circumstances. Physicians should use caution when using Erelzi in such

		patients. If patients notice any signs of worsening heart failure, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips, they may need urgent medical attention.
Inflammatory condition of colon and small intestine in children with juvenile idiopathic arthritis [JIA] (Inflammatory bowel disease in juvenile idiopathic arthritis subjects)	There have been cases of Inflammatory Bowel Disease like Crohn's disease or ulcerative colitis in patients with Juvenile Idiopathic Arthritis (JIA) treated with etanercept.	Parents should tell the doctor if the child develops any abdominal cramps and pain, diarrhea, weight loss or blood in the stool.

Table 1-3 Important potential risks – all indications

Risk	**What is known** **(Including reason why it is considered a potential risk)**
Kidney disease caused by the body's own immune system (Autoimmune renal disease)	Autoimmune renal disease is when a person's own body attacks his or her kidneys. As etanercept is associated with other autoimmune diseases such as lupus-like syndrome, there is a possibility that etanercept use can be associated with autoimmune renal disease.
Rare skin diseases due to the body's own immune system causing blisters and sores (Pemphigus/pemphigoid)	Pemphigus or pemphigoid is a skin disease that results in blisters (bullae) in the skin. There is a possibility that etanercept could induce autoimmune skin diseases.
A chronic, progressive disease of nerve cells that that move muscles when we speak, walk, swallow and move our body (Amyotrophic lateral sclerosis)	ALS is a rare disease that results in gradual weakness of the body. In theory, TNF - may be beneficial to the nervous system in certain cases. Therefore, there is a possibility that TNF inhibition could possibly be associated with ALS. However, there is no evidence proving this for etanercept.
A muscle disease caused by the body's own immune system and resulting in weak muscles and tiredness (Myasthenia gravis)	Myasthenia gravis is an autoimmune disease which results in muscle weakness such as difficulty in moving around. There is a possibility that etanercept might induce autoimmunity to cause or worsen myasthenia gravis. However, there are no clear data, and in fact, in some cases, etanercept is thought to be beneficial for myasthenia gravis.
Inflammation of the brain and spinal cord (Encephalitis/leukoencephalomyelitis)	Brain inflammation can be caused by immunologic reasons. There is a possibility that etanercept use may alter the immune system and lead to encephalitis.
A life-threatening progressive inflammation of the brain caused by virus infection (Progressive multifocal	JC virus infects a large number of normal people and usually does not cause any harm - most people are unaware they have been infected. In people infected with JC virus, etanercept may suppress the immune system and

Risk	**What is known** **(Including reason why it is considered a potential risk)**
leukoencephalopathy)	allow the virus to become active and cause progressive inflammation and damage leading to PML.
Liver failure	Rarely, an inflammation of the liver caused by the body's own immune system and elevated liver blood tests have been observed in patients (in 1 out of 1000 patients) treated with etanercept. Increased etanercept concentrations were not observed in patients with acute hepatic failure.
Conditions resulting replacement of normal liver tissue by scar tissue (Hepatic cirrhosis and fibrosis)	Hepatic cirrhosis is a disease that results in hardening of the liver and gradual decrease of liver function. Whether etanercept can cause this is unclear since methotrexate, a drug that is also commonly used in rheumatoid arthritis, is also associated with this condition.
Severely elevated blood pressure with an increased risk of organ damage (Severe hypertensive reactions)	There are cases of severe increase in blood pressure after use of etanercept; however, the exact mechanism or true association with etanercept is unknown.
Adverse pregnancy outcomes	The effects of etanercept in pregnant women are not known as no studies have been performed in pregnant women, and so the use of etanercept during pregnancy is not recommended. Patients should consult their doctor if they become pregnant, think may be pregnant, or are planning to have a baby. If a patient received etanercept during pregnancy, the baby may have a higher risk for getting an infection. It is important that patients tell the baby's doctors and other healthcare professionals about the use of etanercept during pregnancy before the baby receives any vaccine. Women of childbearing potential should be advised to use appropriate contraception to avoid becoming pregnant during Erelzi therapy and for three weeks after discontinuation of therapy.
Potential for male infertility	There are a few case reports of male patients who experienced infertility after the use of etanercept. However, the true relationship is unclear so far.
Weight Gain	There have been reports of weight gain after etanercept use. Since rheumatic diseases are associated with muscle wasting or weight loss, the improvement of such conditions could possibly lead to recovery of such wasting, resulting in weight gain.
Problems handling the pre-filled pen (autoinjector) leading to incorrect administration of the drug (Potential for medication errors)	Other etanercept products are available. Switching between etanercept products is expected to become common practice and design of the devices varies from product to product. To reduce the potential for medication errors, the package leaflet of Erelzi provides very specific step-by-step directions. In addition, educational material has been developed to demonstrate the correct use of the Erelzi pre-filled pen for care givers and health care professionals.

Table 1-4 Important potential risks – specific indications

Risk	What is known (Including reason why it is considered a potential risk)
Impaired growth and development in young patients (Impaired growth and development in juvenile subjects)	The mechanism for a potential effect on growth and development associated with etanercept is not known.
Acute effects on the heart in adult patients due to decreased blood flow to the heart (Acute ischemic cardiovascular events in adult subjects)	Cardiovascular events such as heart attacks or strokes might possibly occur during etanercept use. The exact mechanism or true association with etanercept is not clear.

Table 1-5 Missing information

Risk	What is known
Use in patients with impaired liver and kidney function (Use in hepatic and renal impaired subjects)	Based on pharmacokinetics, i.e. data on how etanercept enters, moves through and exits the body, no dose adjustment is needed in patients with impairment of liver or kidney function. Clinical experience in such patients is however limited because such patients have not been included in clinical studies.
Use in different ethnic origins	There is no evidence to suggest that the etanercept is absorbed, altered (metabolized) or got rid of (eliminated) any differently by people of different races.
Use in pregnant women	The effects of etanercept in pregnant women are not known, and so the use of etanercept during pregnancy is not recommended. Patients should consult their doctor if they become pregnant, think may be pregnant, or are planning to have a baby. If a patient received etanercept during pregnancy, the baby may have a higher risk for getting an infection. It is important that patients tell the baby's doctors and other healthcare professionals about the use of etanercept during pregnancy before the baby receives any vaccine. Information on the use of etanercept in pregnant women is limited because pregnant women were excluded from the clinical studies.

1.1.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures). Full details on these conditions and the key elements of any

educational material can be found in Annex II of the product information which will be published after approval in Erelzi (Etanercept)'s EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimization measures are for the following risks:

Table 1-6 Serious infections including those which only occur in cases of damaged "good" bacteria or damaged immune system (including tuberculosis, Legionella, Listeria, or parasite infections) [Serious opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection)]

Risk minimization measure(s): Patient Alert Card
Objective and rationale: To provide information to patients to make them aware that during treatment with Erelzi, there is an increased risk of acquiring serious infections, or that existing infections may get worse during treatment with Erelzi. **Additional risk minimisation measure(s):** All healthcare professionals (HCPs) who are most likely to prescribe Erelzi are provided with a Patient Alert Card for distribution to patients receiving Erelzi. This card provides important safety information for patients, including information relating to infections related to Erelzi. Key elements: • Brief introduction to the aim of the Patient Alert Card • Request to show the Patient Alert Card to any treating doctor • Request to keep the Patient Alert Card during and after treatment • Information that Erelzi can increase risk for getting serious infection

Table 1-7 Worsening heart failure in adult patients (Worsening of congestive heart failure in adult subjects)

Risk minimization measure(s): Patient Alert Card
Objective and rationale: To provide adequate information to patients to make them aware of the increased risk of worsening of heart failure during treatment with Erelzi. **Additional risk minimisation measures:** All healthcare professionals (HCPs) who are most likely to prescribe Erelzi are provided with a Patient Alert Card for distribution to patients receiving Erelzi. This card provides important safety information for patients, including information relating to infections related to Erelzi. Key elements: • Brief introduction to the aim of the Patient Alert Card • Request to show the Patient Alert Card to any treating doctor • Request to keep the Patient Alert Card during and after treatment • Warning that if symptoms suggestive of worsening heart failure occur, medical attention needs to be sought

Table 1-8 Potential of medication errors (pre-filled pen)

Risk minimization measure(s): Educational material and demonstration device
Objective and rationale: To provide adequate information to care givers and health care professionals to make them aware of the potential risk of medication errors with the use of the pre-filled pen **Additional risk minimisation measures:** Educational material will be launched to reduce the potential of medication errors that can occur with the use of Erelzi and to help healthcare professionals and care givers to use Erelzi properly. As other etanercept products are available, switching between etanercept products is expected to become common practice and design of the devices varies from product to product. Key elements: • Availability of a needle free demonstration device. This device allows patients to practice administration prior to using Erelzi. These devices will be made available to clinicians for training purposes in the clinician's office. • Educational material relating to the correct use of the pre-filled pen (autoinjector) for care givers and healthcare professionals with the aim to facilitate training of the patients in the use of the pre-filled pen (see Annex 10/11).

1.1.6 Part VI.2.6 Planned post authorization development plan

Table 1-9 List of studies in post authorization development plan

Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
RABBIT (GER): Rheumatoid Arthritis Observation of Biologic Therapy Category 3	Evaluation of long-term safety and effectiveness of tumor necrosis factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA). Data for TNF–inhibitor therapies in the treatment of RA patients will be compared to a cohort of RA patients who are treated with non-biologic DMARDs.	Monitoring of all safety concerns described in RMP, including malignancy, serious and opportunistic infections, central demyelinating disorders, aplastic anaemia or, pancytopenia, worsening of congestive heart failure, acute ischemic cardio vascular events; use in pregnant woman	Planned (Start at time of drug availability in country following EMA approval)	Final report planned within 6-12 months after study completion. Summary reports provided to the MAH every 6 months.
ARTIS (SWE): Anti-rheumatic Therapies in Sweden Category 3	Evaluation of long-term safety and effectiveness associated with	Monitoring of all safety concerns described in RMP, including malignancy, serious and	Planned (Start at time of drug availability in	Summary reports provided to MAH every 6 months. An interim analysis is planned to be provided at 3 years after study start and and final planned within 6-12

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	TNF-inhibitor therapies in the treatment of rheumatoid arthritis. The risk of selected AEs in RA, juvenile idiopathic arthritis, and other rheumatic disese patients treated with etanercept will be evaluated.	opportunistic infections, central demyelinating disorders, aplastic anaemia or, pancytopenia, worsening of congestive heart failure, acute ischemic cardio vascular events; use in pregnant woman	country following EMA approval)	months after study completion.
BSRBR (UK): British Society for Rheumatology Biologics Register – rheumatoid arthritis Category 3	Register is designed as national prospective study obtaining data from routine clinical practice and whose objective is to evaluate long-term safety from the use of these agents in routine practice.	Monitoring of all safety concerns described in RMP, including malignancy, serious and opportunistic infections, central demyelinating disorders, aplastic anaemia or, pancytopenia, worsening of congestive heart failure, acute ischemic cardio vascular events; use in pregnant woman	Planned (Start at time of drug availabili ty in country following EMA approval)	Summary reports provided to the MAH every 6 months. Final report planned within 6-12 months after study completion
BADBIR (UK): British Association of Dermatologists Biologic Interventions Register (BADBIR, UK) Category 3	Assessment of long-term safety of biological treatments for psoriasis	Long-term safety of biologic treatments for psoriasis	Planned (Start at time of drug availabili ty in country following EMA approval)	Summary reports provided to the MAH every 6 months. Final report planned within 6-12 months after study completion

1.1.6.1 Studies which are a condition of the marketing authorization

N/A

1.1.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable, as this is the first RMP.