VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

The immune system is the body's frontline defence to fight infection by viruses, bacteria, and other foreign organisms/materials. To do its job properly, the immune system has to distinguish between the body tissues (cells, tissues, and organs of the body) and foreign organisms/materials[211].

The nervous system is made up of neurons. Each neuron consists of a cell body and its long extension - the axon. And each axon is covered by a protective protein coating called myelin. In autoimmune diseases like multiple sclerosis (MS) the immune system loses the ability to distinguish the body

tissues from foreign organisms/materials. In MS, this autoimmune response destroys the myelin and the axons[211].

MS begins as a relapsing-remitting disease (RRMS) about 85% of the time. RRMS is characterized by unpredictable periods of worsening (relapses, exacerbations, or attacks) followed by remissions. A remission may be complete, *i.e.* the person returns to his or her pre-relapse level of functioning, or partial, *i.e.* some of the symptoms are likely to be permanent[211].

VI.2.2 Summary of treatment benefits

The benefits of using glatiramer acetate have been shown in three main clinical studies, which are:

1. Borstein and colleagues[88] studied glatiramer acetate use in 25 RRMS patients whilst 25 patients received a dummy product psychologically indicating the presence of glatiramer. They observed that 56% of patients receiving glatiramer acetate and 28% of patients receiving the dummy product remained relapse-free for two years.
2. Johnson and colleagues[91] studied glatiramer acetate use in 125 RRMS patients compared to 126 patients using a dummy product. They observed that 34% of patients receiving glatiramer acetate and 27% receiving the dummy product remained relapse-free for two years.
3. Comi and colleagues[89] studied 119 RRMS patients using glatiramer acetate and 120 using a dummy product. They used brain scanning to evaluate the effect of glatiramer acetate versus the dummy product. They observed that in average, patients using glatiramer acetate presented 11 nerve abnormalities and patients using the dummy product presented 17 nerve abnormalities.

Therefore, it appears that glatiramer acetate would benefit patients by keeping them attack-free whilst decreasing or not letting the nerve tissues being further injured.

VI.2.3 Unknowns relating to treatment benefits

The clinical studies performed with glatiramer acetate did not:

- Include children/adolescents.
- Include pregnant and/or breast feeding woman.
- Focus on elderly.
- Include subjects with neoplastic disease, seizure disorders, psychiatric disease, positive for human immunodeficiency virus, hepatitis, renal impairment and cardiovascular problems.

VI.2.3 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Anxiety	Anxiety may affect up to one in 10 people during treatment with glatiramer acetate. Anxiety, in general, can arise suddenly, as in panic, or gradually	Prevention of anxiety essentially involves an awareness of life's stresses and the ability to cope with them. Strategies might include[151]: • Physical well-being through exercise, healthy eating habits,

Risk	What is known	Preventability
	over many minutes, hours, or even days. It may be a only-once occurrence or may be part of a chronic disease which may last for years; longer duration is more characteristic of anxiety disorders. Anxiety ranges from barely noticeable qualms to complete panic. The ability to tolerate a given level of anxiety varies from person to person. Anxiety disorders can be so distressing and disruptive that depression may result. Alternatively, an anxiety disorder and a depressive disorder may coexist, or depression may develop first, with symptoms and signs of an anxiety disorder occurring later[138].	and adequate rest • Avoiding the use of caffeine, illicit drugs, or the inappropriate use of stimulants or other prescription medications • Meditation • Relaxation exercises including deep breathing
Benign tumours of the skin and soft tissues (Benign neoplasms of the skin and soft tissues)	Bening neoplasm of skin and other neoplasms may affect up to one in 10 people during treatment with glatiramer acetate. Abnormal tissue changes (lesions) that are benign (not invading neighbouring tissue) must be differentiated from malignant (invading neighbouring tissues) lesions. To determine whether a tumour is benign or malignant, a sample of the affected tissue - or, in some cases, the entire suspicious area - is removed and studied under a microscope. This is known as a biopsy[212].	All benign lesions must be watched by the patient and examined by a clinician should any changes occur[161].
Seizures (Convulsions)	Convulsions may affect up to one in 100 people during treatment with glatiramer acetate. A seizure is an abnormal, unregulated electrical discharge that occurs within the brain and transiently interrupts normal brain function. A seizure typically causes, abnormal feelings, or rapid and uncontrollable shaking (convulsions; widespread violent involuntary contraction of voluntary muscles[165]).	A seizure might be prevented by eliminating the cause of the seizure. If the cause cannot be identified, medication (anticonvulsants) is often required. Patients should be advised to avoid cocaine and some other illicit drugs (*e.g.* amphetamines), which can trigger seizures, and to avoid alcohol[165].
Allergic reactions (hypersensitivity): serious allergic reaction (anaphylactic reaction and anaphylactoid reaction); rash-red spots or nettle rash (urticaria);	These reactions might affect less than 1 in 10,000 and more than 1 in 1,000 people during treatment with glatiramer acetate.	Prevention is achieved by avoiding the allergen or trigger of the allergic reaction *i.e.* glatiramer acetate. If a person is not aware he/she is allergic

Risk	What is known	Preventability
swelling of the eyelids, face or lips (oedema); sudden shortness of breath (bronchospasm); fits (convulsions); fainting (unconsciousness).	A person develops an allergic reaction when he/she is sensitive to a substance. This substance is called allergen, which comes in contact with the skin, nose, eyes, respiratory and gastrointestinal tract[213]. Anaphylactic reaction and anaphylactoid reactions are potentially life-threatening types of allergic reactions. Clinically, these two types of reactions are indistinguishable. Symptoms vary from mild, *e.g.* urticaria to severe, *e.g.* airway obstruction, refractory shock[168]. Baumgartner and colleagues[172] reported six cases in which patients developed such reactions after three and or six months of exposure to Copaxone®. Rauschka *et al.*[173] reported a patient who developed a severe anaphylactic reaction that occurred about one year after Copaxone® initiation. Such reactions have also been reported with mannitol[214,215].	to a certain substance, prevention is difficult. However, awareness among doctors and patients should be created by informing them that an allergic reaction may occur. Further, to avoid worsening of the allergic reaction, glatiramer should be stopped and the doctor should be contacted immediately after noticing any of the following signs: rash, swelling of the eyelids, face or lips, sudden shortness of breath, convulsions, fainting.
Immediate post-injection reaction: flushing of the chest or face (vasodilatation); a feeling of tightness in the chest (chest pain); shortness of breath (dyspnoea); rapid heartbeats, rapid and throbbing heartbeat (palpitations/tachycardia).	Chest pain, shortness of breath and flushing of the chest or face may affect more than one in 10 people. Rapid heartbeats, rapid and throbbing heartbeat may affect up to one in10 people. These reactions have been described as Immediate post-injection reactions. Some people may get one of these symptoms within minutes after injecting glatiramer. Normally, they do not cause problems and will disappear within 30 minutes. In clinical trials with Copaxone®, 31% of the patients receiving Copaxone® and 13% of the patients receiving placebo reported at least	Prevention might be difficult. If this type of reaction occurs it should go away within several minutes. However, if it occurs, it is important to relax, be calm, sit down, keep the head upright, breath slowly, if you are not alone, asked the person with you to get a cool cloth for your forehead, remember the reaction will be over in a few minutes. If the reaction does not disappear in few minutes, or if additional symptoms are present, such as swelling tongue, face or eyes or difficulty swallowing or wheezing, please contact your doctor immediately[176].

Risk	What is known	Preventability
	one of the symptoms of the immediate post-injection reaction[216].	
Loss of subcutaneous fat (lipoatrophy); death of the skin tissue (skin necrosis)	At the injection site loss of subcutaneous fat and death of the skin tissue have been reported during the post-marketing experience with glatiramer. Loss of subcutaneous fat may occur at different times after the treatment onset (sometimes after several months) and is thought to be not reversible[176].	There is no known treatment for lipoatrophy. To assist in minimizing these events, the patient should be advised to follow proper injection technique and to rotate injection sites daily[176].
Skin reactions at the injection site (Injection site reactions): redness of skin (erythema); formation of wheals (urticaria); itching (pruritus); tissue swelling (oedema) and inflammation; (Injection site reactions excluding necrosis and atrophy)	Skin reactions at the site of injection may affect more than one in 10 people. Pain may affect more than one in 10 people. Swelling, itching and hypersensitivity may affect up to one in 10 people. Redness of skin and inflammation may affect up to 1 in 100 people. In all clinical trials with Copaxone®, skin reactions at the site of injection were seen to be the most frequent side effects and were reported by the majority of patients receiving Copaxone®. In controlled studies (comparing placebo and Copaxone®), the proportion of patients reporting these side effects, at least once, was higher after treatment with Copaxone (70%) than placebo injections (37%)[58].	Rotating the location of injection may help reduce the risk of injection site reactions. Avoid the sites of skin if they present birthmarks, bruising, indentations, lesions, lumps (hardness of the skin), redness, scar tissue, stretch marks, swelling, tattoo, tenderness and warts. Do not rub or massage the injection site on the same day after the injection[176].

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Any disease of the filtering units (glomeruli) of the kidney that does not include an inflammation (Glomerulonephropathies)	An antigen (*e.g.* bacteria, drugs) is any substance capable of causing the body to produce an antibody. An antibody is a protein produced by the immune system to fight antigens. When an antibody binds with an antigen an immune complex is formed. Glatiramer is antigenic and may activate the body to produce antibodies. Immune complexes were observed during animal studies with glatiramer acetate in the kidneys. Therefore, the possibility that immune complexes will be formed and that these complexes might cause damage in the kidneys cannot be excluded.
Liver injury	During clinical studies with glatiramer acetate liver abnormalities have been commonly reported. Further, some case reports on liver toxicity associated with glatiramer acetate have been reported in the literature[103,127-129,205-207]. Therefore, the risk that glatiramer acetate might cause liver injury cannot be excluded.

Missing information

Risk	What is known
Elderly patients	Glatiramer acetate was not specifically studied in the elderly population (≥ 65 years of age). Until additional data is collected elderly patients should use glatiramer acetate with caution. The immune system in the elderly is less effective and the additional suppression of this system using glatiramer acetate, might have different effects than in younger people[115].
Paediatric patients (below 18 years of age)	Glatiramer acetate is not indicated to be used in children and adolescents. Children have been excluded from the studies performed with Glatiramer acetate. However, since children can also develop RRMS physicians have been prescribing glatiramer acetate in this population.
Patients with impaired renal or hepatic impairment	Patients with kidney or liver damage/impairment have been excluded from glatiramer acetate clinical trials. Therefore, the risks associated with the use of glatiramer acetate by patients with kidney or liver dysfunction cannot be excluded. Patients with kidney dysfunction should have their renal function monitored while on treatment with glatiramer acetate[58].
Pregnant or breastfeeding women	Pregnant and breast-feeding women were excluded from glatiramer clinical trials. Glatiramer acetate should not be used during pregnancy and breast-feeding. Therefore, before stating treatment with glatiramer acetate, pill, condom or other effective birth control method should be initiated. In studies with animals (rats or rabbits) no adverse effects were observed after treatment with glatiramer acetate in the offspring[176]. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During pre- marketing clinical trials with Copaxone®, seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment after learning they were pregnant; all delivered healthy babies. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with glatiramer acetate should only be considered after careful risk/benefit assessment and be used with caution[121].

VI.2.5 Summary of additional risk minimisation measures by safety concern

No additional risk minimisation measures have been proposed.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

This is the first risk management written for applicant's glatiramer acetate. Therefore, this section is not applicable.