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 (94).

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 (94).

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 (94).

VI.2.2 Summary of treatment benefits

The benefits of using glatiramer acetate 40 mg/mL TIW have been shown in the GALA study.

Khan *et al*. (101) compared the use of glatiramer acetate 40 mg/mL TIW with a dummy product (placebo) in patients with RRMS. In total, 943 patients received glatiramer acetate 40 mg/mL TIW and 461 patients received placebo. Copaxone® 40 mg TIW was associated with a 34.0% reduction in risk of confirmed relapses compared with placebo. Copaxone® 40 mg TIW was safe and well tolerated.

The results of this study, in addition to the benefits demonstrated for glatiramer acetate 20 mg/mL daily (23, 37, 93) indicate that glatiramer acetate 40 mg TIW 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.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability

Anxiety	Anxiety may affect more than one in 10 people during treatment with glatiramer acetate. Anxiety, in general, can arise suddenly, as in panic, or gradually over many minutes, hours, or even days. It may be a once-only 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 (203).	Prevention of anxiety essentially involves an awareness of life's stresses and the ability to cope with them. Strategies might include (59): • Physical well-being through exercise, healthy eating habits, 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 (non-malignant) skin growth (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 (127).	All benign lesions must be watched by the patient and examined by a clinician should any changes occur (89).
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	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 (210).

Risk	**What is known**	**Preventability**
	involuntary contraction of voluntary muscles (210)).	

Allergic reactions (hypersensitivity): serious allergic reaction (anaphylactic reaction and anaphylactoid reaction); rash-red spots or nettle rash (urticaria); swelling of the eyelids, face or lips (oedema); sudden shortness of breath (bronchospasm); fits (convulsions); fainting (unconsciousness).	Serious allergic reactions may affect up to one in 1,000 people during treatment with glatiramer acetate 20 mg/mL and up to one in 100 people during treatment with glatiramer acetate 40 mg/mL. 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 (130). 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 (199). Baumgartner *et al*. (21) reported six cases in which patients developed such reactions after three and or six months of exposure to Copaxone®. Rauschka *et al.* (156) 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 (86, 117).	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 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' and might occur with glatiramer acetate 20 mg/L administered daily or with glatiramer acetate 40 mg/L administered TIW. During clinical trials, immediate post-injection reactions happened less often with glatiramer acetate 40 mg/L administered TIW (8%) than with glatiramer acetate 20 mg/L administered daily (31%). Some people may get one of the symptoms of the immediate post-injection reactions within minutes after injecting glatiramer. Normally, they do not cause problems and will disappear within 30 minutes.	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 (174).

Risk	**What is known**	**Preventability**

Loss of subcutaneous fat (lipoatrophy); death of the skin tissue (skin necrosis)	Injection site atrophy, including lipoatrophy, may affect up to one in10 people during treatment with glatiramer acetate. 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 (174).	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 (174).
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. During clinical trials, injection site reactions happened at lower frequency for glatiramer acetate 40 mg/L administered TIW (35.5%) than for glatiramer acetate 20 mg/L administered daily (70%).	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 (174).

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.

Risk	What is known (Including reason why it is considered a potential risk)
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 (8, 55, 111, 124, 143, 171, 177). 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 (13).
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 (183).
Pregnant or breastfeeding women	Pregnant and breast-feeding women were excluded from glatiramer clinical trials. Glatiramer acetate should be used during pregnancy and breast-feeding only if the benefits outweighs the risks. In studies with animals (rats or rabbits) no adverse effects were observed after treatment with glatiramer acetate in the offspring (174). 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 (196).

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.

Summary EU-Risk Management Plan